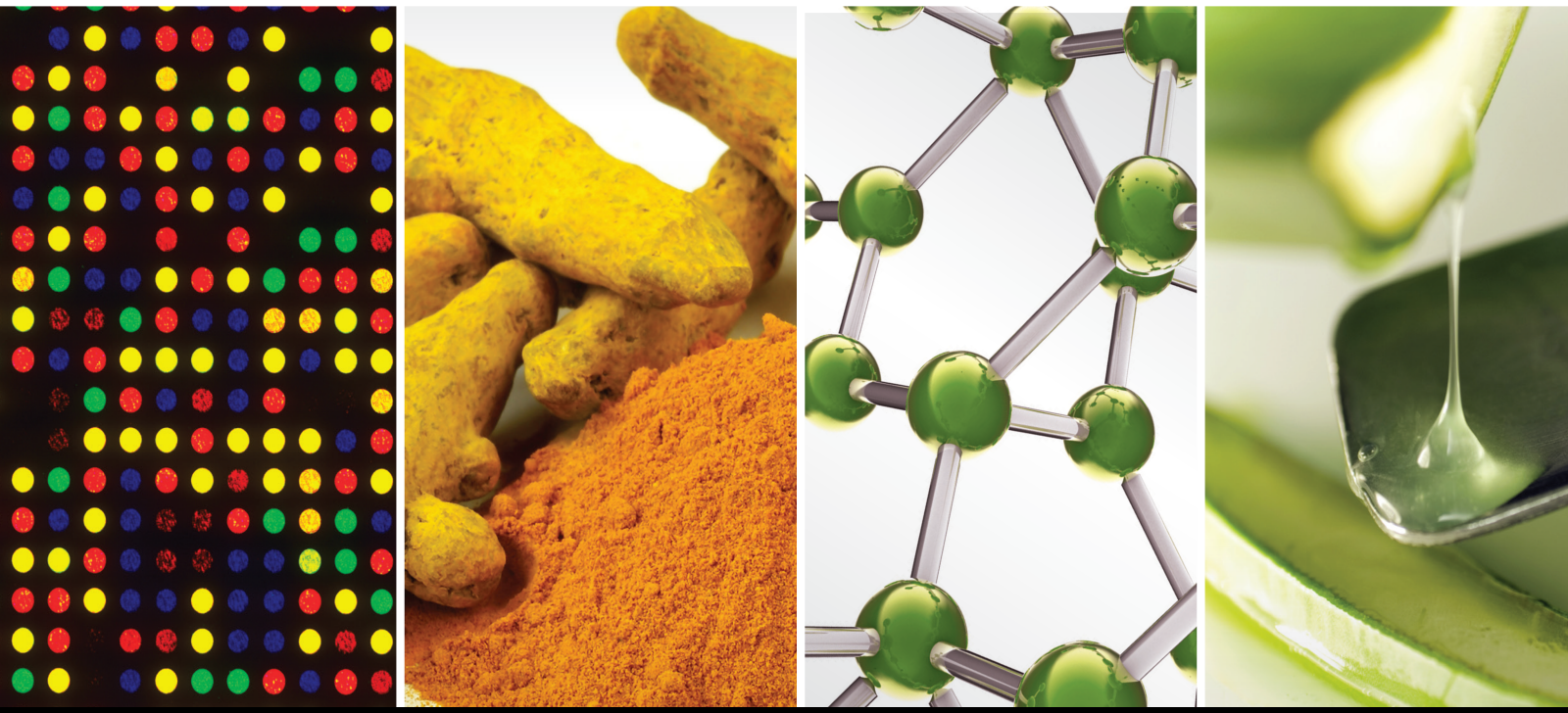
Evidence-Based Complementary and Alternative Medicine

Natural Oxidative Medicines with Bioactive Functions for Chronic Disease Treatment

Lead Guest Editor: Weiguo Li
Guest Editors: WenHu Zhou and Fenglin Liu



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Volume 2023, Article ID 9870405, 1 page
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Retraction

Retracted: Comparative Study on the Clinical Effects of Different Surgical Methods in the Treatment of Gastrointestinal Stromal Tumors

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

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Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] J. Wu, B. Mao, T. Jin, X. Xu, X. Xu, and S. Jiang, "Comparative Study on the Clinical Effects of Different Surgical Methods in the Treatment of Gastrointestinal Stromal Tumors," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 1280756, 7 pages, 2022.

Hindawi
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Retraction

Retracted: Analysis of Immunotherapy Combined with Radiotherapy in Patients with Brain Metastasis of Driver Gene-Negative Non-Small-Cell Lung Cancer

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Retraction

Retracted: Effects of Continuous Infusion of Lidocaine under Ultrasound-Guided Cervical Sympathetic Ganglion Catheterization on Cerebral Hemodynamics and Thermal Imaging Characteristics of Head and Neck in Patients with Angioneurotic Headache

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Hindawi
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Retraction

Retracted: The Low Endometrial Expression of Long Non-Coding RNA NORAD Is Associated with Recurrent Pregnancy Losses and Unexplained Infertility

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Retraction

Retracted: Type 2 Diabetes Mellitus (T2DM) and Carbohydrate Metabolism in Relation to T2DM from Endocrinology, Neurophysiology, Molecular Biology, and Biochemistry Perspectives

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Hindawi
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Retraction

Retracted: Clinical Efficacy Analysis of Biofeedback Electrical Stimulation Combined with Doxycycline in the Treatment of Type IIIA Chronic Prostatitis

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Retraction

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Retraction

Retracted: Analysis of the Efficacy of Multidrug Combination Chemotherapy Regimens for Osteosarcoma and the Management of Chemotherapeutic Reactions

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Retraction

Retracted: Outcome of Percutaneous Transforaminal Endoscopic Lumbar Decompression for Multisegment Lumbar Spinal Stenosis and the Effect on VAS Scores

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Retraction

Retracted: A Retrospective Study of Diaphragmatic Breathing Training Combined with Discharge Care Bundles in Patients with Chronic Obstructive Pulmonary Disease

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Retraction

Retracted: Effects of Positive Psychological Nursing Combined with Free Posture on the Prognosis of Primipara with Singleton Spontaneous Delivery

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Retraction

Retracted: Study on the Relationship between MMP-2, MMP-9 Gene Polymorphisms, and the Risk of Colorectal Cancer

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Retraction

Retracted: Levels of Serum IGF-1, HCY, and Plasma BNP in Patients with Chronic Congestive Heart Failure and Their Relationship with Cardiac Function and Short-Term Prognosis

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Retraction

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Retraction

Retracted: Analysis of the B2M Expression in Colon Adenocarcinoma and Its Correlation with Patient Prognosis

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Hindawi
Evidence-Based Complementary and Alternative Medicine
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Retraction

Retracted: Protective Role of Amiodarone on Reperfusion Arrhythmia in Patients of Acute Myocardial Infarction with Percutaneous Coronary Intervention Treatment

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

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We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] J. Wang, J. Leng, X. Sun et al., "Protective Role of Amiodarone on Reperfusion Arrhythmia in Patients of Acute Myocardial Infarction with Percutaneous Coronary Intervention Treatment," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2597173, 5 pages, 2022.

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Retracted: Influencing Factors of Physical Activity in Patients with Lung Cancer Surgery and Its Correlation with Exercise Self-Efficacy and Perceived Social Support

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[1] N. Zhang, X. He, H. Zhang, Y. Zhu, and Y. Liu, "Influencing Factors of Physical Activity in Patients with Lung Cancer Surgery and Its Correlation with Exercise Self-Efficacy and Perceived Social Support," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7572530, 7 pages, 2022.

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Retraction

Retracted: Inhibition of miR-29b-1-5p Attenuates Inflammatory Response and Pulmonary Fibrosis in LPS-Induced Acute Lung Injury by Regulating RTN4 Expression

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Retraction

Retracted: Hyal1 Expression in Colorectal Carcinoma Cell Migration and Invasiveness: Significance and Mechanism

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[1] S. Zhao, J. Zhao, and N. Zhang, "Hyal1 Expression in Colorectal Carcinoma Cell Migration and Invasiveness: Significance and Mechanism," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4418300, 5 pages, 2022.

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Retraction

Retracted: Correlation and Prognostic Action of SAA, Hcy, and BNP Levels with the Condition of Patients with Spontaneous Intracerebral Hemorrhage

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Retraction

Retracted: Clinical Curative Effects and Influencing Factors of Uterine Artery Chemoembolization Combined with Uterine Curettage Treating with Cesarean Scar Pregnancy Patients

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Retraction

Retracted: Prognostic Value of MUC16 Mutation and Its Correlation with Immunity in Hepatocellular Carcinoma Patients

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Retraction

Retracted: The Low Endometrial Expression of Long Non-Coding RNA NORAD Is Associated with Recurrent Pregnancy Losses and Unexplained Infertility

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Research Article

The Low Endometrial Expression of Long Non-Coding RNA NORAD Is Associated with Recurrent Pregnancy Losses and Unexplained Infertility

Ying Huang,[1] Chengyong Wu,[1] Chunmei Wei,[1] Yekun Chen,[1] and Fei Xing[2]

[1]*Department of Reproductive Medicine, Yichun People's Hospital, Yichun, Jiangxi 336000, China*
[2]*Department of Clinical Laboratory, Huai'an Second People's Hospital and The Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an, Jiangsu 223001, China*

Correspondence should be addressed to Fei Xing; xinghy2016@sina.com

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Objective. Unexplained infertility (UIF) or recurrent pregnancy loss (RPL) affects 10%–15% of couples in their reproductive years and is multifactorial and not completely elucidated. In this study, we attempt to determine the endometrial expression pattern of non-coding RNA activated by DNA damage (NORAD) in women with UIF and RPL, as well as its clinical significance. *Methods*. The microarray dataset GSE165004 was used to identify differentially expressed RNAs in the endometrial samples between women with RPL and fertile women and between women with UIF and fertile women. A total of 142 women were included in this retrospective analysis, including 32 women with UIF, 48 women with RPL, and 62 fertile women. The relative expression level of NORAD in the endometrial tissues was quantified by qRT-PCR. *Results*. NORAD stood out as an only overlapped lncRNA among differentially expressed RNAs in the endometrial samples between RPL and fertile women and between UIF and fertile women. It was showed that the endometrial tissues of UIF and RPL both were demonstrated with lower relative expression levels of NORAD (UIF: 2.09 ± 0.68; RPL: 1.98 ± 0.65) than the endometrial tissues of normal fertility (4.32 ± 1.04) ($P < 0.001$). Pearson correlation analysis demonstrated that the serum level of E2 was negatively correlated with the relative expression level of NORAD in the endometrial tissues of UIF ($r = -0.630$) and RPL ($r = -0.696$). Results of ROC curves showed that the endometrial expression of NORAD could be used to differentiate RPL and UIF with an AUC of 0.977 (95% CI: 0.956–0.999) and 0.970 (95% CI: 0.941–0.998), sensitivity of 0.873 and 0.955, and specificity of 0.845 and 0.948, respectively. *Conclusion*. The findings obtained from the study showed that the low endometrial expression of NORAD was linked to fertility-related problems, such as UIF and RPL.

1. Introduction

Infertility refers to the inability to establish clinical pregnancy after 1 year of regular and unprotected sexual intercourse, affecting 10–15% of reproductive-aged couples worldwide [1]. Approximately 72.4 million populations are estimated to suffer from infertility and 40.5 million people are currently seeking medical care [2]. Identifiable causes, such as ovulatory dysfunction, male factor infertility, and tubal disease, have been confirmed in 85% of those who experience infertility. Unexplained infertility (UIF) exists in the remaining 15% of infertile couples [3]. No direct explanations are identified in the couples with UIF presenting normal spermatogenesis and ovulation. Despite extensive research on unexplained infertility has been explored for decades, UIF still remains to a great extent unexplained [4]. Recurrent pregnancy loss (RPL) is a painful pregnancy disorder. It is defined as a failure of spontaneous pregnancy clinically recognized twice or more before 20–24 weeks of gestation including embryo and fetal loss but excludes ectopic pregnancies and molar pregnancies [5]. The progress in predicting and preventing RPL has been advanced. However, the diagnosis of RPL remains difficult due to its highly variable clinical manifestations and the uncertainty of pathogenesis [6].

Infertility in female is extremely heterogeneous in etiology, which may be due to complex interaction female development, hormone, and environment and genetic factors [7]. The non-coding RNA does not have the ability to encode proteins but contains information and function. These RNAs regulate gene expression in physiology and development including chromatin structure or epigenetic memory and transcription through activating or inactivating internal signals [8]. Non-coding RNA activated by DNA damage (NORAD) also known as LINC00657 is a highly conserved long non-coding RNA (lncRNA) compared to other lncRNAs, which is profusely expressed in a great quantity of cells due to DNA damage. Considerable studies revealed that NORAD has been involved in numerous processes concerning cancer promotion, such as cell proliferation, apoptosis, invasion, and metastasis. It may be a potential biomarker in pancreatic cancer, lung cancer, and colorectal cancer by regulating the downstream mechanisms [8, 9]. Another study demonstrated that lower expression of NORAD was detected in the breast milk exosomes of mothers of preterm infants compared with mothers who gave birth at term. It suggested that NORAD participated in the early human development [10]. The functional role of NORAD in female infertility is unclear at present. Therefore, this study recruited females with RPL or UIF and fertile females to explore the impacts of NORAD on occurrence of RPL or UIF and provide some evidences for clinical treatment.

2. Materials and Methods

2.1. GEO2R Bioinformatics Analysis. A microarray dataset deposited in the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/gds, submission date: Jan 2021) and accessioned as GSE165004 was used to identify differentially expressed RNAs. This dataset was generated on the GPL16699 platform and contained endometrial samples from 24 women with RPL, 24 women with UIF, and 24 fertile women at days 19–21 of the menstrual cycle. Differentially expressed RNAs in the endometrial samples between women with RPL and fertile women and between women with UIF and fertile women were, respectively, sorted using the online tool GEO2R [11] based on the R software limma package. Sorted differentially expressed RNAs must fulfill $\log2|\text{fold change (FC)}| > 1$ and adjusted $P < 0.05$.

2.2. Study Subjects. This retrospective study included women diagnosed with either UIF or RPL with no offspring from spontaneous pregnancies in our infertility center between January 2020 and December 2021. Women were diagnosed with UIF after routine fertility tests showing (i) infertility of more than 12 months, (ii) normospermic male partner according to the World Health Organization (2010) criteria [12], (iii) regular menstrual cycle of 25–35 days, positive ovulation tests, and/or progesterone levels ≥ 25 mmol/l, (iv) normal uterine cavity and bilateral tubal patency on the hysterosalpingogram or laparoscopy, and (v) normal hormonal tests (follicle stimulating hormone (FSH) ≤ 13 UI/l and anti-Müllerian hormone (AMH) ≥ 0.4 ng/ml) [13]. Women were diagnosed with RPL if they failed to conceive after ≥2 fresh IVF-ET/ICSI (in vitro fertilization-embryo transfer cycles/intracytoplasmic sperm injection) or had ≥3 consecutive miscarriages occurring before 20 weeks of gestation, documented by ultrasonography or histopathological examination. Eligible women with either UIF or RPL must have age between 18 and 40 years and detailed reports of laparoscopy and hysteroscopy (done within 1 month) and sign a written consent to participate in the study. Those with an identifiable cause of reproductive failure such as chromosomal abnormalities or anatomic defects identified on initial screen, with known endometriosis, adenomyosis, endocrine disorders (polycystic ovary syndrome), autoimmune diseases, or thrombophilia (inherited or acquired), with previous use of hormone therapy, with severe obesity (body mass index (BMI) > 35), or using antibiotics within at least two weeks before sample collection were excluded from this retrospective analysis. Women undergoing dilatation and curettage in our hospital at the same period, with regularly cycling women, at least one live birth, no history of infertility/treatment, no previous miscarriages and no associated gynecologic (endometriosis, fibroids, active or history of pelvic inflammatory disease) or other medical comorbidities such as hyperprolactinemia and thyroid disease were served as fertile controls. The study was approved by the Ethics Committee of our hospital.

2.3. Endometrial Sample Collection. Endometrial tissue was obtained from included women in 7–9 days after the luteinizing hormone surge detected using urine luteinizing hormone tests at the time of their medically indicated hysteroscopic endometrial biopsy or endometrial curettage.

2.4. RNA Extraction and Quantitative Real-Time PCR (qRT-PCR). Total RNA was extracted from obtained endometrial tissues using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) following the manufacturer's manual. The generation of complementary DNA (cDNA) template was carried out using the PrimeScript RT Reagent kit (Takara, Dalian, China) following the manufacturer's manual. The qPCR was carried out using the SYBR® Premix Ex Taq™ II kit (Takara) and a ABI PRISM®7500 System (Applied Biosystems, Foster City, CA, USA) under the thermocycling conditions (95°C for 5 min, followed by 40 cycles at 95°C for 15 s, 60°C for 30 s, and 72°C for 1 min). The primer sequence information of NORAD was 5′-AAGCTGCTCTCAACTCCACC-3' (forward) and 5′-GGACGTATCGCTTCCAGAGG-3' (reverse), and that of GAPDH was 5′-GGAGCGAGATCCCTCCAAAAT-3' (forward) and 5′-GGCTGTTGTCATACTTCTCATGG-3' (reverse). The cycle threshold (Ct) values were normalized to the level of GAPDH, and results were then converted into fold change using the $2^{-\Delta\Delta Ct}$ formula.

2.5. Enzyme-Linked Immunosorbent Assay (ELISA). All included women were subjected to venous blood collection in the morning for detection of serum levels of hormones

Table 1: Identification of differentially expressed RNAs in the endometrial samples between women with RPL and fertile women and between women with UIF and fertile women.

Gene symbol	GB_ACC	Log2FC	RPL or UIF vs. control
NORAD	NR_027451	−1.53	RPL vs. control
ZNF90	AK298173	−1.24	RPL vs. control
SUMO1P3	NR_002190	−1.14	RPL vs. control
ANXA2	NM_001002857	−1.12	RPL vs. control
CAPZA2	NM_006136	−1.05	RPL vs. control
SFRP4	NM_003014	−1.21	RPL vs. control
NORAD	NR_027451	−1.20	UIF vs. control
MAGEA6	NM_175868	−1.06	UIF vs. control
RNA18SN5	NR_003286	1.08	UIF vs. control

NORAD, non-coding RNA activated by DNA damage; ZNF90, zinc finger protein 90; SUMO1P3, SUMO1 pseudogene 3; ANXA2, annexin A2; CAPZA2, capping actin protein of muscle Z-line subunit alpha 2; SFRP4, secreted frizzled related protein 4; MAGEA6, MAGE family member A6; RNA18SN5, RNA, 18S ribosomal N5.

including FSH, estradiol (E2), progesterone (P), luteinizing hormone (LH), testosterone (T), and prolactin (PRL) by ELISA methods. All ELISA procedures were performed in accordance with the protocol supplied by the kits' manufactures (R&D Systems, USA).

2.6. Statistical Analysis. Statistical analysis and figure creation were performed using GraphPad Prism 8 (GraphPad Software, CA, USA) and SPSS version 22.0 statistical package (IBM Corp, Armonk, NY, USA). Categorical data were shown by number with percentage and analyzed by chi-square test or Fisher's exact test ($P < 0.05$ regarded as significant difference). Measurement variables normally distributed are shown as mean ± standard deviation and analyzed by independent Student's t-test ($P < 0.05$ regarded as significant difference). The Pearson correlation test was used to assess the association between NORAD and serum levels of E2 and P. The receiver operating characteristic (ROC) and logistic regression analysis were performed to estimate the diagnostic values of NORAD in UIF and RPL.

3. Results

3.1. NORAD as a Differentially Expressed lncRNA in RPL and UIF. After GEO2R bioinformatics analysis, we identified six downregulated RNAs (log2FC > 1 and $P < 0.05$) in the endometrial samples between women with RPL and fertile women and three differentially expressed RNAs (two downregulated RNAs and an upregulated RNA, $\log2|FC| > 1$ and $P < 0.05$) in the endometrial samples between women with UIF and fertile women (Table 1). NORAD stood out as an only overlapped lncRNA among differentially expressed RNAs in the endometrial samples between RPL and fertile women and between UIF and fertile women.

3.2. Demographics and Clinical Characteristics of Included Women. A total of 142 women were included in this retrospective analysis, including 32 women with UIF, 48 women with RPL, and 62 fertile women. Demographics and clinical characteristics of three groups of women are listed in Table 2, showing no significant difference on age, body mass index (BMI), the proportions of history of taking oral contraceptives, algomenorrhea, and family history among them. Of note, the serum levels of FSH, LH, T, PRL, and E2 were higher but the serum level of P was lower in women with either UIF or RPL than those in fertile women ($P < 0.05$). No significant difference was noted in these serum levels of hormones between the women with UIF and those with RPL ($P > 0.05$).

3.3. Low Endometrial Expression of NORAD in RPL and UIF. The relative expression level of NORAD in the endometrial tissues obtained from 32 women with UIF, 48 women with RPL, and 62 fertile women was quantified by qRT-PCR. It was showed that the endometrial tissues of UIF and RPL both were demonstrated with lower relative expression levels of NORAD (UIF: 2.09 ± 0.68; RPL: 1.98 ± 0.65) than the endometrial tissues of normal fertility (4.32 ± 1.04) ($P < 0.001$, Figure 1(a)). No evident significance was noted in the endometrial expression of NORAD between UIF and RPL ($P > 0.05$). Pearson correlation analysis demonstrated that the serum level of E2 was negatively correlated with the relative expression level of NORAD in the endometrial tissues of UIF (Figure 1(b), $r = -0.630$) and RPL (Figure 1(c), $r = -0.696$), but the serum levels of FSH, LH, T, PRL, and P were not correlated ($P > 0.05$).

3.4. Diagnostic Value of NORAD in RPL and UIF. Results of ROC curves showed that the endometrial expression of NORAD could be used to differentiate RPL and UIF with an AUC of 0.977 (95% CI: 0.956–0.999) and 0.970 (95% CI: 0.941–0.998), sensitivity of 0.873 and 0.955, and specificity of 0.845 and 0.948 (Figure 2), respectively.

4. Discussion

Placenta is the active interface between mother and fetus, which is related to the rapid development and exposure of molecular markers in the uterus. Genomic imprinting is involved in the development of placenta. For instance, increased mRNA expression of IGF2 and decreased expression of H19 were detected in endometrial tissues of females with UIF [14]. A variety of factors such as chromosomal abnormalities, maternal immunological rejection, and hormonal imbalance are associated with RPL. Normal cellular regulation of these factors is essential for maintaining normal pregnancy, and differential gene expression affects the biological processes of RPL [15]. lncRNAs have attracted extensive attention in disease development because of their enormous diversity in evolutionary conservation, expression level, molecular function, and cellular localization [16]. Previous studies have indicated that lncRNAs including lnc32058, lnc09522, and lnc98497 were differentially expressed in male infertility. Regulation role of lncRNAs on gene expression has been identified in female reproductive disorders [17]. The patients with polycystic ovary syndrome

Table 2: Demographics and clinical characteristics of women with UIF, women with RPL, and fertile women.

Characteristics	UIF ($n = 32$)	RPL ($n = 48$)	Normal fertility ($n = 62$)
Age (year)	30.56 ± 4.83	29.06 ± 4.17	29.45 ± 4.45
BMI	23.72 ± 3.03	23.51 ± 3.11	22.68 ± 2.87
History of taking oral contraceptives (n(%))	10 (31.25%)	18 (37.50%)	15 (24.19%)
History of algomenorrhea (n(%))	15 (46.88%)	22 (45.83%)	23 (37.10%)
History of family history (n(%))	2 (6.25%)	2 (4.15%)	2 (3.22%)
FSH (mIU/ml)	6.29 ± 2.07*	6.62 ± 2.11*	4.40 ± 1.30
LH (mIU/ml)	7.79 ± 2.33*	8.37 ± 2.50*	5.80 ± 2.05
T (nmol/L)	1.74 ± 0.30*	1.80 ± 0.32*	1.45 ± 0.28
PRL (mIU/L)	493.81 ± 150.03*	501.73 ± 149.69*	316.47 ± 120.03
E2 (pmol/L)	115.47 ± 38.12*	120.72 ± 41.55*	81.63 ± 29.04
P (nmol/L)	1.05 ± 0.41*	0.95 ± 0.30*	2.53 ± 0.80

BMI, body mass index; FSH, follicle stimulating hormone; E2, estradiol; P, progesterone; LH, luteinizing hormone; T, testosterone; PRL, prolactin; *$P < 0.001$ compared to normal fertility, analyzed by independent Student's t-test.

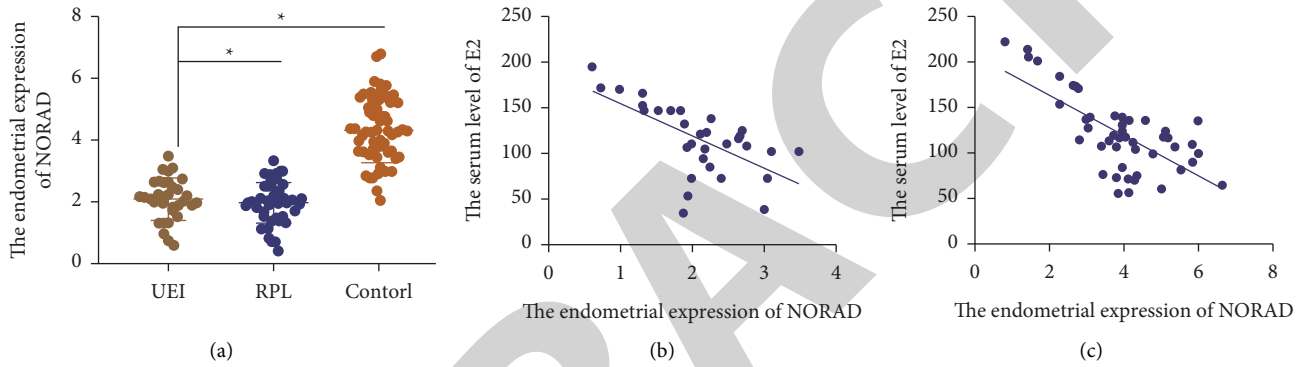

Figure 1: Low endometrial expression of NORAD in RPL and UIF. (a) The relative expression level of NORAD in the endometrial tissues obtained from women with UIF ($n = 32$), women with RPL ($n = 48$), and fertile women ($n = 62$) was quantified by qRT-PCR. (b) Pearson correlation analysis of the serum level of E2 and the relative expression level of NORAD in the endometrial tissues of UIF. (c) Pearson correlation analysis of the serum level of E2 and the relative expression level of NORAD in the endometrial tissues of RPL.

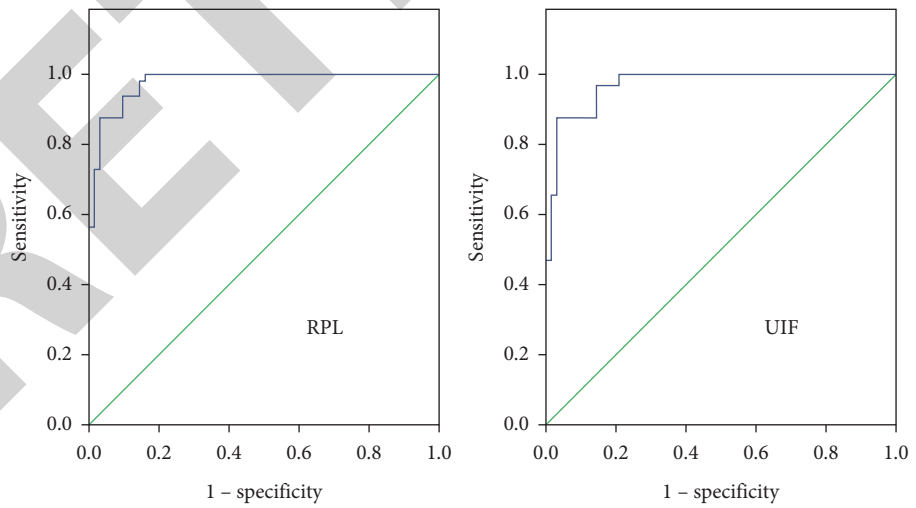

Figure 2: ROC curves of the endometrial expression of NORAD used to differentiate RPL and UIF.

showed elevated expression of lnc-MAP3K13-7:1 in inhibited granulosa cell [18]. HZ07 lncRNA was upregulated induced by benzo(a)pyrene in RPL and overexpression of HZ07 inhibited trophoblast cell migration [19].

Human LINC00657 RNA or alternatively named as NORAD is abundantly expressed in human tissues and cell lines after DNA damage. NORAD was reported as an oncogene of most cancer-related diseases. The role of NORAD

in increasing cell viability, proliferation, migration, and invasion while inhibiting apoptosis has been explored in colorectal cancer study presented by Wang et al. [20] and Zhang et al. [21]. Besides, Yang et al. revealed that overexpression of NORAD enhanced migration and invasion of hepatocellular carcinoma cells by suppressing miR-202-5p [22]. However, upregulation of NORAD contributed to suppress tumor growth and enhance apoptosis of endometrial cancer cells. The effects have been exerted through interaction between NORAD and far upstream element binding protein 1 (FUBP1), resulting in attenuation of nuclear localization of this anti-apoptotic protein and releasing pro-apoptotic gene promoters [23]. In this study, we compared the relative expression of NORAD in endometrial tissues from females with UIF, females with RPL, and fertile females. The qRT-PCR manifested that lower expression of NORAD was detected from females with UIF and females with RPL compared with females with normal fertility. UIF and RPL females showed no significant difference concerning NORAD expression. Abnormal female hormone levels lead to negative impact on the reproductive system. FSH is the most commonly used indicator in determining ovarian reserve and represents an indispensable part of fertility treatment [24]. LH plays a vital role in role in promoting follicular growth and maturation in ovarian function. It can be used as an effective predictor of ovarian function when it is combined with FSH [25]. P is essential for the establishment and maintenance of pregnancy through its role in endocrine and immunity [26]. This study found that the fertile females had lower level of FSH, LH, T, PRL, and E2 in serum but showed higher P level than the females with either UIF or RPL. A slight difference in these hormones was noted in females with UIF and females with RPL. Furthermore, Pearson correlation analysis in our study also confirmed that no correlations were identified between NORAD expression and these hormones levels except for E2, whereas E2 level was negatively correlated with NORAD expression. Lastly, we detected the diagnostic value of NORAD in RPL and UIF and found that NORAD yielded AUC of 0.977 and 0.970, respectively, for differentiating RPL and UIF.

However, some limitations should be noted in this study. First, the study consisted of bioinformatics analysis, and qPCR experiment, RNA-sequencing, or arraying in included endometrial tissues will be required in further study. Second, small sample size used for NORAD expression relation to RPL and UIF may reduce reliability of results. Third, there is no evidence presenting the discriminatory nature of this lncRNA in RPL or UIF, and the functions of this lncRNA are yet unclear. Finally, two different datasets were used in the study, but how their endometrial tissues were collected remains unclear.

In conclusion, the present study identified that NORAD expression in endometrial tissues was associated with the occurrence of UIF and RPL in females, and negative correlation was observed between E2 level in serum and NORAD expression. The result may trigger a series of special diagnostics and treatment options for females with UIF and RPL.

Data Availability

The dataset (accession number: GSE165004) analyzed during the current study is available in the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE165004). Other data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Influence of Ginsenoside Rh2 on Cardiomyocyte Pyroptosis in Rats with Acute Myocardial Infarction

Wanmei Song,[1] Bin Dai,[1] and Yuntang Dai[2]

[1]*Department of Cardiovascular Medicine, Longhui Country People's Hospital, Shaoyang 422200, Hunan, China*
[2]*Clinical Laboratory, Longhui Country People's Hospital, Shaoyang 422200, Hunan, China*

Correspondence should be addressed to Yuntang Dai; dyt20220528@126.com

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Objective. This paper intends to verify through *in* vivo experiments whether ginsenoside Rh2 (G-Rh2) can play an anti-inflammatory role by modulating cardiomyocyte (CM) pyroptosis in rats with acute myocardial infarction (AMI), thereby alleviating myocardial injury. *Methods*. Twenty SD rats were randomized into control, L-Rh2, M-Rh2, and H-Rh2 groups, among which the latter three groups were modeled for AMI and given an intraperitoneal injection of G-Rh2 (L-Rh2: 2 mg/kg; M-Rh2: 4 mg/kg; H-Rh2: 8 mg/kg), while the control group was only treated with thoracotomy and sodium chloride injection. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), left ventricular systolic pressure (LVSP), and left ventricular end-diastolic pressure (LVEDP) were recorded by ultrasonic diagnosis. Rats were killed under anesthesia, and the morphological characteristics of ventricular tissue were observed by electron microscope. Additionally, cardiac blood and ventricular tissues were collected to quantify the contents of myocardial injury markers (creatine phosphate kinase (CK), creatine phosphokinase-MB isoenzyme (CK-MB), and lactate dehydrogenase (LDH) by ELISA, as well as the expression of pyroptosis-related genes cysteinyl aspartate specific proteinase 1 (Caspase-1), gasdermin D (GSDMD), interleukin (IL)-1β, and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) by qRT-PCR and Western blot). *Results*. Ultrasonic examination identified lower HR, SBP, DBP, MAP, and LVSP in the three Rh2 injection groups compared with the control group ($P < 0.05$); and in comparison with M- and H-Rh2 groups, HR, SBP, DBP, MAP, and LVSP were all lower in L-Rh2 group, while LVEDP was higher ($P < 0.05$). Microscopically, CMs and organelles in the L-RH2, M-RH2, and H-RH2 groups were damaged to varying degrees compared with the control group, with those in the L-RH2 group being the most serious. CK, CK-MB, and LDH were also the highest in the L-Rh2 group and the lowest in the control group, while their levels were obviously reduced in M- and H-Rh2 groups ($P < 0.05$). Finally, GSDMD, IL-1β, NLRP3, and Caspase-1 were found to be reduced in the control group, while pyroptosis-related gene expression in the M-Rh2 group was improved markedly ($P < 0.05$). *Conclusion*. G-Rh2 can inhibit the pathological development of AMI by relieving the focal death of CM and inhibiting the release of proinflammatory factors in the body, and the effect is significantly related to the dosage, which is expected to become a new treatment option for AMI in the future.

1. Introduction

Cardiovascular disease (CVD), with a predilection for middle-aged and elderly people, is a high-risk condition with mortality second only to malignancies [1]. Among them, acute myocardial infarction (AMI) is one of the most prevalent cardiovascular disorders, accounting for about 14–20% of the total CVD cases [2]. AMI is a disease primarily caused by acute coronary artery obstruction and myocardial necrosis, characterized by a high incidence, rapid progression, and high mortality [3]. According to statistics, there were over 2 million new AMI patients worldwide in 2019, an increase of about 7 times compared with a decade ago [4]. Moreover, the incidence of AMI also shows a trend of getting younger, with patients under 45 years old becoming increasingly common in recent years [5]. Meanwhile, as one of the high-risk types of CVD, the mortality rate of AMI has exceeded 60%, seriously threatening

patients' life safety [6]. At present, the most effective clinical treatment for AMI is still coronary artery intervention or coronary artery bypass surgery. These two surgical methods are difficult to operate and invasive to some extent, and their application is limited for some patients. Moreover, due to the limitation of surgery, when a patient suffers from a sudden illness, emergency rescue cannot be performed by surgery, which undoubtedly increases the risk of adverse events [7]. Therefore, the search for an effective and rapid treatment for AMI has become a hotspot in modern clinical research, but no significant results have been achieved yet.

Undoubtedly, traditional Chinese medicine (TCM) is the safest therapy among all kinds of treatments in the field of modern medicine. However, as TCM treatment is generally a long-term and continuous therapy, it can hardly take effect quickly and is therefore rarely used in emergency treatment [8]. But by extracting the main active ingredients of TCM separately, their efficacy can be rapidly brought into play while ensuring the safety profile. Ginsenoside Rh2 (G-Rh2) is the hydrolyzed product of ginsenoside, the active component of ginseng. Compared with ginsenoside, Rh2 has higher purity and a faster drug metabolism rate [9]. At present, it has been found clinically that Rh2 can participate in the treatment of tumor diseases in multiple ways such as inhibiting tumor growth and reversing tumor cell drug resistance, with health and rehabilitation-promoting effects like improving human immune resistance and relieving fatigue [10, 11]. In a variety of CVD, Rh2 has also been found to have a good effect on reducing cardiac fibrosis, but its application value in AMI is still unclear [12]. We believe that Rh2 may also be expected to become a new treatment direction for AMI in the future, providing a more reliable guarantee for the life safety of AMI patients. Besides, Cellular apoptosis is a new programmed cell death, which is characterized by its dependence on inflammatory Caspase-1 and the release of a large number of proinflammatory factors through NLRP3 and other pathways. Cellular apoptosis is widely involved in the development of infectious diseases, nervous system-related diseases, and atherosclerotic diseases. Arterial injury and inflammation always run through the pathophysiological process of AMI progression to ventricular remodeling and heart failure. Therefore, cellular apoptosis is closely related to the development of AMI.

Consequently, this study intends to analyze the influence of Rh2 on cardiomyocytes (CMs) of AMI rats, aiming at confirming the effect and mechanism of Rh2 on AMI and laying a foundation and reference for future clinical application of Rh2.

2. Materials and Methods

2.1. Main Reagents. Western blot kit and BCA kit (Beijing Dingguo Changsheng Biotechnology); NLRP3, Caspase-1, GSDMD, IL-1β, and β-actin primary antibodies and HRP goat anti-rabbit IgG (ABclonal, USA); high-efficiencyenhanced-enhanced chemiluminescence (ECL) Kit (Genview, USA); TRIzol extraction kit (Thermo Fisher Scientific, USA); miRNA 1st Strand cDNA Synthesis Kit and miRNA Universal SYBR qPCR Master Mix (Nanjing Vazyme Biotech); DEPC water (Shanghai Beyotime Biotechnology); ELISA kit (Wuhan Fine Biotech).

2.2. Rat Data. Twenty SPF SD rats ordered from Hunan SJA Laboratory Animal Co., Ltd. (Animal License Number: SYXK (Xiang) 2019–0017) were caged with 5 rats each and raised in an environment of 18–26°C, 40–70% humidity, and 12 : 12 h light-dark regime. They were given standard chow and allowed free access to water. This experiment was carried out in strict accordance with the Declaration of Helsinki and has been approved by the Animal Ethics Committee of our hospital (KYSQ 2020–07).

2.3. Grouping and Modeling. Twenty SD rats were randomized into 4 groups, each with 5 rats. Three groups were established as AMI model rats by referring to the study of Wu et al. [13]. Anesthesia was performed, and after trachea incision and intubation, an animal ventilator and ECG detection equipment were externally connected. The rat heart was then exposed by a tip of 3 cm in length along the gap between the third and fourth ribs. After confirming the position of the left anterior descending coronary artery at the junction of the pulmonary artery conical and left atrial appendage, ligation was performed 2 mm from the root of the left atrial appendage. If the anterior wall of the left ventricle was pale locally, the wall motion was weakened, and the ST segment of leads I and II of ECG was obviously increased, a syringe was used to extract the gas in the thoracic cavity. The chest was closed after the thoracic pressure was restored. The other group was treated as the control group only with thoracotomy. Then, three groups of AMI rats were intraperitoneally injected with 2 mg/kg (L-Rh2 group), 4 mg/kg (M-Rh2 group), and 8 mg/kg(H–Rh2 group) of Rh2, respectively, and the control group rats were given 0.9% sodium chloride injection intraperitoneally. The four groups of rats were continuously administered for 2 weeks.

2.4. Rat Hemodynamics and Cardiac Function Detection. Fourteen days after modeling, the rats were weighed, and the heart rate (HR), systolic/diastolic blood pressure (SBP/DBP), mean arterial pressure (MAP), left ventricular systolic pressure (LVSP), and left ventricular end-diastolic pressure (LVEDP) were examined by ultrasound under anesthesia. Then 3–5 ml of 10% potassium chloride was injected, the thorax was opened to take out the whole heart, and the right ventricle was cut off. The rest was dried with filter paper and weighed to calculate the left ventricular mass index.

2.5. Detection of Myocardial Injury Markers. The rat heart blood was collected into the coagulation-promoting tube and left standing for half an hour, and serum was obtained after 10 min of centrifugation (1500 × g, 4°C) to quantify creatine phosphate kinase (CK), creatine phosphokinase-MB isoenzyme (CK-MB) and lactate dehydrogenase (LDH) contents by ELISA. The testing process was strictly in accordance with the manufacturer's instructions.

2.6. CM Injury Determination. The rat's left ventricle was divided into three portions, one of which was placed into glutaraldehyde fixative and rinsed with a phosphate buffer solution at 4°C for 0.4–2.0 h. After fixation in osmic acid fixative for 2 hours, it was dehydrated by 50% ethanol for 15 min, 70% ethanol for 15 min, 80% ethanol for 15 min, 90% ethanol for 15 min, and 100% ethanol for 20–30 min. Following sufficient dehydration, it was soaked with an embedding agent first, and then with a new embedding agent for 30 min before embedding. Finally, it was sliced into 40–50 nm ultrathin slices and placed in a 3 mm diameter copper net for electron microscopy observation.

2.7. Pyroptosis-Related Gene Expression Detection. The other two portions of the left ventricular tissues were taken, one of which was extracted with a TRIzol extraction kit for total RNA. After purity verification by ultraviolet spectrophotometer, the RNA was reverse transcribed into cDNA. The sequences of primers used were designed and synthesized by Sangon Biotech, Shanghai (Table 1). ABI7500 quantitative PCR instrument was used for real-time quantitative PCR. The reaction procedure was 95°C for 5 min, and 30 cycles of 95°C for 5 s and 60°C for 30°s. High resolution melting: 95°C, 60°s; 55°C 30°s; and 95°C 30°s. NOD-like receptor thermal protein domain associated protein 3 (NLRP3), cysteinyl aspartate specific proteinase 1 (Caspase-1), gasdermin D (GSDMD), and interleukin (IL)-1β levels were normalized with β-actin and computed via $2^{-\Delta\Delta Ct}$. The last portion of the left ventricular sample was extracted by RIPA lysis buffer to retrieve the total protein, which was then quantified by BCA and subjected to SDS-PAGE gel electrophoresis. Following denaturation at 95°C for 10 min, cooling, sample loading, and electrophoresis, the protein was treated with membrane transfer, sealing, incubation with primary and secondary antibodies, as well as development with a chromogenic agent. The protein bands were finally observed by the gel image analysis system to determine NLRP3, Caspase-1, GSDMD, and IL-1β levels relative to β-actin or GAPDH. For the sequences of primers see Table 1.

2.8. Statistics and Methods. SPSS22.0 performed statistical analysis in this research. Each test in this study was run in duplicate, and the results were expressed as ($\overline{\chi} \pm s$). Variance analysis and the Bonferroni test were used for multigroup and intragroup comparisons, respectively, with the difference, deemed significant when $P < 0.05$.

3. Results

3.1. Modeling Results. No peritonitis or death occurred in rats in this study. After 2 weeks of modeling, control rats were observed to be more active in diet and water intake, with shiny hair and certain mobility. However, L-Rh2 group rats showed no obvious signs of activity, dull hair color, and no self-feeding ability. In contrast, M-Rh2 group rats were occasionally active, and some could still eat autonomously. And the activity ability of H-Rh2 group rats was slightly lower compared with control rats, with the ability to eat independently.

3.2. Comparison of Hemodynamics and Cardiac Function. Control rats presented higher HR, SBP, DBP, MAP, and LVSP levels than the three groups of rats injected with Rh2, as indicated by the Ultrasonic examination. And the control group had a LVEDP level similar to the M-Rh2 group ($P > 0.05$), which was lower compared with the L-Rh2 group and higher than the H-Rh2 group ($P < 0.05$). A multigroup comparison of the three groups of rats injected with Rh2 revealed lower HR, SBP, DBP, MAP, and LVSP and higher LVEDP in the L-Rh2 group compared with M- and H-Rh2 groups ($P < 0.05$). Likewise, the M-Rh2 group had lower HR, SBP, DBP, MAP, and LVSP while higher LVEDP than the H–Rh2 group (Figure 1).

3.3. Comparison of Myocardial Injury Markers. Among the four groups, serum CK, CK-MB, and LDH contents were the lowest in the control group and the highest in the L-Rh2 group ($P < 0.05$). And in comparison with H–Rh2 group, CK, CK-MB, and LDH were higher in the M-Rh2 group ($P < 0.05$) (Figure 2).

3.4. Comparison of CM Injury. As indicated by the electron microscopic examination, the ultrastructure of CMs in the control group was basically intact, with a clear structure and no obvious apoptotic bodies observed. L-Rh2 group rats exhibited obviously damaged and seriously broken CMs, with visible apoptotic bodies as well as disordered and partially broken myofibrils, and the degree of injury in the L-Rh2 group was significantly higher than that in the M-Rh2 group and H–Rh2 group. M-Rh2 group showed relatively intact CM morphology, with a small number of nuclei destroyed, slight swelling of mitochondrial aggregation, partial disappearance of mitochondrial ridges, local vacuoles, and occasional apoptotic bodies. In the H-RH2 group, the morphological structure of CM was the most intact of the three modeling groups, and its structural characteristics were similar to that of the control group (Figure 3).

3.5. CM Pyroptosis-Related Gene Expression. qPCR results determined lower GSDMD, IL-1β, NLRP3, and Caspase-1 mRNA levels in the control group compared with the three Rh2 intervention groups ($P < 0.05$). The multigroup comparison of GSDMD, NLRP3, and Caspase-1 mRNA identified that the L-Rh2 group had the highest levels while the H-Rh2 group had the lowest levels ($P < 0.05$). However, no statistical significance was found in IL-1β mRNA between L- and H–Rh2 groups ($P > 0.05$), while the IL-1β mRNA in L- and H–Rh2 groups were lower than that of the M-Rh2 group ($P < 0.05$) (Figure 4).

3.6. CM Pyroptosis-Related Protein Expression. At last, the Western blot analysis showed lower GSDMD and IL-1β protein while higher NLRP3 and Caspase-1 protein levels in

Table 1: Primer sequences.

Gene name	F (5′–3′)	R (5′–3′)
GSDMD	TTGAGTGTCTGGTGCTCGAC	ATGGGGTGCTCTGTTCCAAG
NLRP3	GGTGACCTTGTGTGTGCTTG	ATGTCCTGAGCCATGGAAGC
IL-1β	GGTTCAAGGCATAACAGGCTC	TCTGGACAGCCCAAGTCAAG
Caspase-1	TTATCAGGGTTGACCCCTTGG	TTGCCCTCAGGATCTTGTCAG
GAPDH	ACACGAGTCCTGGTGACTTTG	GGGCTTAGGTCCACACAGAA

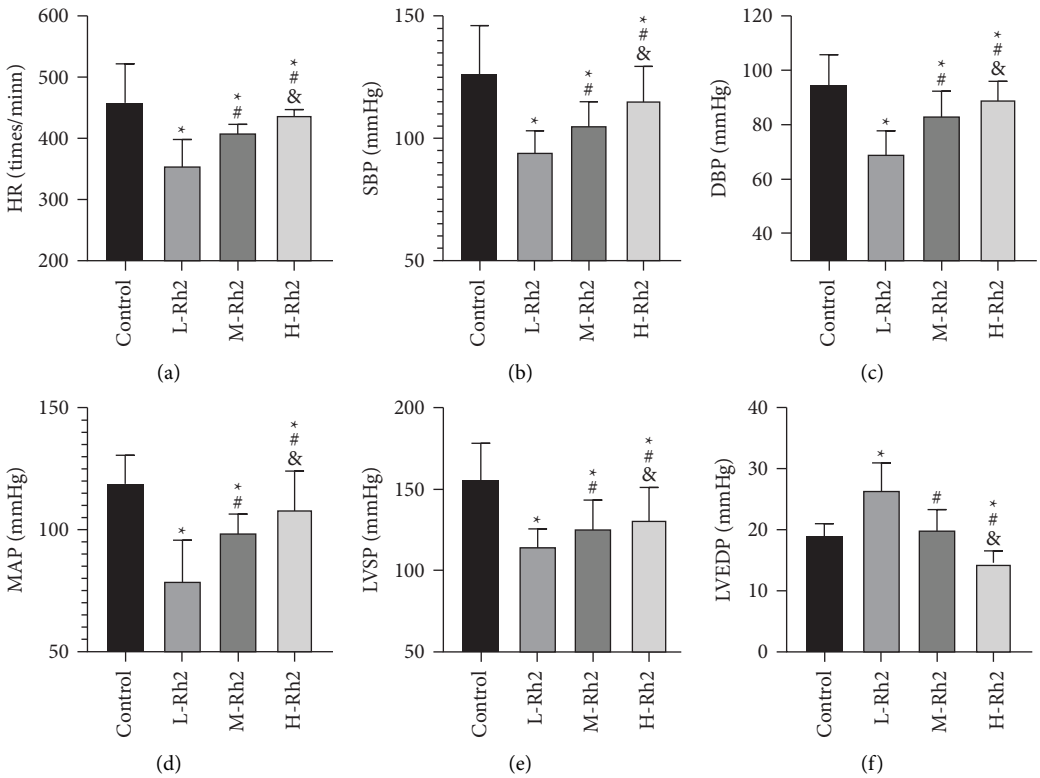

Figure 1: Comparison of hemodynamics and cardiac function. (a) Comparison of HR. (b) Comparison of SBP. (c) Comparison of DBP. (d) Comparison of MAP. (e) Comparison of LVSP. (f) Comparison of LVEDP. *: Compared with the control group, the difference was statistically significant ($P < 0.05$). #: Compared with the L-Rh2 group, the difference was statistically significant ($P < 0.05$). &: Compared with the M-Rh2 group, the difference was statistically significant ($P < 0.05$).

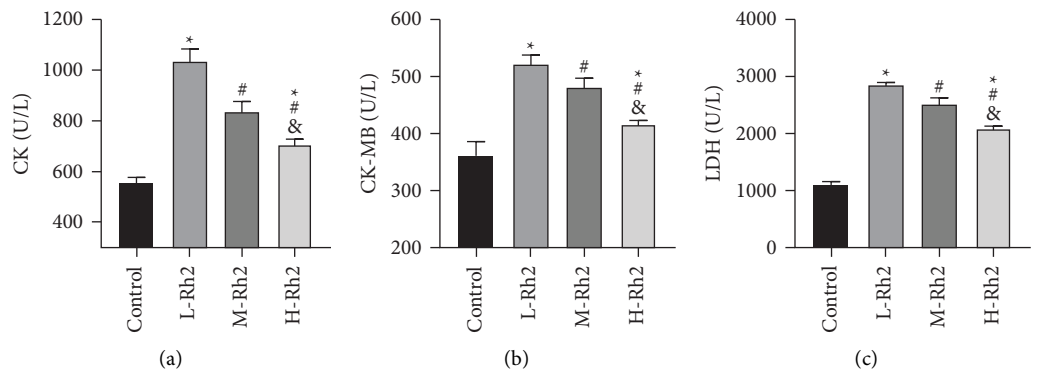

Figure 2: Comparison of myocardial injury markers. (a) Comparison of CK. (b) Comparison of CK-MB. (c) Comparison of LDH. *: Compared with the control group, the difference was statistically significant ($P < 0.05$). #: Compared with the L-Rh2 group, the difference was statistically significant ($P < 0.05$). &: Compared with the M-Rh2 group, the difference was statistically significant ($P < 0.05$).

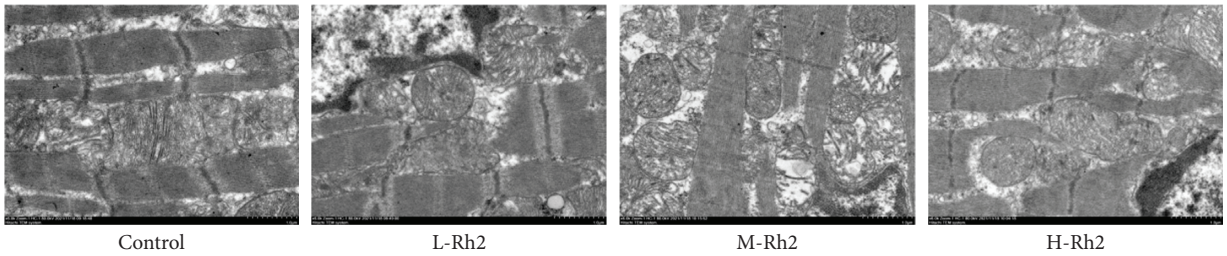

Figure 3: Electron microscopy was used to observe myocardial injury.

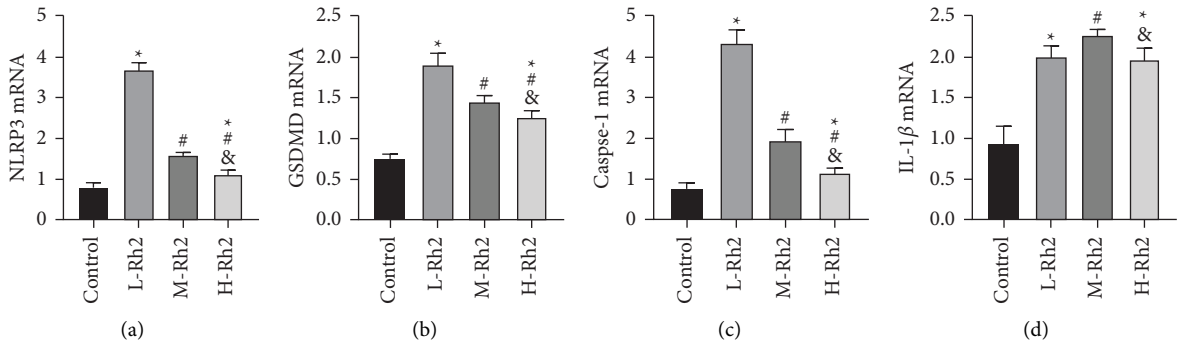

Figure 4: CM pyroptosis-related gene expression. (a) Comparison of NLRP3 mRNA. (b) Comparison of GSDMD mRNA. (c) Comparison of Caspase-1 mRNA. (d) Comparison of IL-1β mRNA. *: Compared with the control group, the difference was statistically significant ($P < 0.05$). #: Compared with the L-Rh2 group, the difference was statistically significant ($P < 0.05$). &: Compared with the M-Rh2 group, the difference was statistically significant ($P < 0.05$).

the control group compared with L-, M-, and H-Rh2 groups ($P < 0.05$). Among the three groups treated with Rh2 injection, L-Rh2 had the lowest GSDMD, NLRP3, and Caspase-1 levels, while the H-Rh2 group showed lower levels than the M-Rh2 group ($P < 0.05$) (Figure 5).

4. Discussion

At present, the high incidence and mortality of CVD have caused a great burden on global medical care, among which AMI is one of the primary causes of death [14]. Therefore, improving the treatment level of AMI and controlling its incidence have become a research focus in the cardiovascular field. As a new type of programmed cell death, apoptosis has been confirmed to participate in the pathogenesis and progression of AMI by regulating the inflammatory response and stimulating the release of proinflammatory factors, but the exact mechanism has not yet been clearly elucidated [15]. Rh2, the main active component of ginseng, has shown excellent effects in multiple pathological improvements, such as antitumor, antiallergy, anti-inflammation, enhancing immunity, and resisting hypoxia, in addition to a certain protective role in CVD [16–19]. Therefore, this paper intends to verify in vivo whether Rh2 can exert anti-inflammatory action by regulating CM pyroptosis in AMI rats, thus alleviating myocardial injury and providing a reliable theoretical basis for future treatment of AMI.

Compared with the control group, a number of indicators of cardiac function and hemodynamics were found to be abnormal in rats after AMI modeling, while these indicators of AMI rats recovered after Rh2 administration, among which the recovery effect of the H-RH2 group was the most significant, indicating that Rh2 has the effect of alleviating AMI. In previous studies, we found that Rh2 can validly reduce nerve damage caused by cerebral ischemia and cardiotoxicity after breast cancer [20, 21], which can also preliminarily verify our results and confirm the improvement effect of Rh2 on CVD. Moreover, under electron microscope observation of left ventricular tissue, we found seriously damaged rat CMs and organelles post-AMI modeling, which were later significantly improved with the increase of Rh2 dosage. Similarly, the decrease of CK, CK-MB, and LDH contents in the H-Rh2 group can also verify our view. Past evidence has shown that Rh2 has a stable regulatory effect on cell pyroptosis in diabetic nephropathy [22]. Therefore, we detected pyroptosis-related genes in four groups of rats. The results were also in line with our expectations, that is, the control group had lower GSDMD, IL-1β, NLRP3, and Caspase-1 levels, while pyroptosis-related gene expression was improved in the three groups of rats injected with RH2, with the most significant improvement found in H-Rh2 group. This demonstrates that Rh2 can relieve CM scorch and inhibit the progress of AMI, and its effect is related to the dosage used. As the main executor of pyroptosis, GSDMD is mainly hydrolyzed by Caspase to release a large quantity of inflammatory factors, promoting cell membrane rupture [23]. NLRP3, being a member of the pattern recognition receptor family, is directly induced by many external stimuli (such as

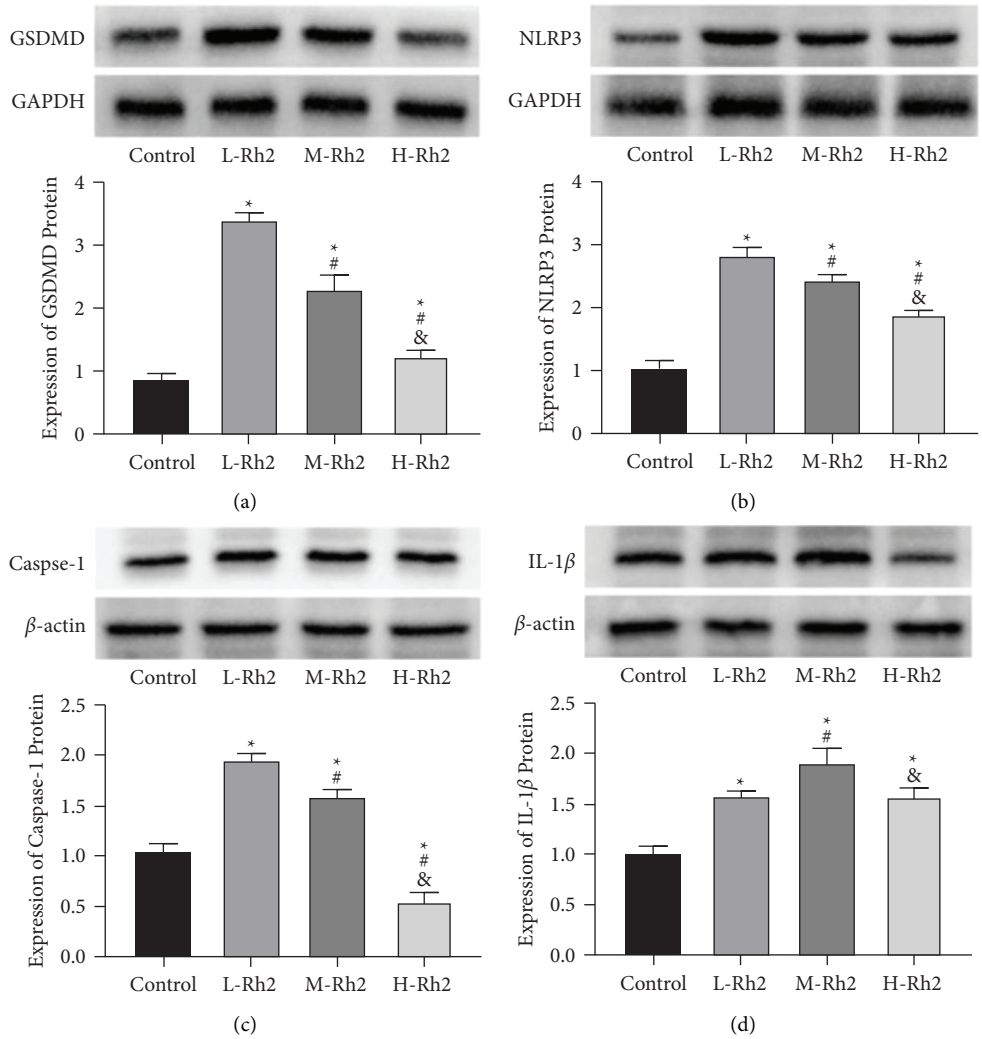

Figure 5: CM pyroptosis-related protein expression. (a) Comparison of GSDMD protein expression. (b) Comparison of NLRP3 protein expression. (c) Comparison of Caspase-1 protein expression. (d) Comparison of IL-1β protein expression. *: Compared with the control group, the difference was statistically significant ($P < 0.05$). #: Compared with the L-Rh2 group, the difference was statistically significant ($P < 0.05$). &: Compared with the M-Rh2 group, the difference was statistically significant ($P < 0.05$).

ischemia), which in turn activates Pro-Caspase-1 into Caspase-1 to bind to IL-1β precursor, resulting in the increase of synthesis and secretion of IL-1β and TNF-α and thus participating in immunoreaction [24]. Integrating previous literature and the findings we obtained, we believe that NLRP3 is activated when CMs injury occurs in rats. while activating Caspase to promote CM scorch death and inflammation release, NLRP3 can also directly induce the synthesis of inflammatory factors and inhibit the immune function of patients, and finally lead to the occurrence of AMI through a variety of pathways. And Rh2 can directly block the activation of NLRP3, inhibit the aggravation and expansion of the body's inflammatory response, and repair the above pathological changes, thereby achieving the purpose of relieving and treating AMI.

In previous studies, Rh2 has also been found to modulate the oxidative stress response of nerve tissue and the autophagy capacity of cells [25, 26], which may also be the mechanism by which Rh2 influences AMI. Hence, it is worthwhile to carry out more in vitro experiments to confirm. In addition, due to the differences between experimental animals and humans, the specific clinical effect of Rh2 in AMI needs to be confirmed through clinical trials. In addition, we compared different doses in this study, and the highest dose appeared to be the best. Therefore, whether further increases in doses can achieve a better effect and the optimal dose threshold of Rh2 need to be further studied. In order to obtain the most convincing experimental results, we will conduct a more comprehensive experimental analysis as soon as possible to solve the above limitation.

To sum up, G-Rh2 can inhibit the pathological development of AMI by relieving CM pyroptosis and is expected to become a new treatment option for AMI in the future, providing a more reliable safety guarantee for patients.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest, financial or otherwise.

Acknowledgments

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Volume 2023, Article ID 9808315, 1 page
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Retraction

Retracted: Effects of Shenkang Injection Combined with Jinshuibao on Early Diabetic Nephropathy and Effects on Coagulation Fibrinolysis System and Urinary Protein

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi, as publisher, following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of systematic manipulation of the publication and peer-review process. We cannot, therefore, vouch for the reliability or integrity of this article.

Please note that this notice is intended solely to alert readers that the peer-review process of this article has been compromised.

Wiley and Hindawi regret that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] J. Zhu, T. Yang, J. Luo et al., "Effects of Shenkang Injection Combined with Jinshuibao on Early Diabetic Nephropathy and Effects on Coagulation Fibrinolysis System and Urinary Protein," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 3958049, 6 pages, 2022.

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Volume 2022, Article ID 3958049, 6 pages
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Research Article

Effects of Shenkang Injection Combined with Jinshuibao on Early Diabetic Nephropathy and Effects on Coagulation Fibrinolysis System and Urinary Protein

Jianhua Zhu, Tingting Yang, Jie Luo, Mian Wei, Hanyu Li, Yue Qi, Jiali He, and Min Chen

Department of Nephrology, Chengdu Hospital of Integrated Traditional Chinese and Western Medicine, Chengdu, Sichuan 610000, China

Correspondence should be addressed to Min Chen; ccmmsnk@163.com

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Purpose. To explore the effect of Shenkang injection (SKI) combined with Jinshuibao for early diabetic nephropathy (DN) and its effect on the coagulation fibrinolysis system and urinary protein. *Methods*. 136 patients with early DN admitted to our hospital from March 2018 to October 2019 were divided into the observation group ($n = 68$) and the control group ($n = 68$) randomly. On the basis of the conventional treatment, the control group was treated with SKI, and the observation group was treated with SKI and Jinshuibao. Two weeks later, the therapeutic effects of the 2 groups were compared. The prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), tissue plasminogen activator (*t*-PA), plasminogen activator inhibitor-1 (PAI-1), and D-dimer (D-D) were observed and compared before and after the treatment. 24 hour urine total protein (24 h-UTP), urine albumin excretion rate (UAER), and urine β_2 microglobulin (β_2-MG) were measured and compared before and after the treatment. Adverse reactions in the two groups were recorded during the treatment. *Results*. The effective rate of the observation group after treatment was 92.65% higher than the control group 79.41%. the difference was statistically significant ($P < 0.05$). The levels of PT, APTT, TT, FIB, PAI-1, and D-D in the two groups after treatment were lower, and t-PA levels after treatment were higher than those before, and all of the above indicators were significantly changed in the observation group than in the control group. The difference was statistically significant ($P < 0.05$). The 24 h-UTP, UAER, and β_2-MG in the two groups after treatment were lower than those before, and all of the above indicators were significantly changed in the observation group than in the control group. The difference was statistically significant ($P < 0.05$). There was no statistically significant difference during the treatment for 2 groups in terms of adverse reactions. The difference was statistically significant ($P > 0.05$). *Conclusion*. SKI combined with Jinshuibao has a significant effect in the treatment of early DN, which can reduce the risk of hyperfunction of coagulation and fibrinolysis system, further reduce the content of urine protein, and delay the process of DN.

1. Introduction

Diabetes mellitus (DM) is a group of chronic metabolic diseases characterised by high blood sugar. Persistent hyperglycaemia directly causes chronic damage to various tissues and organs in the body, such as the retina, heart, kidneys, and vascular nerves, leading to a series of chronic complications of DM [1, 2]. Nephropathy is one of the serious microvascular complications of DM, an important cause of chronic renal insufficiency and also an important cause of disability and death in DM patients [3]. Patients with early diabetic nephropathy (DN) usually present with trace proteinuria, oedema, and few clinical symptoms. At the same time, microcirculatory disorders can occur due to abnormal blood glucose and lipid metabolism, which can lead to changes in the coagulation and fibrinolytic systems such as hypercoagulability and fibrinolytic abnormalities. It is now believed that effective intervention in the early stages of DN can delay or even reverse further deterioration of renal function.

The pathogenesis of DN involves hemodynamic abnormalities, hemorheological changes, glomerular basement

membrane thickening (biochemical metabolic disorders), genetic susceptibility, and other factors [4–7]. Shenkang injection (SKI) is a new class II Chinese medicine consisting of four Chinese herbs, namely rhubarb, *Astragalus* membranaceus, *Salvia miltiorrhiza,* and safflower, which are effective in dredging the bowels and purging turbidity, supplementing qi, and activating blood circulation. In recent decades, SKI has been most commonly used in clinics to treat kidney-related diseases. It can inhibit the proliferation of glomerular mesangial cells (MC), reduce the accumulation of extracellular matrix (ECM), and delay glomerular sclerosis so as to improve the renal function of patients and delay the progression of kidney disease [8]. The curative effect is accurate. At the same time, a large number of studies have also confirmed that SKI can improve cardiorenal syndrome, hepatorenal syndrome, COPD, and other diseases. Jinshuibao is a kind of Cordyceps sinensis extract, which has the effects of being antibacterial, anti-inflammatory, reducing serum cholesterol, triglycerides, and lipid peroxides, increasing blood supply to the myocardium and brain, and nourishing the lungs and kidneys [9]. This study investigated the efficacy of SKI combined with Jinshuibao in the treatment of early DN and its effect on the coagulation fibrinolysis system and urinary protein.

2. Materials and Methods

2.1. Research Object. 136 patients with early DN admitted to our hospital from March 2018 to October 2019 were divided into the observation group ($n = 68$) and the control group ($n = 68$) randomly. In the control group, there were 37 males and 31 females, with a mean age of 52.1 ± 3.9 years and a mean duration of illness of 5.9 ± 3.5 years; in the observation group, there were 35 males and 33 females, with a mean age of 51.3 ± 3.6 years and a mean duration of illness of 6.4 ± 2.7 years. All the above basic data were compared, and the differences were not statistically significant ($P > 0.05$) and comparable.

2.2. Diagnostic Criteria

2.2.1. DM Diagnostic Criteria. Referring to the 2004 Chinese guidelines for the prevention and treatment of diabetes [10], with clinical signs of DM + determination of plasma glucose ≥11.1 mmol/L (200 mg/dL); determination of fasting blood glucose (FBG) ≥7.0 mmol/L (126 mg/dL); 2 hours after *f*OGTT test, plasma glucose ≥11.1 mmol/l (200 mg/dl). If any of the above three items were met, it could be used as a diagnostic basis. In the absence of hyperglycaemic crisis, a single blood glucose level up to the diagnostic criteria for DM must be rechecked at a later date for verification.

2.2.2. DN Staging Criteria. Referring to the internationally accepted Mogensen staging [11], i.e., DN stage III: 2 positive urine tests for microalbumin (MA) [urine albumin to creatinine ratio (ACR) 2.5~30.0 mg/mmol (men) and 3.5~30.0 mg/mmol (women) at any time point]; or 24 hour urine microalbumin (U-MA) quantification of 20~200 mg/L; or urine albumin excretion rate (UAER) 20~200 μg/min (30~300 mg/24 h); urine routine protein negative, 24 hour urine total protein (24 h-UTP) <0.5 g; and excluded other factors causing increased urine protein.

2.3. Inclusion Criteria. (1) Meeting the above diagnostic criteria for DM and the Mogensen staging criteria for DN stage III; (2) those who volunteered to participate in this study; and (3) those who were not taking ACEI or ARB class antihypertensive drugs.

2.4. Exclusion Criteria. (1) Persons with chronic glomerulonephritis, nephrotic syndrome, urinary tract infections, urinary stones, and other urological disorders; (2) persons with primary renal insufficiency or renal artery stenosis; (3) persons with elevated blood potassium or abnormal blood creatinine; (4) persons with diabetic ketosis, ketoacidosis or co-infections, and other systemic diseases; (5) patients with cardiovascular and cerebrovascular diseases and disorders of blood clotting; (6) women during pregnancy and breastfeeding; (7) persons who had recently taken antiplatelet or anticoagulant medication or were allergic to the study medication; and (8) persons who had interrupted treatment before completing the prescribed course of treatment, whose efficacy could not be judged or whose data were incomplete.

2.5. Research Methods. Both groups were given oral hypoglycaemic drugs or subcutaneous insulin for blood glucose control, a diabetic diet, and moderate exercise as a general treatment, depending on the condition of the patients. In the control group, SKI (Xi'an Century Shengkang Pharmaceutical Co., Ltd., State Drug Administration Z20040110) was administered 100 ml + 0.9% sodium chloride injection, 250 ml intravenous drip, 1 time/d. In the observation group, Jinshuibao (Jiangxi Jimin Kexin Jinshuibao Pharmaceutical Co., Ltd., State Drug Administration Z10890003) was added on top of the control group for oral administration, 3 capsules/time, 3 times/d. Both groups were treated continuously for 2 weeks.

2.6. Observation Indicators. Efficacy was determined after 2 weeks of treatment [12]. Apparently cured: significant improvement in symptoms such as oedema, significant improvement in all urine protein-related indicators, and control and cessation of the progression of the disease; improved: symptoms such as oedema had improved, all urine protein-related indicators had improved, and renal disease was progressing slowly; invalid: symptoms such as oedema and proteinuria remain and did not improve or the kidneys deteriorate further. Total effective rate = (number of apparently cured cases + number of improved cases)/total number of cases × 100%.

Then, 10 ml of the fasting venous blood was collected from patients before and 2 weeks after treatment, centrifuged, and the serum was prepared. Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB) by the coagulation method

and tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), and D-dimer (D-D) by the ELISA method.

Patients' urine were collected 24 h before treatment and 24 h after 2 weeks of treatment, and 10 ml was taken after thorough mixing for examination. The 24 h-UTP was measured by urine protein precipitation and the biuret method, and urine β_2 microglobulin (β_2-MG) and MA concentrations were measured by immunoturbidimetric assay and UAER was calculated.

The adverse reactions of patients in both the groups were observed during the treatment period.

2.7. Statistical Methods. The SPSS22.0 software was applied for processing and the count data were expressed as rate (%) using the χ^2 test. The measurement data were expressed as mean ± standard deviation ($\overline{x} \pm s$) and the t-test was used for two-way comparison between groups. The test level was $\alpha = 0.05$ and $P < 0.05$ was considered a statistically significant difference.

3. Results

3.1. Comparison of Post-Treatment Outcomes for 2 Groups. As shown in Table 1, after treatment, the effective rate of the observation group 92.65% was higher than the control group 79.41%, the difference was statistically significant ($P < 0.05$).

3.2. Comparison of Coagulation and Fibrinolytic Parameters for 2 Groups. As shown in Figure 1, before treatment, there was no significant difference in all coagulation and fibrinolytic parameters for 2 groups ($P > 0.05$); after treatment, the levels of PT, APTT, TT, FIB, PAI-1, and D-D in the two groups were lower and t-PA levels was higher than those before treatment, and the levels of PT, APTT, TT, FIB, PAI-1, and D-D in the observation group were lower, and the levels of t-PA were higher in the observation group than those in the control group. The difference was statistically significant ($P < 0.05$).

3.3. Comparison of Urine Protein Indicators for 2 Groups. As shown in Figure 2, before treatment, there was no significant difference in the comparison of all urine protein indicators for the 2 groups ($P > 0.05$); after treatment, 24 h-UTP, UAER, and β_2-MG in the two groups were lower than those before treatment, and 24 h-UTP, UAER, and β_2-MG in the observation group were lower than those in the control group; the difference was statistically significant ($P < 0.05$).

3.4. Comparison of Adverse Reactions for 2 Groups. During the treatment period, there were 2 cases of nausea, 1 case of vomiting, and 1 case of dizziness in the control group, for a total of 4 cases, with an incidence of 5.88% (4/68); 2 cases of nausea, 2 cases of dizziness, and 2 cases of abdominal distension in the observation group, for a total of 6 cases, with an incidence of 8.82% (6/68). Comparison of adverse reactions for 2 groups revealed no statistically significant difference ($P > 0.05$).

4. Discussion

DN is a serious group of microvascular complications of DM. Its pathogenesis is very complex, including microcirculation disorders caused by abnormal glucose and lipid metabolism, activation of the RASS system, accumulation of advanced glycoprotein products, tissue oxidative stress response, and abnormal expression of the coagulation and fibrinolysis systems [13]. Early DN is mostly manifested by a high glomerular filtration rate, increased renal volume, thickened basement membrane, microalbuminuria, edema, etc. [14, 15]. With the further development of the disease, the intensification of oxidative stress reactions and the continuous destruction of microvascular permeability, the glomerular sclerosis speed is accelerated, and then it develops into a large amount of proteinuria, elevated blood creatinine, hypertension, and even uremia [16]. Therefore, early treatment of DM is of great significance.

DN belongs to the category of "oedema," "deficiency labour," and "thirst" in traditional Chinese medicine. The early stage of the disease is characterised by clear evidence of "stasis" and "deficiency." Thus, the treatment of early DN focuses on controlling urine protein, improving kidney microcirculation (i.e., activating blood circulation and removing blood stasis), and nourishing kidney qi. SKI is composed of four herbs: rhubarb, *Astragalus* membranaceus, *Salvia miltiorrhiza,* and safflower. Among them, rhubarb can dredge the viscera, remove dirt, eliminate edema, reduce blood creatinine and urea nitrogen, and delay glomerular interstitial fibrosis [17]. *Astragalus* membranaceus can replenish qi and nourish blood, invigorate righteousness and eliminate pathogenic factors, nourish the heart and dredge the pulse, invigorate the spleen and diuresis, improve glucose metabolism, and expand renal blood vessels and cardiac blood vessels at the same time [18]. Pharmacological research [19] found that the main components of *Astragalus* membranaceus are astragalus polysaccharides, amino acids, linoleic acid, alkaloids, etc., which can enhance the immune function of the body, reduce the excretion of MA, and inhibit glomerular hypertrophy. At the same time, *Astragalus* can inhibit the production of transforming growth factor (TGF-B), reduce the level of vascular endothelin and the permeability of renal basement membrane so as to protect renal function and delay the deterioration of the renal function. When the two herbs mentioned above are used together, they both contribute to the improvement of gastrointestinal function. One falls and the other rises in their medicinal properties, dispelling turbidity, resolving stasis, and slowing down the deterioration of the kidney function. Both Salvia miltiorrhiza and safflower can activate blood circulation and improve blood circulation in the glomerulus. Animal experiments [20] showed that SKI could significantly reduce blood creatinine and urea nitrogen levels in 5/6 nephrectomized rats, reduce renal pathological damage, and lower urinary albumin, which may be the mechanism of its action to delay

Table 1: Comparison of post-treatment outcomes for 2 groups (n, %).

Group	n	Apparently cured	Improved	Invalid	Total effective
Control group	68	19 (27.94%)	35 (51.47%)	14 (20.59%)	54 (79.41%)
Observation group	68	25 (36.76%)	38 (55.88%)	5 (7.35%)	63 (92.65%)
χ^2 value					4.956
P value					0.026

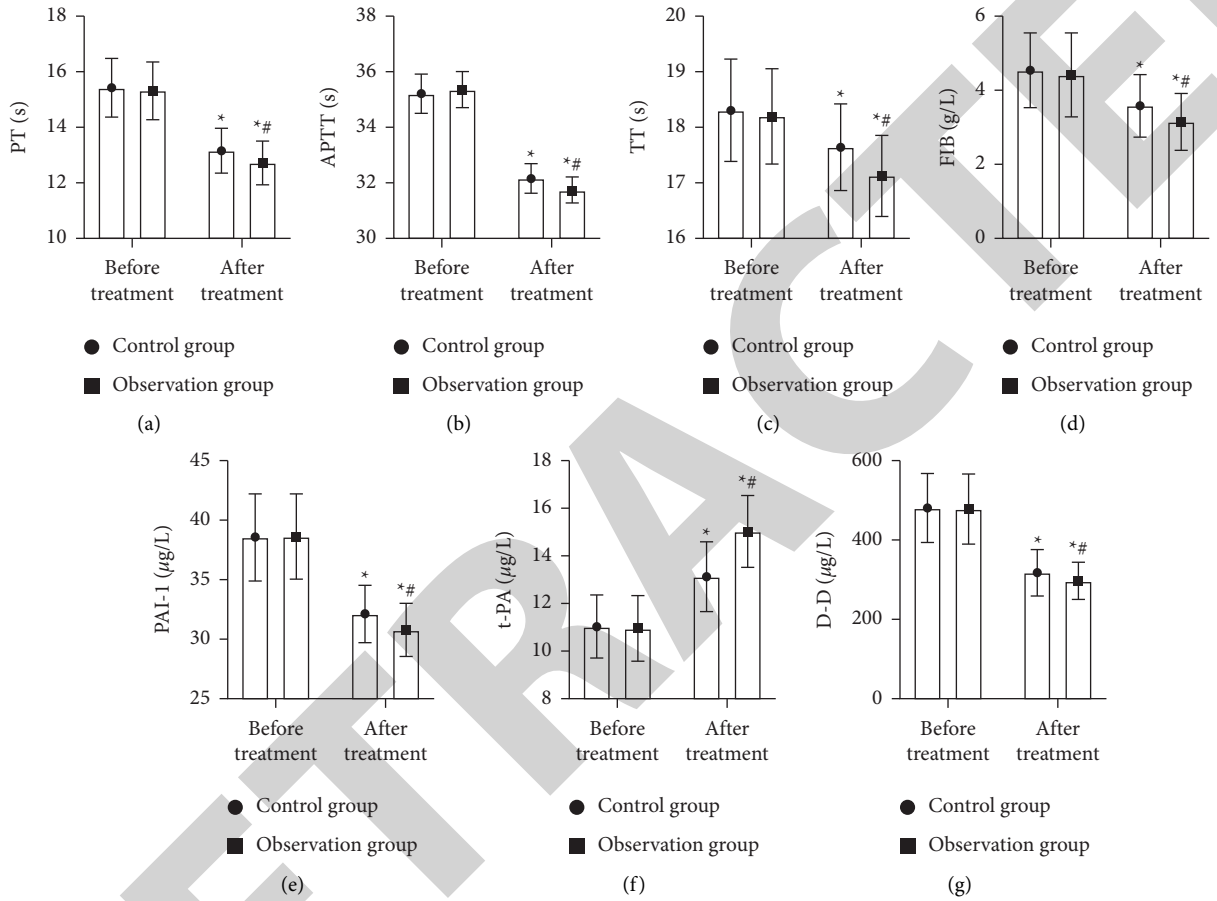

Figure 1: Comparison of coagulation and fibrinolytic parameters for 2 groups (n, $\overline{x} \pm s$). Note: (a) PT (s). (b) APTT (s). (c) TT (s). (d) FIB (g/L). (e) PAI-1 (μg/L). (f) t-PA (μg/L). (g) D-D (μg/L). * and # represent comparison with the same group before treatment and comparison with the control group after treatment, respectively, $P < 0.05$.

the progression of renal function deterioration. In addition, SKI has been shown to improve anaemia, increase plasma colloid osmotic pressure, raise plasma albumin, and reduce the amount of albumin in urine [21].

The main component of Jinshuibao is fermented Cordyceps powder. The adenosine, vitamin E, zinc, selenium, and copper contained in it directly participate in the metabolism of SOD, increase SOD, remove free radicals, reduce lipid peroxide, and protect the patient's kidney from damage. At the same time, it can improve renal blood flow, inhibit platelet aggregation, stabilize the lysosomal membrane, reduce NAG enzyme, maintain renal tubular function, reduce azotemia, protect and maintain renal function, and promote the repair of renal cells; and by regulating hormone secretion, it can enhance cellular immune function and phagocytosis of phagocytes, and play a certain role in the regulation and clearance of blood creatinine, urea nitrogen, and other metabolites. As a result, the internal environment of DN patients is brought from imbalance to balance, thus improving and stabilizing the condition, delaying the process of DN and renal insufficiency, reducing or decreasing the excretion of urinary protein, promoting the repair of renal tubular epithelial cells, inhibiting tubular atrophy and interstitial fibrosis, and achieving renal protection.

Several studies [22, 23] have shown that SKI plays an active role in activating blood circulation and removing blood stasis, improving hemodynamics, and reducing inflammatory reactions in the blood and urinary protein. Jinshuibao can regulate the expression level of signal pathway proteins in patients with DN, which not only has a good curative effect and reduces renal inflammatory reaction but also has the effect of nourishing the kidney

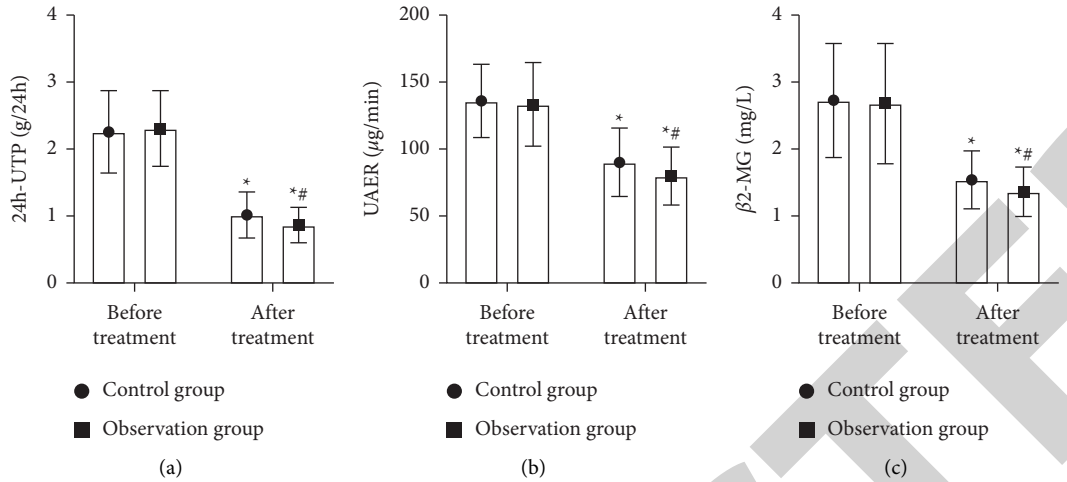

Figure 2: Comparison of urine protein indicators for 2 groups ($n, \overline{x} \pm s$). Note: (a) 24 h-UTP (g/24 h). (b) UAER (μg/min). (c) β2-MG (mg/L). * and # represent comparison with the same group before treatment and comparison with the control group after treatment, respectively, $P < 0.05$.

[24, 25]. The results of this study show that after treatment, the observation group was more effective; the indexes related to urinary protein and coagulation and fibrinolysis for 2 groups were better than before, and the observation group changed significantly; there was no significant increase during the treatment in adverse reactions in the observation group. The results further showed that SKI in combination with Jinshuibao for early DN improved the coagulation and fibrinolysis system and did not significantly increase the incidence of adverse effects. The possible reasons for this are that early DN patients mostly have urinary protein, hypercoagulation, and fibrinogenic abnormalities. In this study, the application of SKI has obvious effects of dilating blood vessels, regulating blood lipids, reducing blood viscosity, and inhibiting platelet and red blood cell aggregation, thus increasing renal blood flow, reducing glomerular capillary pressure, improving glomerular blood hypercoagulation, and finally achieving the effect of reducing urinary protein; and the combination of Jinshuibao can further protect the kidney and regulate the oxidative stress response in the kidney so as to effectively improve the course of early DN.

In summary, SKI combined with Jinshuibao has a significant effect in the treatment of early DN, which can reduce the risk of hyperfunction of coagulation and fibrinolysis system, further reduce the content of urine protein, and delay the progression of renal disease in DM patients.

Data Availability

The data used or analysed during the study can be obtained from the corresponding author upon request.

Ethical Approval

Studies involving human participants were reviewed and approved by the Institutional Review Board and the Ethics Committee of our hospital.

Consent

Informed consent was obtained from all participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Efficacy of Fangfeng Tongsheng Granule Combined with Levocetirizine in the Treatment of Chronic Urticaria and Its Effect on Serum Complement, IL-4, IgE, and IFN-γ Levels in Patients

Duanni Xu,[1] Zhenjie Li,[1] and Yinan Wang[2]

[1]*Department of Outpatient, Guangzhou Institute of Dermatology, Guangzhou, Guangdong 510000, China*
[2]*Department of Dermatology, Hospital of Traditional Chinese Medicine of Yantai City, Yantai, Shandong 264000, China*

Correspondence should be addressed to Yinan Wang; wyn6807068@126.com

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Objectives. To investigate the efficacy of Fangfeng Tongsheng granule combined with levocetirizine in the treatment of chronic urticaria and its effect on serum complement, interleukin (IL)-4, immunoglobulin E (IgE), and interferon-γ (IFN-γ) levels in patients. *Methods*. A total of 98 patients with chronic urticaria who were admitted to our hospital from July 2021 to March 2022 were selected and divided into random odd-even numbers. The odd numbers were included in the observation group, with a total of 49 cases, and they were treated with Fangfeng Tongsheng granule combined with levocetirizine; the even numbers were included in the control group, with a total of 49 cases and were treated with levocetirizine alone. The two groups of patients were treated continuously for 4 weeks, and the clinical efficacy of the two groups was observed. Before treatment, 2 weeks and 4 weeks after treatment, evaluate the clinical symptom scores of patients such as itching, flushing, wheal, edema, observe the improvement of clinical symptoms of patients, and the changes in Dermatology Life Quality Index (DLQI). Serum complement C3, C4, T lymphocyte subsets CD_3^+, CD_4^+, CD_8^+ levels and CD_4^+/CD_8^+ ratio, IL-4, IgE, and IFN-γ levels and the occurrence of adverse reactions in the two groups were calculated and observed. All patients were followed up for 2 months after treatment to observe the recurrence of patients. *Results*. The scores of clinical symptoms such as wheal, itching, flushing, edema, and attack frequency in the observation group at each time point after treatment were lower than those in the control group (F times were 725.365, 851.521, 936.411, 3943.136, and 2226.147, all $P < 0.05$ (F between-group were 40.642, 102.124, 188.523, 259.291, and 23.92, $P < 0.05$); the total effective rate of the observation group was 93.88% (46/49), which was significantly higher than that of the control group, 73.47% (36/49) ($\chi^2 = 7.470$, $P = 0.006$). The DLQI scores of the observation group at each time point after treatment were lower than those of the control group (F time was 282.214, $P < 0.05$; F between-group was 6.546, $P < 0.05$). There was no significant difference in serum C4 levels between the two groups at each time point (F time was 1.225, $P > 0.05$; F between-group was 0.408, $P > 0.05$); serum complement C3, CD_3^+, and CD_4^+/the ratio of CD_8^+ and IFN-γ were higher than those in the control group (F time was 407.352, 107.823, 32.941, and 2354.147, $P < 0.05$; F between-group was 40.941, 24.710, 54.982, and 264.921, $P < 0.05$); the observation group at each time after treatment the levels of IgE and IL-4 were lower than those of the control group (F time were 373.124 and 395.612, $P < 0.05$; F between-group were 21.802 and 62.591, $P < 0.05$). The incidence of adverse reactions in the observation group was 12.24% (6/49) compared with 10.20% (5/49) in the control group, which had no significant difference ($\chi^2 = 0.102$, $P = 0.749$). Both groups were followed up for 2 months after treatment. The recurrence rate in the observation group was 12.24% (6/49), which was lower than that in the control group, which was 32.65% (16/49) ($\chi^2 = 5.861$, $P = 0.015$). *Conclusion*. The application of Fangfeng Tongsheng granules combined with levocetirizine in patients with chronic urticaria can effectively improve the clinical symptoms of patients, improve clinical efficacy, reduce the impact of the disease on life, improve the immune status of patients, and reduce the risk of recurrence.

1. Introduction

Urticaria is a common allergic skin disease, of which chronic urticaria is the most common, which can recur frequently and last for months or years. Chronic urticaria is characterized by irregular wheals in the skin, often accompanied by erythema, pruritus, or local edema response, with the course of disease often exceeding six weeks [1]. Chronic urticaria is stubborn and complicated in etiology. It often recurs after drug withdrawal, which brings great trouble to the daily life of patients [2]. Histamine is a commonly used drug in the clinical treatment, of which levocetirizine is the most common, and its clinical efficacy has been recognized, but there are still some patients with poor drug response and unsatisfactory clinical effect [3–6]. Traditional Chinese medicine (TCM) classifies chronic urticaria into the category of "addiction rash," and believes that it is caused by the invasion of "wind pathogens" and the insufficiency of external defenses. If the Qi is not dispersing, the disease occurs on the surface, and the treatment should be based on expelling wind and promoting blood circulation, strengthening the surface and benefiting Qi [7, 8]. Fangfeng Tongsheng granule is modified on Fangfeng Tongsheng powder created by Liu Wansu, one of the four famous artists in the Jin and Yuan Dynasties, and it has the effects of relieving exterior syndrome and internal invasion, sweating to exterior syndrome, dispelling wind, and reducing fever. Therefore, in this study, Fangfeng Tongsheng granule combined with levocetirizine was applied in the treatment of chronic urticaria, and its clinical efficacy and effects on the immune system and inflammatory response were observed, which was a clinical supplementary evidence-based basis.

2. Materials and Methods

2.1. General Information. A total of 98 patients with chronic urticaria who were admitted to our hospital from July 2021 to March 2022 were selected. The inclusion criteria include the following: ① patients who meet the clinical diagnostic criteria of chronic urticaria (urticaria occurs repeatedly for more than 6 weeks and at least twice a week, which is defined as chronic urticaria) [9]; ② patients who are in line with TCM "addiction rash" syndrome of gastrointestinal damp-heat [10], the main syndrome is wheal and flushing on the skin; the secondary symptoms are abdominal pain, chest tightness, loss of appetite, and anorexia; tongue and pulse symptoms are red tongue with yellow and greasy coating and slippery pulse; ③ the patients and their families understood the research content and gave written consent. The exclusion criteria include the following: ① patients who have taken immunosuppressive drugs or had related treatment in the past 3 months; ② patients with immune or blood system dysfunction; ③ women who are pregnant or breastfeeding; ④ patients with induced urticaria; ⑤ patients with severe organic impairment or malignant tumor; and ⑥ patients who are allergic to the drugs used in this study.

We grouped the patients by random parity number. Odd numbers were included in the observation group ($n = 49$); even numbers were included in the control group ($n = 49$). In the observation group, there were 24 males and 25 females; the age ranged from 20 to 42 years, with an average of (30.96 ± 5.08) years; the course of disease was 0.5 to 6 years, with an average of (3.21 ± 1.24) years. In the control group, there were 26 males and 23 females; the age ranged from 19 to 42 years, with an average of (30.42 ± 5.29) years; the course of disease was 0.5 to 6 years, with an average of (3.26 ± 1.14) years. There were no significant differences in the baseline data such as gender, age, and the course of disease between the two groups (sex: $\chi^2 = 0.163$, $P = 0.686$; age: $t = 0.515$, $P = 0.607$; the course of disease: $t = 0.208$, $P = 0.836$).

2.2. Treatment Methods. Levocetirizine alone treatment (control group): levocetirizine hydrochloride tablets (Switzerland: UCB Farchim SA, registration number H20150522, 5 mg/tablet) were given orally, 5 mg/time, 1 time/day. Fangfeng Tongsheng granule combined with levocetirizine treatment (observation group): Fangfeng Tongsheng granule (Shandong Runzhong Pharmaceutical Co., Ltd., Z20174069, 3 g/bag) brewed with warm water, 1 bag/time, 2 times/day. The administration method of levocetirizine was the same as that of the control group. The patients in both the groups were treated continuously for 4 weeks.

2.3. Observation Indicators

2.3.1. Clinical Symptom Score. Before treatment, 2 weeks and 4 weeks after treatment, the scores of clinical symptoms such as wheal, itching, flushing, edema, and attack frequency were evaluated in the two groups [11]. Each symptom was scored on a scale of 0 to 3 according to the severity. A lower score indicated milder symptoms.

2.3.2. Clinical Efficacy. The results after 4 weeks of treatment were used as the criterion for the clinical efficacy evaluation [12]. Clinically cured: after treatment, the patient's symptom score was decreased by 95% or more as compared with that before treatment, and his wheal, flushing, and itching completely disappeared. Excellent: after treatment, the patient's symptom score decreased by 70%–94% as compared with that before treatment, his wheal mass dissipated by more than 70%, and his itching sensation was significantly reduced. Effective: after treatment, the patient's symptom score decreased by 30%–69% as compared with that before treatment, his wheal mass dissipated by more than 30%, and his itching sensation was relieved. Ineffective: patients who do not meet the above conditions are regarded as ineffective in treatment.

2.3.3. Quality of Life. Before treatment, 2 weeks and 4 weeks after treatment, the Dermatology Life Quality Index (DLQI) [13] was used to observe the improvement of the degree of disease-related life impact of patients. The DLQI covers 10 aspects including psychology, physiology, entertainment, work, life, daily activities, and sports, with a total score of 0 to 30. The higher score means greater the impact of the disease on life.

2.3.4. Serological Indicators. Before treatment, 2 weeks and 4 weeks after treatment, fasting venous blood was drawn from patients to detect peripheral blood serum complement C3, C4, T lymphocyte subsets CD_3^+, CD_4^+, CD_8^+ levels and calculated CD_4^+/CD_8^+ ratio, IL-4, IgE, and IFN-γ levels. Automatic biochemical analyzer (Roche cobas-c702) detected serum complement C3 and C4 levels, flow cytometer (Beckman CytoFLEX) detected CD_3^+, CD_4^+, and CD_8^+ levels; the levels of IL-4, IgE, and IFN-γ were detected by ELISA (kit: Shanghai Enzyme Research Biotechnology Co., Ltd.).

2.3.5. Adverse Reactions. The occurrence of adverse reactions such as gastrointestinal discomfort, abdominal pain, dry mouth, drowsiness, headache, and other adverse reactions during treatment in the two groups were observed and compared.

2.3.6. Recurrence Rate. All the patients were followed up for two months after treatment. They were informed of the changes of the patients' conditions by phone or return visit every two weeks, and the recurrence situations of the two groups were observed and compared.

2.4. Statistical Processing. Data was organized by the double entry method, and SPSS 22.0 statistical software was used for data analysis. The measurement data with normal distribution and homogeneous variance are expressed as (mean ± SD), and the difference between the groups with time factor is analyzed by repeated measures of variance. Differences between the groups without time factor were tested by the independent sample t-test, count data were expressed by rate, and the χ^2 test was used. $P < 0.05$ indicated statistical significance.

3. Results

3.1. Comparison of Clinical Symptom Scores between the Two Groups before and after Treatment. The scores of clinical symptoms such as wheal, itching, flushing, edema, and seizure frequency in the observation group at each time point after treatment were lower than those in the control group (F time were 725.365, 851.521, 936.411, 3943.136, and 2226.147, all $P < 0.05$; the groups are 40.642, 102.124, 188.523, 259.291, and 23.92, respectively, $P < 0.05$), as shown in Figure 1.

3.2. Comparison of Clinical Efficacy between the Two Groups. The total effective rate of the observation group was 93.88% (46/49), which was significantly higher than 73.47% (36/49) of the control group ($\chi^2 = 7.470$, $P = 0.006$), as shown in Figure 2.

3.3. Comparison of the Degree of Disease-Related Life Impact between the Two Groups before and after Treatment. The DLQI scores of the observation group at each time point after treatment were lower than those of the control group (F time was 282.214, $P < 0.05$; F between-group was 6.546, $P < 0.05$), as shown in Figure 3.

3.4. Comparison of Serum Complement C3 and C4 Levels between the Two Groups before and after Treatment. There was no significant difference in serum C4 levels between the two groups at each time point (F time was 1.225, $P > 0.05$; F between-group was 0.408, $P > 0.05$); the serum C3 level in the observation group at each time point after treatment was higher than that in the control group (F time was 407.352, $P < 0.05$; F between-group was 40.951, $P < 0.05$), as shown in Figure 4.

3.5. Comparison of Peripheral T Lymphocytes and IgE Levels in the Two Groups before and after Treatment. The ratio of CD_3^+ and CD_4^+/CD_8^+ in the observation group at each time point after treatment was higher than that in the control group (F time were 107.823 and 32.941, $P < 0.05$; F between-group were 24.710 and 54.982, $P < 0.05$); the IgE level in the observation group was lower than that in the control group at each time point after treatment (F time was 373.124, $P < 0.05$; F between-group was 21.802, $P < 0.05$), as shown in Figure 5.

3.6. Comparison of IL-4 and IFN-γ Levels between the Two Groups before and after Treatment. The levels of IL-4 in the observation group were lower than those in the control group at each time point after treatment (F time was 395.612, $P < 0.05$; F between-group was 62.591, $P < 0.05$); the levels of IFN-γ in the observation group were higher than those in the control group at each time point after treatment (F time was 2354.147, $P < 0.05$; F between-group was 264.921, $P < 0.05$), as shown in Figure 6.

3.7. The Incidence of Adverse Reactions and Follow-Up Recurrence in the Two Groups. The incidence of adverse reactions in the observation group was 12.24% (6/49), while that in the control group was 10.20% (5/49), and there was no significant difference in the incidence of adverse reactions between the two groups ($\chi^2 = 0.102$, $P = 0.749$). Both the groups were followed up for 2 months after treatment. The recurrence rate was 12.24% (6/49) in the observation group, lower than 32.65% (16/49) in the control group ($\chi^2 = 5.861$, $P = 0.015$), as shown in Figure 7.

4. Discussion

Chronic urticaria is stubborn and difficult to heal, which brings great inconvenience to the patient's life and has a great adverse impact on the patient's physical, mental, and economic conditions [14]. It is clinically believed that the onset of the disease is closely related to the patient's autoimmunity [15, 16]. Histamine drugs are often used in the treatment of urticaria in modern medicine, which can effectively control the symptoms of skin allergy in patients, but the regulation of the immune system of patients is poor, and it is easy to relapse after drug discontinuation. Therefore, it is

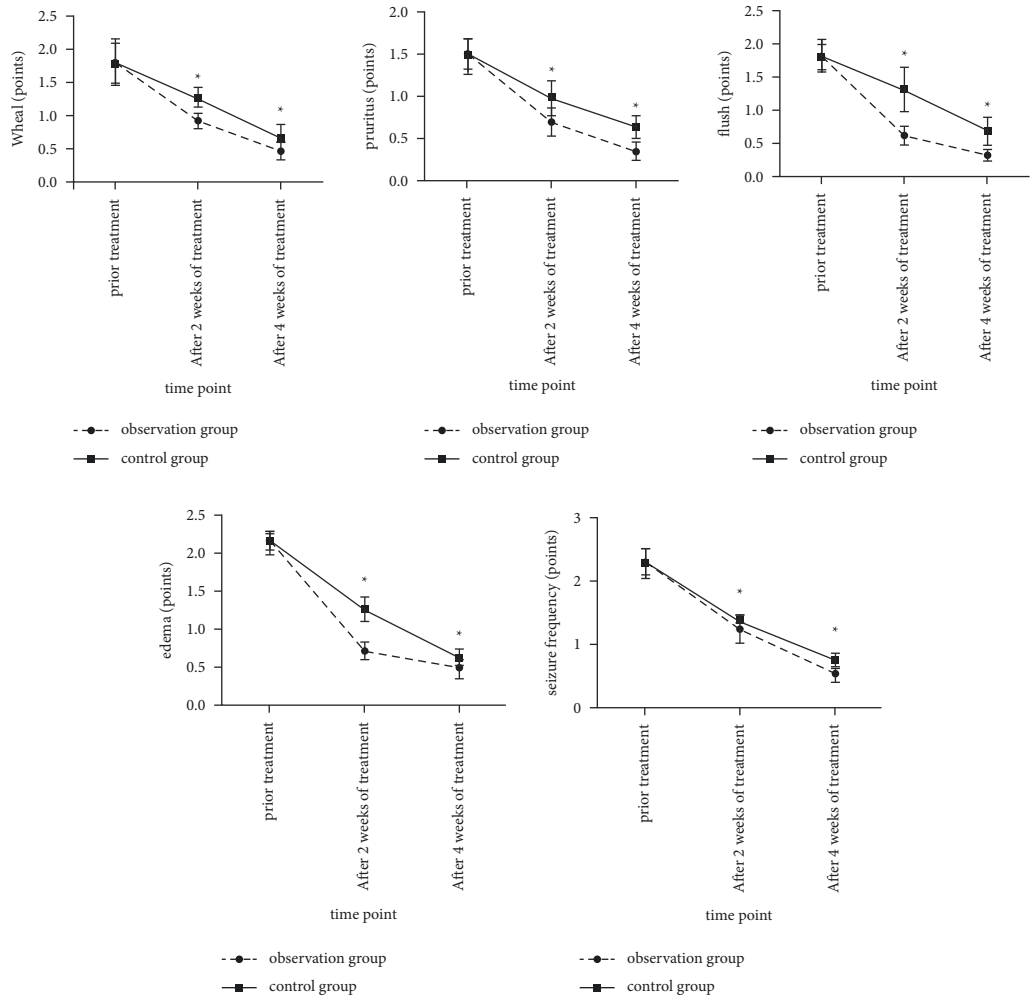

Figure 1: The comparison of clinical symptom scores between the two groups before and after treatment. (Note: compared with the control group, $^{*}P < 0.05$).

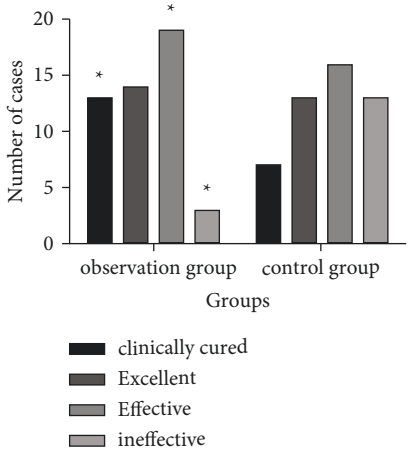

Figure 2: Comparison of clinical efficacy between the two groups. (Note: compared with the control group, $^{*}P < 0.05$.)

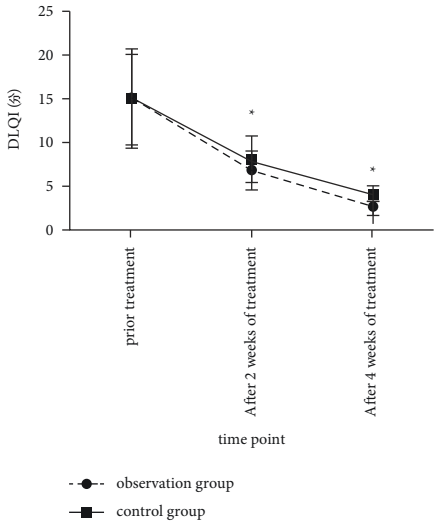

Figure 3: Comparison of the degree of disease-related life impact between the two groups before and after treatment. (Note: compared with the control group, $^{*}P < 0.05$).

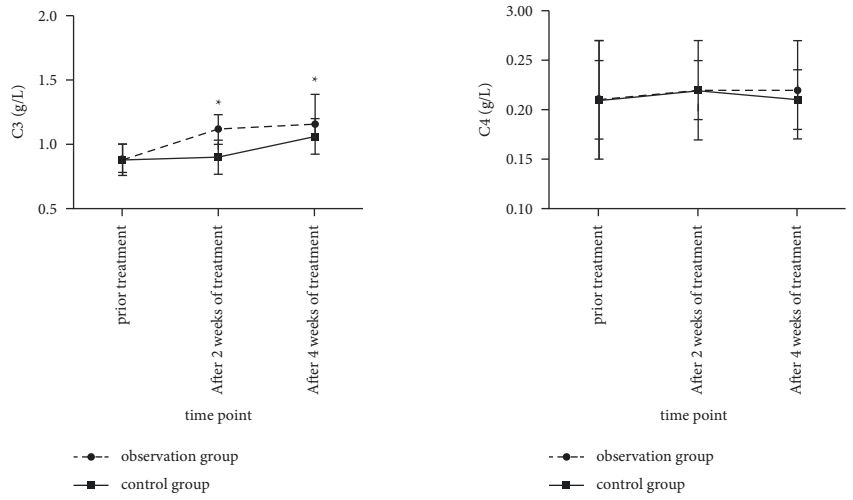

Figure 4: Comparison of serum complement C3 and C4 levels between the two groups before and after treatment. (Note: compared with the control group, $^{*}P < 0.05$).

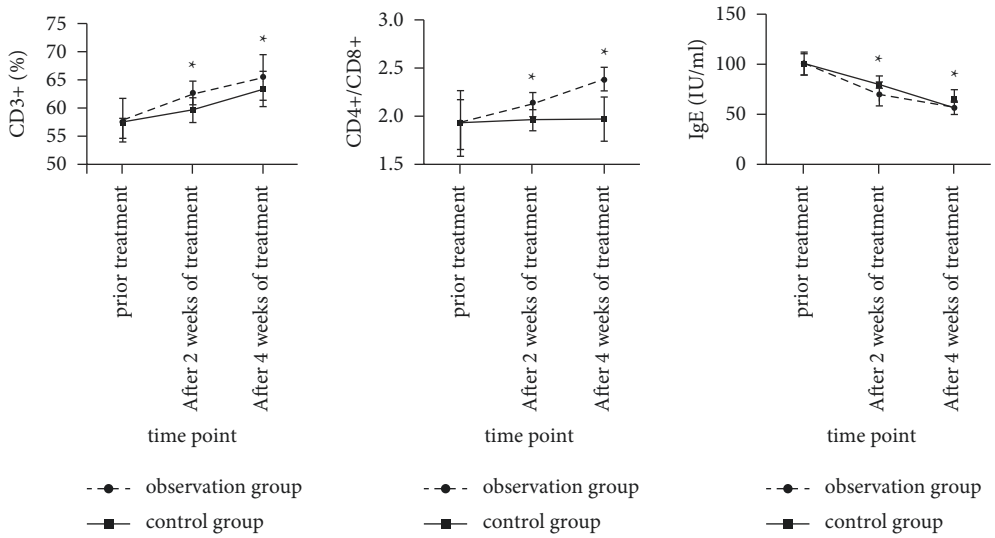

Figure 5: Comparison of peripheral T lymphocytes and IgE levels before and after treatment between the two groups. (Note: compared with the control group, $^{*}P < 0.05$).

necessary to find another drug for synergistic treatment. In China, TCM has been widely used in the treatment of skin diseases in recent years. Clinical efficacy can be effectively improved through TCM syndrome differentiation. It has become a trend to apply TCM therapy to clinical treatment on the basis of modern medicine and so on. In TCM, chronic urticaria is called "addiction rash." It is more common with gastrointestinal damp-heat syndrome. It is mostly caused by abnormal conduction of the spleen and stomach, resensation of wind pathogen, and damp-heat stagnation on the skin. The main treatment methods are dispelling wind and eliminating dampness, clearing heat and detoxicating. In this study, Fangfeng Tongsheng granule combined with levocetirizine treatment showed that the clinical symptom scores of the observation group at each time point after treatment were lower than those of the control group, and the total clinical effective rate was significantly higher than that of the control group, suggesting that the observation group had better clinical symptoms. The clinical efficacy was better than that of the control group. The results showed that after treatment, the DLQI score of the observation group was significantly lower than that of the control group, which may be related to the significant reduction of the clinical symptoms of the patients. The above results suggest that Fangfeng Tongsheng granule are effective in treating chronic urticaria.

Fangfeng Tongsheng granule are refined from Fangfeng, Nepeta spike, mint, ephedra, rhubarb, Glauber's salt, gardenia, talc, platycodon, gypsum, Chuanxiong, Angelica, white peony, skullcap, forsythia, licorice, and fried Atractylodes. Among them, Fangfeng has the effects of dispelling wind and relieving external appearance, removing dampness and activating collaterals and regulating the spleen and stomach; Nepeta paniculata has the effect of sweating,

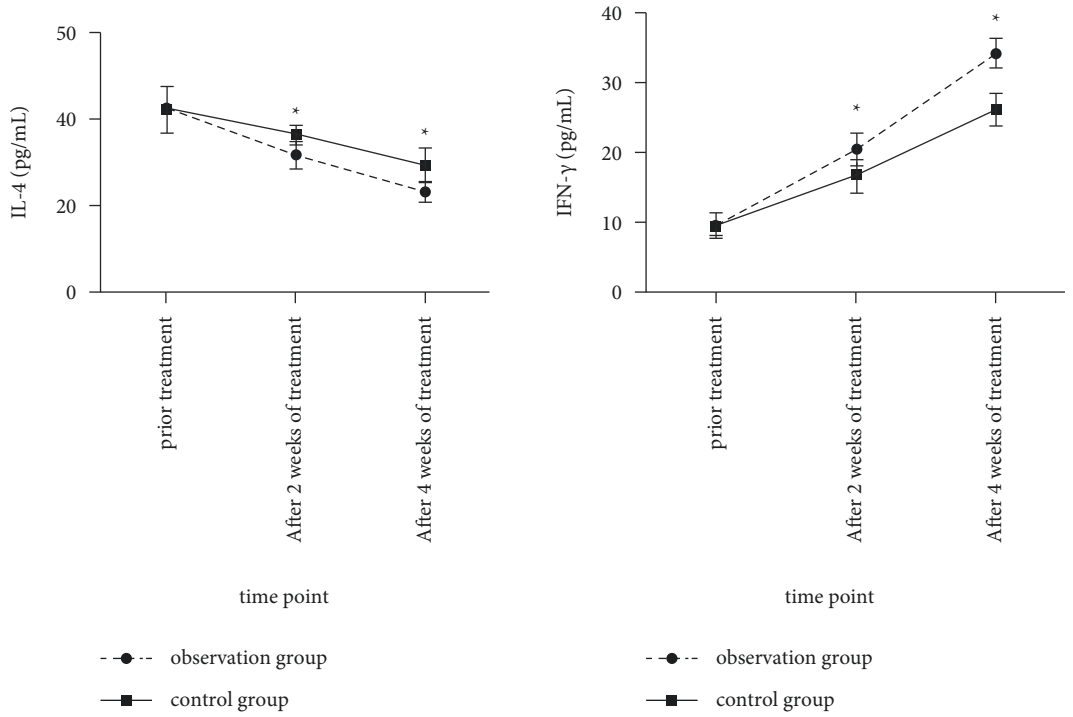

Figure 6: Comparison of the levels of IL-4 and IFN-γ between the two groups before and after treatment. (Note: compared with the control group, $^{*}P < 0.05$).

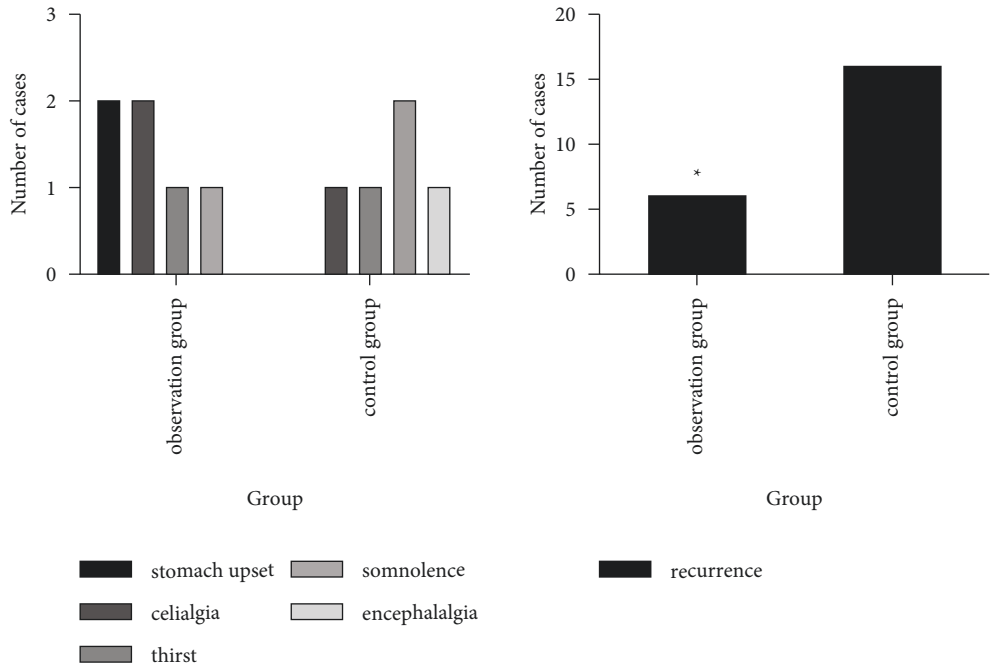

Figure 7: The occurrence of adverse reactions and follow-up recurrence in the two groups. (Note: compared with the control group, $^{*}P < 0.05$).

expelling wind, and relieving pain; peppermint has the effect of dispersing wind-heat, detoxifying, and expelling rash; Ephedra has the function of diaphoresis, diuresis, and detumescence; Rhubarb has the effects in relieving constipation, clearing heat, relieving fire, and detoxicating; Glauber's salt has the effect of eliminating fire and swelling, clearing away heat, and detoxifying; gardenia has the effect of relieving heat and dampness, dispelling fire, and eliminating vexation; talc has the effects of clearing away heat and toxic materials, eliminating dampness, and astringing sore;

Platycodon grandiflorum has the effect of nourishing qi and strengthening the spleen; gypsum has the effects of clearing heat, purging fire, and promoting tissue regeneration to relieve pain; Chuanxiong has the effects of promoting blood circulation and promoting Qi, drying dampness, and dispelling wind; white peony has the effects of reconciling nutrition, nourishing blood, and relieving pain; Scutellaria baicalensis has the effects of clearing away heat and dampness, purging fire, and detoxifying; forsythia has the effects of dispelling wind and dissipating heat, clearing heat, and detoxifying; licorice has the effects of invigorating the spleen and qi, and reconciling medicinal properties; fried Atractylodes has the effects of drying dampness and water, nourishing qi and invigorating the spleen. The whole formula is multidrug compatibility, taking into account both the exterior and the interior, focusing on expelling wind, followed by clearing heat, diuresis, and dehumidification, nourishing blood and qi, strengthening the spleen and nourishing the stomach, supplemented by the functions of dispelling wind and detoxifying, clearing heat and detoxifying, and promoting blood circulation and nourishing qi, and combined with levocetirizine can effectively improve the clinical symptoms of patients.

Earlier, we mentioned that the immune system is related to the pathogenesis of chronic urticaria. Serum complement plays an important role in the body's immune system. Complement C3 is the most abundant complement component in serum. It is involved in cellular immunity, can recognize and remove foreign pathogens, and can activate the part of complement protein, kills invading bacteria [17–19]. CD_3^+, CD_4^+, and CD_8^+ are all cellular immune regulatory T cell subsets. In addition, the ratio of CD_4^+ to CD_8^+ is a sensitive indicator of human immunodeficiency, and the decrease of this ratio indicates that the body's immune function is inhibited [20–22]. IgE is closely related to the pathogenesis of chronic urticaria and is the key immunoglobulin that mediates the pathogenesis of the disease [23]. CD_4^+ lymphocytes can differentiate into Th1, Th2, and other subgroups under the stimulation of antigens, regulate cellular immunity, and Th2 cells secrete IL cytokines such as −4, stimulate B cells to switch antibody classes, produce IgE antibodies, and IgE binds to Fc receptors in basophils and mast cells to activate allergic reactions. IFN-γ is secreted by Th1 cells, which can promote the differentiation of T0 cells to T1 cells and inhibit the differentiation of T0 cells to T2 cells [24–26]. The results showed that after treatment, the serum C3 complement, IFN-γ levels and CD_3^+, CD_4^+/CD_8^+ ratios in the observation group were higher than those in the control group, while the levels of IgE and IL-4 were lower than those in the control group. It shows that the combined treatment of Fangfeng Tongsheng granule can effectively improve the immune status of patients, but its specific mechanism still needs to be further studied. Chuanxiong, Angelica, Atractylodes, and other medicines in Fangfeng Tongsheng granule also have the effect of enhancing human immunity. The study showed that there was no significant difference in the incidence of adverse reactions between the two groups of patients, suggesting that the addition of Fangfeng Tongsheng granule may not increase the risk of adverse reactions. All patients were followed up for two months and the recurrence rate in the observation group was lower than that in the control group. This indicated that the combination of Fangfeng Tongsheng granule and levocetirizine could effectively reduce the recurrence risk of urticaria in patients after drug discontinuation, which might be related to the improvement of immune status in patients with Fangfeng Tongsheng granules.

In conclusion, the application of Fangfeng Tongsheng granules combined with levocetirizine in patients with chronic urticaria can effectively improve the clinical symptoms, improve the clinical efficacy, reduce the impact of the disease on life, improve the immune status of patients, and reduce the risk of recurrence with better efficacy and safety.

Data Availability

The data can be obtained from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Retraction

Retracted: Analysis of the Effectiveness of the Nurse-Led "Outpatient-Ward-Home" Management Model in Chronic Kidney Patients

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] Q. Hu, X. Yang, W. Wang, and M. Meng, "Analysis of the Effectiveness of the Nurse-Led "Outpatient-Ward-Home" Management Model in Chronic Kidney Patients," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4229436, 11 pages, 2022.

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Research Article

Analysis of the Effectiveness of the Nurse-Led "Outpatient-Ward-Home" Management Model in Chronic Kidney Patients

Qi Hu,[1] Xue Yang,[2] Wei Wang,[1] and Man Meng [3]

[1]*Nephrology Internal Medicine Ward, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, Liaoning 121000, China*
[2]*General Surgery (Large Intestine) Ward 1, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, Liaoning 121000, China*
[3]*Endocrinlology and Metabolic Diseases Ward, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, Liaoning 121000, China*

Correspondence should be addressed to Man Meng; mengman19910205@yeah.net

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Objective. To investigate the application and effect of the nurse-led "outpatient-ward-home" management model in the care of patients with chronic kidney disease (CKD). *Methods*. 120 patients with CKD admitted to our hospital between April 2020 and April 2021 were selected as trial subjects. All patients were divided into experimental and control groups according to the random number table method, with 60 cases in each group. The patients in the experimental group implemented the nurse-led "outpatient-ward-home" management model; the patients in the control group were given routine care and telephone follow-up. The self-rating anxiety scale (SAS), self-rating depression scale (SDS), Pittsburgh Sleep Quality Index (PSQI) score, self-management scores, nutritional status, renal function indicators, and chronic renal failure quality of life scale (QLICD-CRF2.0) were compared between the two groups before and 6 months after the intervention. *Results*. Before the intervention, there were no statistically significant differences between the control and experimental groups in SAS, SDS, PSQI scores, self-management scores, QLICD-CRF2.0 scores, body mass index (BMI), prealbumin (PAb), albumin (ALB), serum creatinine (Scr), blood urea nitrogen (BUN), and glomerular filtration rate (GFR) levels ($P > 0.05$). After 6 months of intervention, SAS, SDS, PSQI scores, Scr, BUN, and GFR levels were lower in the experimental group than in the control group; self-management scores, QLICD-CRF2.0 scores, BMI, PAb, and ALB levels were higher in the experimental group than in the control group ($P < 0.05$). *Conclusion*. The nurse-led "outpatient-ward-family" intervention model can improve the negative emotions and sleep disorders of CKD patients, enhance patients' self-management ability, and to a certain extent, slow down the disease process and improve the quality of life.

1. Preface

Chronic kidney disease (CKD) is a progressive clinical syndrome of chronic renal structural and functional disorders caused by various causes, with an insidious early onset, often accompanied by chronic diseases such as diabetes and hypertension, and an irreversible course, eventually developing into end-stage renal disease [1, 2]. A related study [3] showed that the effective treatment of CKD in China is only 7.5% due to the lack of adequate knowledge of the disease, low self-management ability, and the constraints of the current health insurance reimbursement system. The progression of CKD patients is closely related to their lifestyles, and improving patients' self-management ability is the key to slow down the progression of their disease. Related studies [4, 5] showed that the self-management ability of CKD patients is at an intermediate level, and there is still much room for improvement. An effective disease treatment management model is a prerequisite for slowing disease progression, improving patient adherence to treatment, maintaining disease stability, improving patient quality of life, reducing patient health care costs, and promoting the doctor-patient relationship [6]. At present, the management model of CKD patients in China lacks consistency, comprehensiveness, and systematization, which leads to poor patient compliance with treatment and

further results in accelerated loss of renal function, so consistent and comprehensive management of patients on the basis of conventional treatment is also needed. The single ward education model is simple and has low acceptance by patients, so it is necessary to carry out the whole process of nursing management for CKD patients by integrating the application of previous nursing models.

It has been shown that a CKD management team combined with integrated community management can effectively improve renal function, delay disease progression and improve the quality of life in patients with CKD [7, 8]. Several studies [9–11] have shown that integrated outpatient-ward-family management improves fear, depression, anxiety, and sleep disturbances in patients with mild cognitive impairment, hypertension, and stroke. In this study, on the basis of the previous routine continuing care, according to the clinical characteristics of CKD patients, the whole process nursing model based on the ward-outpatient-family was implemented. However, considering the lack of professional knowledge and support experience of patients and their families, they often need professional guidance from healthcare professionals. There are few reports in the literature on how nurses, as the main body of nursing care in China, can play a better role in the nursing management of CKD through nurse-led outpatient-ward-family. In this paper, we constructed a nurse-led outpatient-ward-family intervention model to manage CKD patients in all aspects of the ward, outpatient clinic, and family, and observed the effects of the model on the self-management ability and nutritional status of CKD patients, aiming to provide a reference basis for improving the survival quality of CKD patients.

2. Data and Methods

2.1. General Data. 120 patients with CKD admitted to our hospital between April 2020 and April 2021 were selected as the test subjects. According to the random number table method, all patients were divided into an experimental group and a control group, with 60 patients in each group. The patients in the experimental group implemented the nurse-led "ward-outpatient-family" management model; the patients in the control group were given routine care and telephone follow-up. Inclusion criteria were as follows: (i) all of them fulfilled the relevant CKD diagnostic criteria of the CKD clinical practice guidelines (K/DOKI) [12]. (ii) patients without serious organ disease; (iii) patients who were conscious and able to cooperate with the study; (iv) clinical stage I to III; (v) aged ≥ 18 years. Exclusion criteria were as follows: (i) those with combined mental illness or cognitive dysfunction; (ii) those with hearing or visual impairment affecting normal communication; (iii) the presence of serious comorbidities.

2.2. Intervention Methods

2.2.1. Control Group (Conventional Nursing Intervention)

(1) On Admission. Patients were promptly given an admission health assessment upon admission; the nurse-in-charge conducted bedside education, including an introduction to the nurse-in-charge, supervising physician and ward environment; and answered patients' questions.

(2) During Hospitalization. (i) Basic nursing care: included ward environment organization, medication, and patient safety. (ii) Specialist nursing care: edema care, renal puncture care, notification of 24 h urine specimen retention method, etc. (iii) Group lectures: included diet, medication, activity, and other kidney disease-related knowledge, once/week. (iv) Playing video: half-hour video related to kidney diet, medication, and other precautions is played in the nursing check-in car every morning. (v) Regular rounds: the responsible nurse regularly rounded the patients according to the nursing classification and solved patients' problems at any time; (vi) Psychological care: nurses took the initiative to care for and pay attention to the emotional changes of patients, and provided psychological guidance when necessary.

(3) At the Time of Discharge. (i) Informed patients of the precautions to be taken after discharge, including taking medication according to medical advice, reasonable diet, regular monitoring of blood glucose, and blood pressure; (ii) issued the hospital's homemade CKD health management manual and salt spoon, reconfirmed with patients the time of review, and instructed patients to come to the hospital for review as prescribed by the doctor; (iii) made routine telephone follow-up visits; (iv) informed patients of the telephone numbers of nurses' stations and doctors' offices, and encouraged patients to consult if they had any questions.

2.2.2. Experimental Group

(1) Formation of a Nurse-Led Family Support Intervention Group. The head nurse served as the group leader, and the members included the department head, responsible doctors, nurses, rehabilitation workers, and dieticians. Developed a group management system and division of responsibilities to provide a strong guarantee for the implementation of the care program.

(2) Outpatient Management. The CKD clinic was attended by one CKD specialist nurse daily to establish personal files and conduct a systematic assessment for patients with CKD on their first visit and to inform the department to prepare patients for admission. We provided guidance on oral medication management, self-monitoring, lifestyle, rehabilitation activities, nutritional management, and rest and sleep for repeat patients, as well as health education on risk factors and triggering factors.

(3) Ward Management. (i) Upon admission, physicians promptly assessed the condition and negative emotions of CKD patients, gave timely standardized treatment and health education, and promptly relieved patients' adverse emotions. (ii) Psychological guidance: The responsible nurse analyzed the reasons for the negative emotions of patients through selective in-depth interviews with hospitalized patients and eliminated the negative emotions of patients towards the

disease through encouragement, comfort, and communication. (iii) Health education: Patients were allowed to watch disease-related science videos on mobile TV for a limited period of time, nurses provided disease-related pamphlets and health education prescriptions, and for patients with end-stage CKD, nurses used specific food models to educate patients on the types and amounts of foods that were healthy for CKD disease. (iv) Nutritional intervention: Based on the patient's condition, biochemical indicators, blood pressure, dietary habits, family economic strength, etc., the deployment of a targeted and reasonable diet, as chronic kidney disease could lead to malnutrition, which in turn resulted in the decline of the patient's immunity, so it was also necessary to ensure a reasonable intake of protein.

(4) Home Management Multiform and Multichannel Implementation of Postdischarge Extended Care and Follow-Up Guidance. (i) Set up a CKD discharge patient care Weibo group to answer questions and solve problems for discharged patients, regularly push relevant disease rehabilitation knowledge and self-management knowledge, and provide psychological support and emotional guidance. (ii) WeChat follow-up: follow-up at day 3, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 12 weeks after discharge, with more frequent follow-ups according to patients' needs. In accordance with the follow-up plan and content formulated before discharge, patients were given priority for video follow-up by WeChat, supplemented by QQ, telephone, and SMS. Dynamically understood patients' condition recovery and self-management, asked patients about their objective data related to subjective feelings and self-monitoring, and understood patients' drug efficacy, adverse reactions, and dose adjustment plan. Patients' medication taking, self-monitoring, and rehabilitation exercise compliance were evaluated, self-management goals were checked via video and follow-up rehabilitation plans were made, appointments were made for next communication and follow-up visits, and follow-up records were made. Problems raised by patients during the follow-up visit, such as treatment, rehabilitation, and nutrition, were fed back to team members by the follow-up specialist nurse on the same day, and targeted guidance was provided by dedicated staff. (iii) Regularly carry out doctor-patient association meetings: the patients in the experimental group held a renal friend meeting once every 2 months, at which renal disease medical experts were invited to answer various problems encountered by the patients in the treatment, to provide targeted treatment and mental support to patients, and to increase the interaction between doctors and patients and nurses and patients.

2.3. Evaluation Indexes. Socio-demographic data such as patient age, gender, marital status, medical payment method, per capita monthly household income, and body mass index (BMI) were collected by reviewing patients' medical records. Disease-related information such as primary disease, disease duration, CKD stage, comorbidities or complications, number of hospitalizations, blood pressure (BP), serum creatinine (Scr), blood urea nitrogen (BUN), prealbumin (PAb), albumin (Alb), and glomerular filtration rate (GFR). Before and after 6 months of intervention, patients' Self-Rating Anxiety Scale (SAS) [13], Self-rating depression scale (SDS) [14], Pittsburgh Sleep Quality Index (PSQI) [15], self-management behavior, and quality of life were compared. The team nurses interpreted the entries of all the above scales for the patients one by one, and for patients with low literacy levels who could not fill out the forms independently, their family members filled them out on their behalf, and all the scales were distributed and collected on the spot.

(i) The SAS was used to assess the anxiety status of patients. The SAS was scored according to the SAS Chinese norm, and the SAS score was 1~100. The higher the score, the higher the level of anxiety. 50–59 indicated mild anxiety, 60–69 was moderate anxiety, and 69 or more was severe anxiety. (ii) SDS was used to assess patients' depression status, and the SDS score was 1~100. The higher the score, the more severe the depression. 53–62 was mild depression, 63–72 was moderate depression, and greater than 72 was severe depression. (iii) Sleep quality: the PSQI was used to assess the sleep quality of patients, with a PSQI score of 0–21. The higher the score, the worse the sleep quality. 0~5 was very good sleep quality, 6~10 was good sleep quality, 11~15 was fair sleep quality, and 16~21 was very poor sleep quality. (iv) Self-management behavior: the self-management scale for chronic kidney patients developed by Yu Ping et al. was used, with a Cronbach's alpha coefficient of 0.902. The scale had 31 items with 4 dimensions, namely: dietary management, therapeutic management, physical activity management, and psychosocial management. Each item was scored on a scale of 1 to 4, with a total score of 124, with higher scores indicating better self-management behavior. (v) Quality of life: the chronic kidney disease quality of life measurement scale (QLICD-CRF2.0) was used, which consists of 4 dimensions: psychological functioning (0–55 points), physical functioning (0–35 points), social relationships (0–20 points), and treatment status (0–20 points), with a total of 27 entries. The evaluation criterion was that higher scores indicated better quality of survival. (vi) Laboratory index tests: SCr, BUN and CysC, PAb, and ALB were performed at the time of discharge and 6 months after discharge, along with BMI measurement.

2.4. Data Analysis. The data were numbered, entered into an Excel sheet by the investigator and another person unrelated to this study, and double-checked, and SPSS 21.0 was used to analyze the data. Mean ± SD, median, and interquartile spacing were used for measurement data, and frequency and percentage were used for count data; for comparison of baseline data between the two groups, the chi-square test was used for count data, and t-test and nonparametric test for two independent samples were used for measurement data. $P < 0.05$ was considered a statistically significant difference.

3. Results

3.1. Comparison of General Information of Patients in the Two Groups. By reviewing the patients' medical history data

including patients' age, gender, marital status, and per capita monthly income, and the disease-related data including primary disease, disease duration, CKD stage, and the number of comorbidities or complications, and conducting statistical analysis of the collected data in groups, the results showed that there was no statistically significant difference between the two groups in the above general data ($P > 0.05$), as shown in Table 1.

3.2. Comparison of Psychological Status and Sleep Quality between the Two Groups of Patients before and after 6 Months of Intervention. Before the nursing intervention, the comparison of SAS, SDS, and PSQI scores between the control group and the experimental group was not significant ($P > 0.05$). After 6 months of intervention, the SAS, SDS, and PSQI scores of the experimental group were significantly lower than those of the control group, and the difference was statistically significant ($P < 0.05$). See Figure 1 for details.

3.3. Comparison of Self-Management Scores between the Two Groups before and after 6 Months of Intervention. The differences between the control and experimental groups were not significant ($P > 0.05$) when comparing the dietary management, therapeutic management, physical activity management, and psychosocial management scores before the nursing intervention. After 6 months of intervention, the dietary management, therapeutic management, physical activity management, and psychosocial management scores of the experimental group were significantly higher than those of the control group, and the difference was statistically significant ($P < 0.05$). See Figure 2 for details.

3.4. Comparison of the Nutritional Status of Patients in the Two Groups before and after 6 months of Intervention. Before the nursing intervention, the PAb, ALB, and BMI levels of the control group were not significantly different from those of the experimental group ($P > 0.05$). After 6 months of intervention, the PAb, ALB, and BMI levels of the experimental group were significantly higher than those of the control group, and the differences were statistically significant ($P < 0.05$). See Figure 3 for details.

3.5. Comparison of Renal Function Indexes between the Two Groups of Patients before and after 6 Months of Intervention. Before the nursing intervention, the levels of Scr, BUN, and GFR in the control group and the experimental group were not significantly different from each other ($P > 0.05$). After 6 months of intervention, the levels of Scr, BUN, and GFR in the experimental group were significantly lower than those in the control group, and the difference was statistically significant ($P < 0.05$). See Figure 4 for details.

3.6. Comparison of the Quality of Life of the Two Groups before and after 6 Months of Intervention. The differences between the control group and the experimental group were not significant ($P > 0.05$) when comparing the scores of psychological function, physical function, social relationship, and treatment status before the nursing intervention. After 6 months of intervention, the scores of psychological function, physical function, physiological function, and treatment condition in the experimental group were significantly higher than those in the control group, and the difference was statistically significant ($P < 0.05$). See Figure 5 for details.

4. Discussion

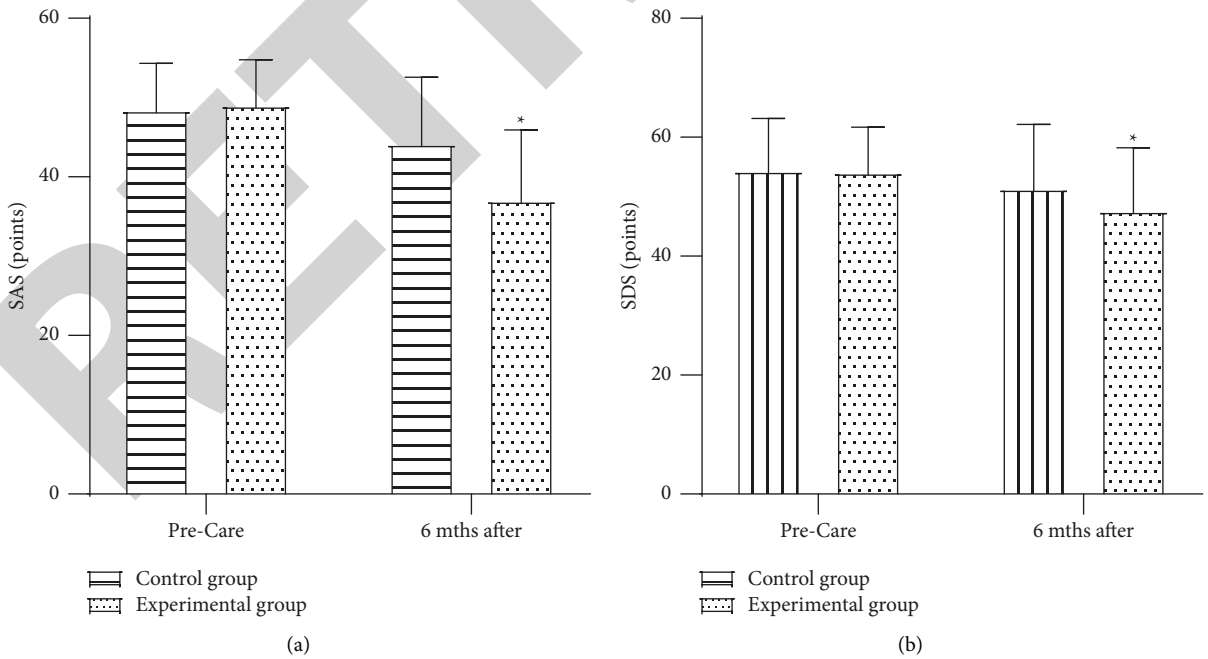
As a common clinical chronic disease, CKD can involve all systems of the body, and the disease is prolonged, which predisposes patients to a series of adverse emotions such as anxiety and depression [16, 17]. Laffin and Bakris [18] found that the use of integrated individualized ward-clinic-home health care management met patients' needs for all 3 aspects of treatment, care, and family and effectively reduced negative patient emotions. This paper examines the effects of integrated outpatient-ward-home healthcare management on negative emotions, sleep disorders, self-management ability, nutritional status, renal function, and quality of life in patients with CKD, with the aim of exploring ways to improve treatment compliance and quality of life in patients with CKD.

4.1. The Nurse-Led "Outpatient-Ward-Home" Intervention Model Improves Negative Emotions and Sleep Quality in CKD Patients. The results of this study showed that after 6 months of intervention, the experimental group showed greater reductions in SAS, SDS, and PSQI scores than the control group ($P < 0.05$). Suggesting that the integrated ward-clinic-family management model improves negative emotions and sleep quality in patients with CKD, in line. Llewellyn's [19] study results are more consistent. Because of the long-term chronic spiral progression of CKD patients, they require not only long-term repeated hospitalization but also long-term outpatient follow-up and home management. In the integrated management model of outpatient-ward-home, the responsible nurses analyze the causes of negative emotions through interviews and assessments of patients' conditions, so that patients can get comprehensive guidance such as systematic drug treatment, exercise, nutrition intake, and psychological counseling in the whole process. And a multidimensional and perfect social support network was constructed, and patients established confidence in controlling the disease, which led to the timely and effective relief of negative emotions while reducing patients' worries about the prognosis of the disease and allowing them to relax physically and mentally, which could improve their sleep disorders and improve their sleep quality [20, 21].

4.2. The Integrated Outpatient-Ward-Home and Management Model can Improve the Self-Management Ability and Nutritional Status of CKD Patients. In this study, the BMI, PAb, and ALB of patients in the experimental group were significantly higher than those in the control group after

Table 1: Comparison of general information of CKD patients in two groups.

Information	Control group ($n = 60$)	Experimental group ($n = 60$)	t/χ^2 value	P value
Gender (male/female)	41/19	39/21	0.150	0.699
Age (years)	46.87 ± 6.45	47.13 ± 6.22	0.225	0.823
Duration of illness (months)	22.15 ± 4.14	23.06 ± 3.97	1.229	0.222
Whether working (yes/no)	26/34	23/37	0.310	0.577
Marriage (unmarried/married)	52/8	54/6	0.324	0.570
Education level				
Primary school and below	11 (18.33)	13 (21.67)		
Junior high school	28 (46.67)	25 (41.67)	0.546	0.909
High school	13 (21.67)	15 (25.00)		
College and above	8 (13.33)	7 (11.66)		
Primary disease				
Glomerulonephritis	18 (30.00)	19 (31.67)		
Hypertensive nephropathy	16 (26.67)	15 (25.00)	0.163	0.983
Diabetic nephropathy	19 (31.67)	20 (33.33)		
Others	7 (11.67)	6 (10.00)		
Disease staging				
Stage I	28 (46.67)	30 (50.00)		
Stage II	19 (3.66)	18 (30.00)	0.136	0.934
Stage III	13 (21.67)	12 (20.00)		
Monthly income per capita (yuan)				
≤1000	18 (30.00)	20 (33.33)		
1001~3000	32 (53.33)	31 (51.67)	0.174	0.917
≥3001	10 (16.67)	9 (15.00)		
Complications				
None/1 kind	13 (21.67)	15 (25.00)		
2 kinds	27 (45.00)	25 (41.67)	0.220	0.896
3 or more	20 (33.33)	20 (33.33)		



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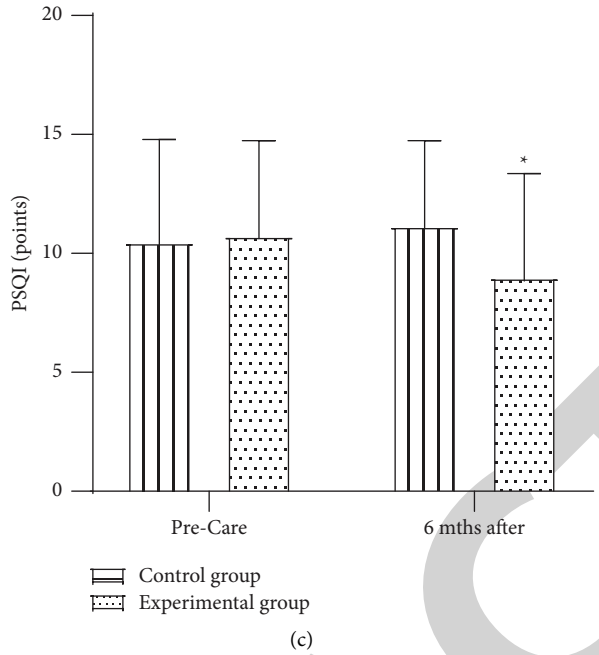
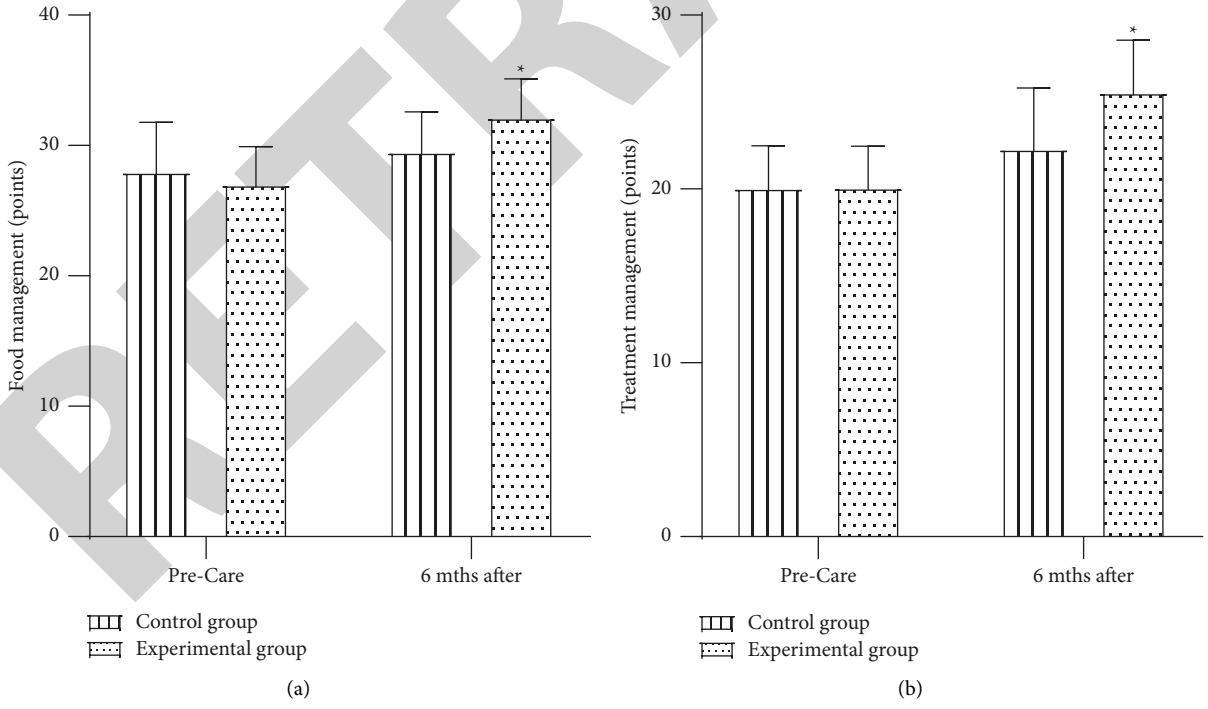


Figure 1: Comparison of psychological status and sleep quality between the two groups of patients before and after 6 months of intervention. Note: (a) to (c) indicate the SAS score, SDS score, and PSQI score, respectively. Compared with the control group in the same period, $^{*}P < 0.05$.



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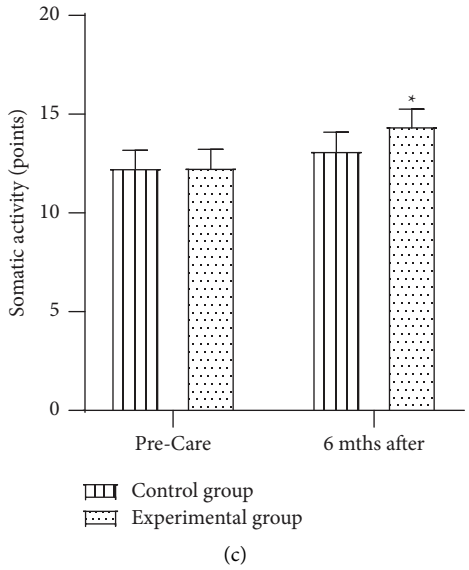


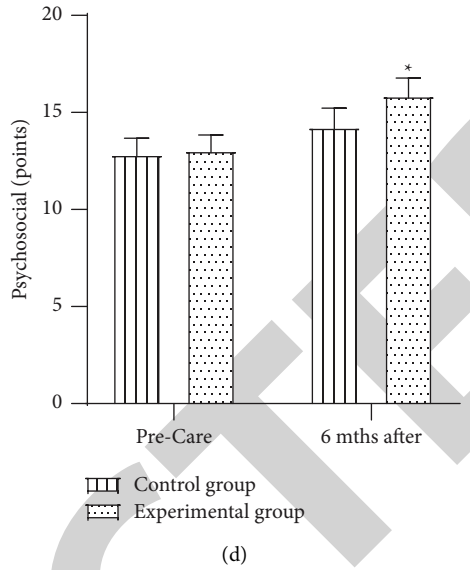
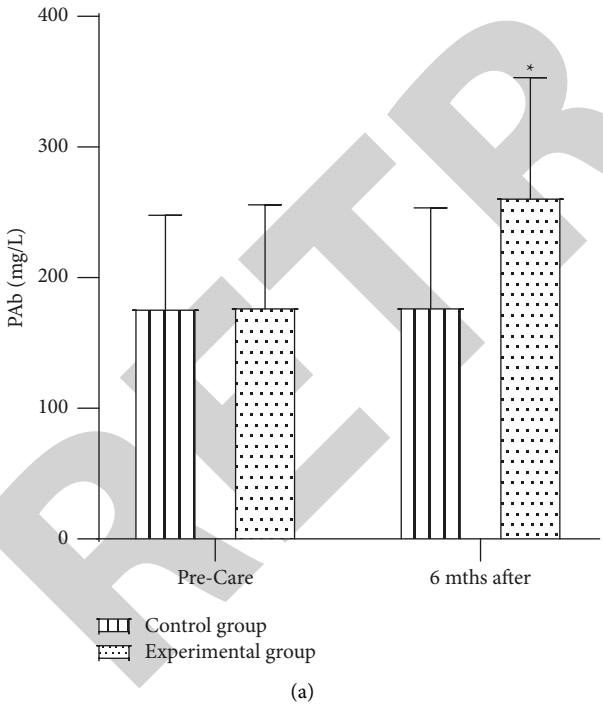
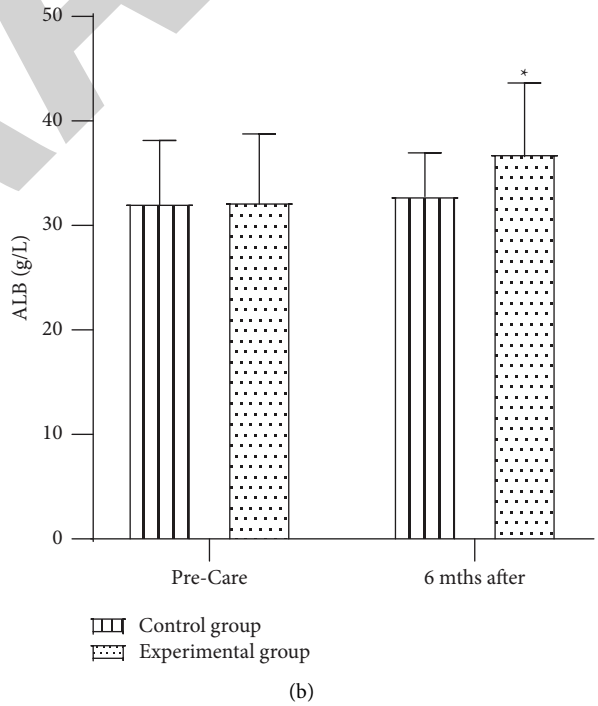


Figure 2: Comparison of self-management scores between the two groups before and after 6 months of intervention. Note: (a)~(d) represents the score of food management, treatment management, somatic activity, and psychosocial, respectively. Compared with the control group in the same period, $^{*}P < 0.05$.





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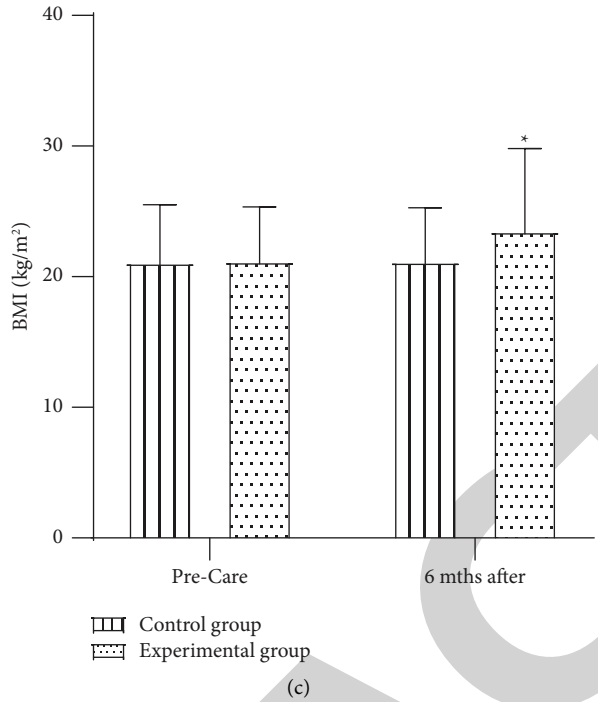
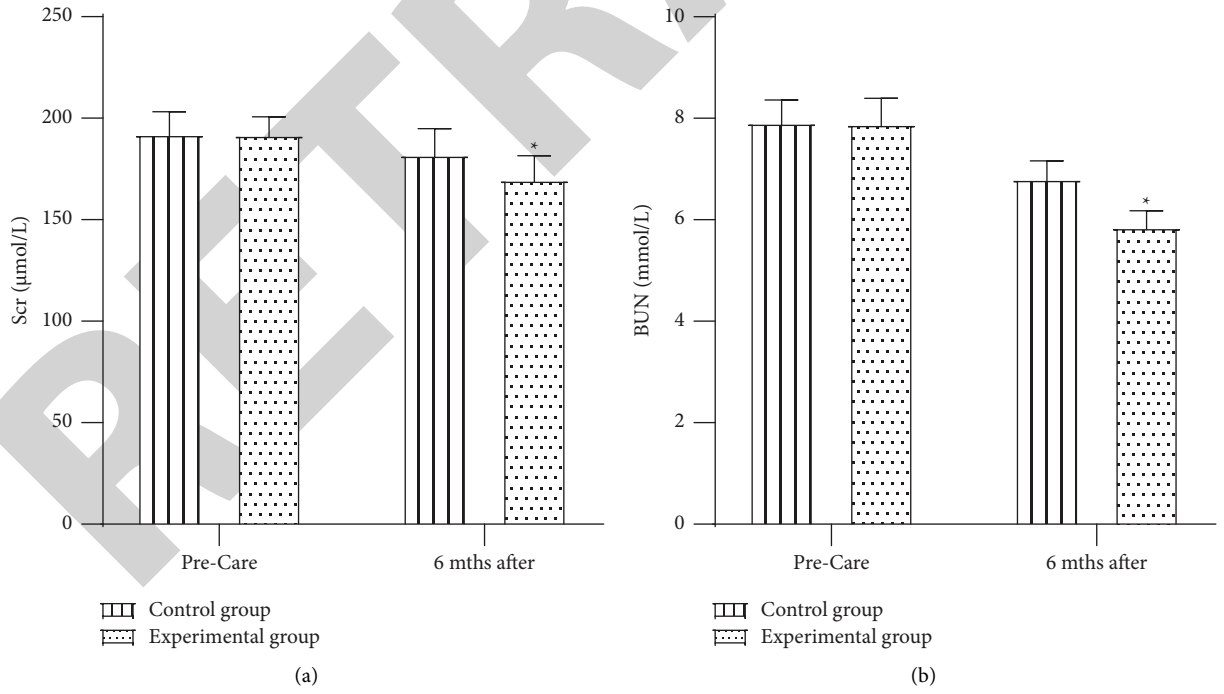


Figure 3: Comparison of the nutritional status of patients in the two groups before and after 6 months of intervention. Note: (a)~(c) represent PAb, ALB, and BMI levels, respectively. Compared with the control group in the same period, $^{*}P < 0.05$.



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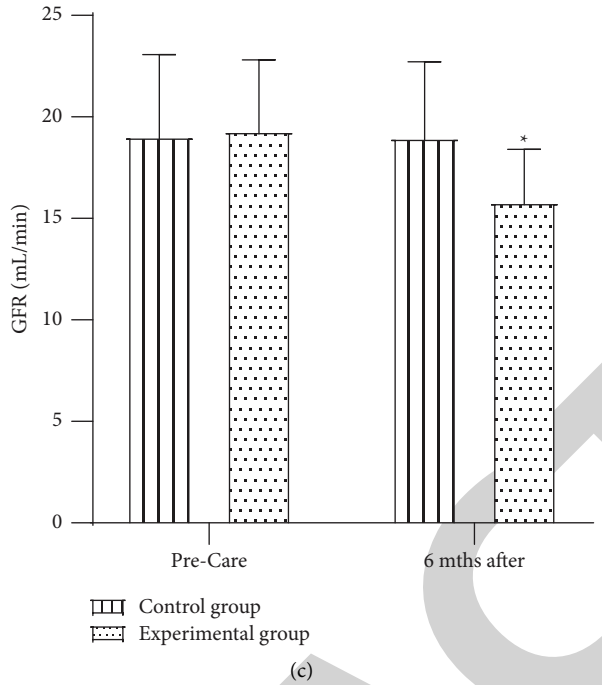
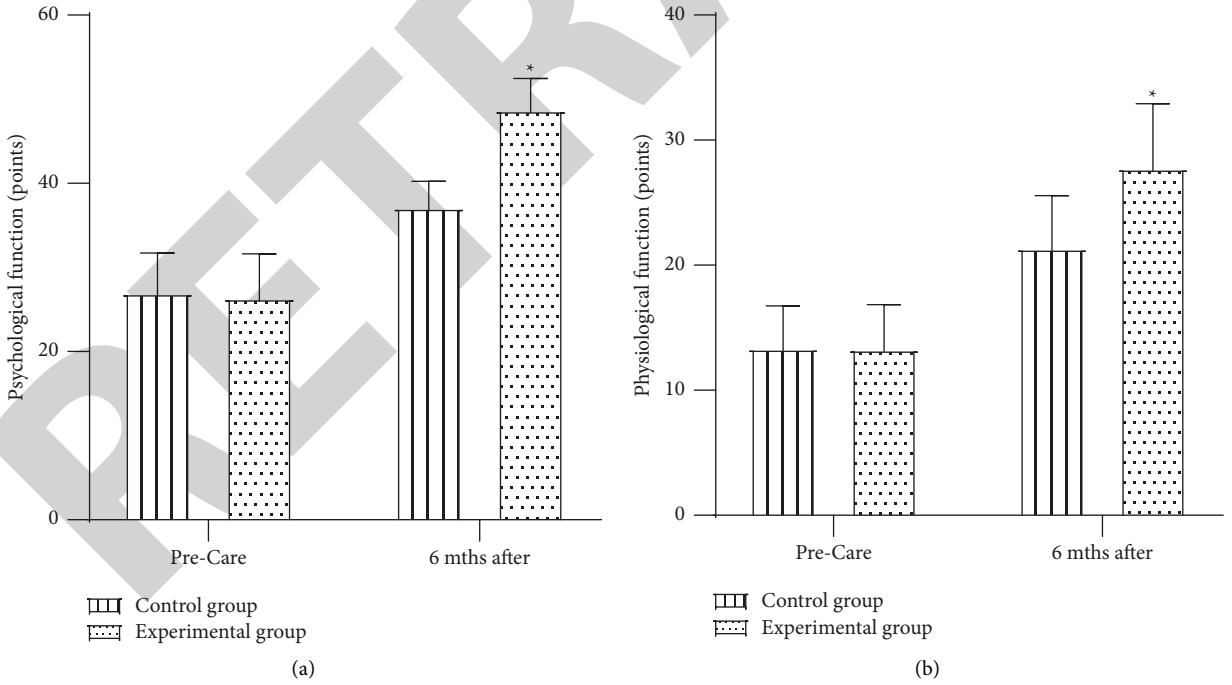


Figure 4: Comparison of renal function indexes between the two groups of patients before and after 6 months of intervention. Note: (a) to (c) represent Scr, BUN, and GFR levels, respectively. Compared with the control group in the same period, $^{*}P < 0.05$.



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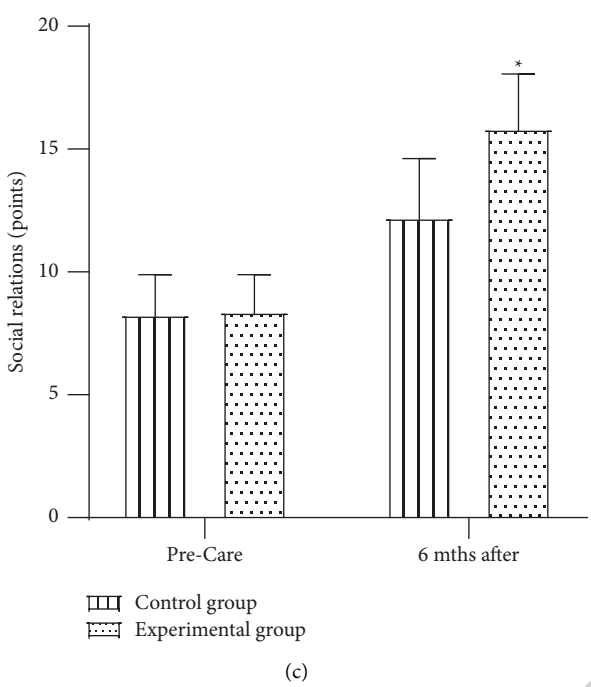

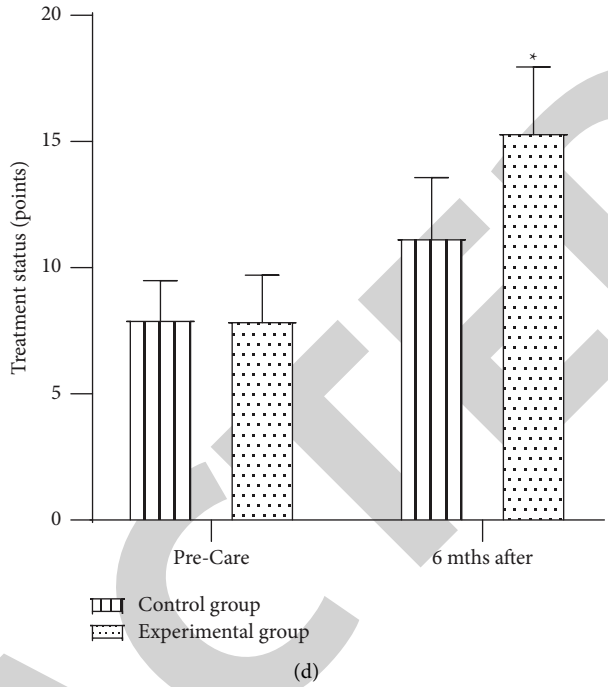

Figure 5: Comparison of the quality of life of the two groups before and after 6 months of intervention. Note: (a)~(d) represent psychological function, physical function, social relation, and treatment status score, respectively. Compared with the control group in the same period, $^{*}P < 0.05$.

6 months of intervention ($P < 0.05$), indicating that the integrated outpatient-ward-home, management model can effectively improve the nutritional status of patients. This is due to the fact that healthcare education and nursing nutritional guidance intervention can promptly understand the inner conflicts of patients, develop a healthy diet plan, reasonably allocate nutrition, change patients' poor lifestyles, and promote the improvement of their nutritional status. The results showed that the self-management scores of patients in both groups improved after 6 months of intervention, and the test group was higher than the control group ($P < 0.05$), indicating that the nursing nutrition guidance intervention could effectively improve patients' self-behavior management ability, and patients could consciously change to healthier behaviors so that patients could actively cooperate with treatment. Through health education and nutritional guidance interventions, patients can also understand the knowledge and treatment methods of CKD, so that they can follow the doctor's advice; Healthy and reasonable diet control and regular exercise can improve health through behavior change [22].

4.3. The Integrated Outpatient-Ward-Home and Management Model can Improve the Renal Function and Quality of Life of CKD Patients. The main clinical manifestation of CKD patients is reduced renal function, and BUN, Scr, and GFR are effective indicators to detect renal function. Some studies [23, 24] have shown that lifestyle changes and dietary control of patients can improve their clinical and biochemical indicators and that this effect is independent of the effect of drug therapy. Therefore, enhancing patient self-management through active and effective interventions during the progression of CKD patients can equally influence the disease progression and outcome. In this study, there were no statistically significant differences in BUN, SCr, and GFR between the two groups before the intervention; after receiving the patients in the control group, they were given conventional care with postdischarge telephone follow-up, and the experimental group adopted the nurse-led integrated outpatient-ward-home, model. Mainly by going into the wards and families to publicize the treatment and care of the disease, making detailed follow-up plans, prioritizing the use of WeChat videos to remind patients of outpatient review, regular medication guidance to avoid the use of nephrotoxic drugs, and multidisciplinary nursing experts to develop personalized diet recipes for different patients. The problems of treatment, rehabilitation, and nutrition raised by the patients during the follow-up period were fed back to the team members by the follow-up specialist nurse on the same day, and targeted guidance was provided by the specialist to control the progress of the disease so that the patients could achieve standardized medical care and live happily [25, 26]. The results of this study showed that the differences in BUN, SCr, GFR, and quality of life between the two groups of patients after 6 months of nursing intervention were statistically significant. The nurse-led ward-outpatient-home intervention model can guide patients in a multifaceted way, help patients establish good self-management behaviors, and delay disease progression to a certain extent, which is a new nursing model with practical significance for the management of patients with chronic diseases.

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Retraction

Retracted: Clinical Efficacy Analysis of Biofeedback Electrical Stimulation Combined with Doxycycline in the Treatment of Type IIIA Chronic Prostatitis

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] X. Sun, T. Lin, J. Fang et al., "Clinical Efficacy Analysis of Biofeedback Electrical Stimulation Combined with Doxycycline in the Treatment of Type IIIA Chronic Prostatitis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7150204, 7 pages, 2022.

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Research Article

Clinical Efficacy Analysis of Biofeedback Electrical Stimulation Combined with Doxycycline in the Treatment of Type IIIA Chronic Prostatitis

Xiaoyong Sun,[1] Tangtang Lin,[1] Jinying Fang,[1] Jinming Liu,[1] Wenliang Yao,[2] Liguo Geng,[3] and Jinfeng Zhang [4]

[1]*Department of Chinese Medicine, First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi 341000, China*
[2]*Department of Andrology, Nanchang Reproductive Hospital, Nanchang, Jiangxi 330000, China*
[3]*Department of Andrology, Guangdong Provincial Hospital of Traditional Chinese Medicine, Zhuhai Hospital, Zhuhai, Guangdong 519000, China*
[4]*Department of Anorectal, Ganzhou Hospital of Traditional Chinese Medicine, Ganzhou, Jiangxi 341000, China*

Correspondence should be addressed to Jinfeng Zhang; zhang-jf2006@163.com

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Purpose. To analyse the clinical efficacy of biofeedback electrical stimulation combined with doxycycline in the treatment of type IIIA chronic prostatitis. *Methods*. Eighty patients who met the diagnostic criteria of type IIIA chronic prostatitis in our hospital between February 2020 and February 2022 were selected and equally divided into the drug group and electrical stimulation group according to the random number table method. The drug group was treated with medication alone for 4 weeks; the electrostimulation group was treated with biofeedback electrostimulation on top of medication for 12 weeks. The expressed prostatic secretious (EPS) routine (lecithin bodies, white blood cells) and the maximum urinary flow rate (Q_{max}) and mean urinary flow rate (Q_{ave}) were measured before and after treatment in both groups, and the National Institutes of Health chronic prostatitis symptom index (NIH-CPSI) was used to score the urinary symptom, pain or discomfort, and quality of life and determine the efficacy of the treatment in both groups. *Results*. After treatment, the number of lecithin bodies and white blood cells in EPS improved significantly in both groups compared to before, and both the electrical stimulation group was better than the drug group ($P < 0.05$). After treatment, the Q_{max} and Q_{ave} were significantly higher in both groups than before, and both the electrical stimulation groups were higher than the drug group ($P < 0.05$). After treatment, the urinary symptom scores, pain or discomfort scores, quality of life scores, and total NIH-CPSI scores were significantly lower in both groups than before, and all were lower in the electrical stimulation group than in the drug group ($P < 0.05$). After treatment, the overall efficiency of patients in the electrical stimulation group was significantly higher than that of the drug group ($P < 0.05$). *Conclusion*. Biofeedback electrical stimulation combined with doxycycline in the treatment of type IIIA chronic prostatitis can synergistically improve the patient's inflammation level, urinary dysfunction, relieve pelvic floor tension myalgia, and improve their quality of life, opening up new avenues for the rehabilitation of patients with type IIIA chronic prostatitis.

1. Introduction

Chronic prostatitis is a chronic inflammation of the prostate caused by specific or nonspecific infection and is a common clinical genitourinary disorder in men, of which type IIIA is the most common [1]. Studies [2] have stated that 30–50% of men will be affected by symptoms of prostatitis at some point in their lives. And because of its repeated attacks, long-lasting pain and discomfort in the perineum, lower abdomen, lumbosacral, and other symptoms, as well as frequent urination, urgency, pain, etc., serious patients even have sexual dysfunction, insomnia, anxiety, depression, and other symptoms, which bring great trauma to the patient's body and mind [3, 4].

At present, there is no specific treatment drug for type III prostatitis, and the clinical treatment of this disease mainly focuses on anti-infection, anti-inflammatory and pain relief, relieving urination symptoms, and symptomatic treatment [5]. Because of its complex aetiology, variable symptoms, and incomplete elucidation of the pathogenesis, various clinical treatments are available, but their efficacy varies, and long-term treatment is prone to greater side effects and a huge economic burden so that most patients have to discontinue treatment. Studies have shown that type III chronic prostatitis is closely related to pelvic floor neuromuscular dysfunction, and biofeedback can convert the electrical activity of the pelvic floor muscles, which cannot be directly perceived by patients, into visual signals that can be directly felt, and guide patients to selectively contract and relax the pelvic floor muscles to inhibit bladder contraction and relax the external sphincter at the same time, thus achieving relief of perineal pain as well as urination symptoms [6]. At present, biofeedback is mainly used clinically for the treatment of functional constipation or fecal incontinence, urinary incontinence, etc., and is less reported in the clinical application of chronic prostatitis. In this study, 80 patients with type IIIA chronic prostatitis who met the inclusion criteria were divided into two groups, and the clinical efficacy of biofeedback electrical stimulation combined with doxycycline treatment was analysed by observing and comparing the expressed prostatic secretious (EPS) routine, the National Institutes of Health chronic prostatitis symptom index (NIH-CPSI) before and after treatment in both groups, in order to explore an effective and reliable treatment method for the clinical treatment of type IIIA chronic prostatitis.

2. Materials and Methods

2.1. General Data. Eighty patients who met the diagnostic criteria for type IIIA chronic prostatitis in our hospital between February 2020 and February 2022 were selected and equally divided into a drug group and an electrical stimulation group according to the random number table method. Patients in the drug group were aged 20 to 49 years, with mean age (32.45 ± 6.69) years, duration of illness 3 to 14 months, mean duration of illness (8.08 ± 2.04) months, BMI 19~25 kg/m^2, and mean BMI (21.57 ± 1.78) kg/m^2; Patients in the electrical stimulation group were aged 22 to 49 years, mean age (32.00 ± 5.71) years, duration of illness 4 to 14 months, mean duration of illness (8.25 ± 2.05) months, BMI 18~25 kg/m^2, and mean BMI (21.64 ± 1.84) kg/m^2. The differences in general clinical data such as age duration of illness and BMI of the two groups were not statistically significant ($P > 0.05$) and were comparable.

2.2. Diagnostic Criteria. In line with the 2014 edition of the Chinese handbook of diagnostic and therapeutic guidelines for urological diseases [7] and the 1995 National Institutes of Health (NIH) classification criteria for type IIIA prostatitis [8]: (1) duration of disease ≥ 3 months; (2) with symptoms of urinary discomfort such as frequent and painful urination, incomplete urination or white discharge from the urethra; (3) perineal, peripubic, lumbosacral and perianal pain and ejaculatory pain; (4) on finger examination, the prostate could be small or normal, tough texture, with nodules of different sizes or local tenderness; (5) negative WBC by urine analysis and urine sediment test; (6) microscopic examination of EPS with WBC ≥ 10/HP; (7) EPS bacterial culture (−); (8) NIH-CPSI > 4 scores.

2.3. Inclusion Criteria. Inclusion criteria were as follows: (1) meet the diagnostic criteria for type IIIA chronic prostatitis; (2) duration of disease ≥ 3 months; (3) age between 18 and 50 years, male; (4) not using other drugs or treatments for prostatitis in the previous 2 weeks; (5) informed consent and voluntary participation; (6) those who did not take their medication regularly or withdrew on their own during treatment; (7) those who required discontinuation of the drug during treatment caused by gastrointestinal reactions or allergies.

2.4. Exclusion Criteria. Exclusion criteria were as follows: (1) those with other prostate diseases such as benign prostatic hyperplasia and prostate cancer in combination; (2)those with nonprostatic conditions that can cause pain in the pelvic region, such as inguinal hernia, ureteral stones, bladder stones, and bladder tumours; (3) persons with mental illness or serious systemic diseases such as cardiovascular, cerebrovascular, liver or kidney diseases; (4) those with allergies or hypersensitivity to the drugs tested in this test; (5) previous history of pelvic-related surgery.

2.5. Treatment Methods. The drug group used 2 tablets (200 mg) of doxycycline hyclate tablets (Jiangsu Lianshui Pharmaceutical Co., Ltd., State Drug Administration H32023940) orally once a day for each dose; supplemented with tamsulosin hydrochloride sustained-release capsules (Jiangsu Hengrui Pharmaceutical Industry Co., Ltd., State Drug Administration H20050392) 1 capsule (0.2 mg) taken orally once a day, for a total of 4 weeks of treatment. The electrical stimulation group was treated with a UROSTYMTM biofeedback electrical stimulation device in addition to medication. The method was: the patient was placed in the supine position, an anal plug electrode was placed to record electromyography and a rectal manometry tube was used to record abdominal pressure. The treatment parameters were: current 25–50 mA, frequency 50–100 Hz, wave width 200–500 μs, and stimulation intensity of stimulation without pain. The patient was asked to contract the anus for 5 s, relax for 20–30 s, and then repeat for 30 min each time. During the treatment, the patient was asked to note the changes in electromyography and abdominal pressure curve so that the abdominal pressure curve did not rise when the patient contracted the anus. Treatment was given once every other day, for 4 weeks as a course of treatment, with a total of 12 weeks of treatment. Both groups were observed for efficacy at the end of the 4th week of treatment and relevant indicators were measured and evaluated.

2.6. Observed Indicators. The EPS routine (lecithin bodies, white blood cells) and the maximum urinary flow rate (Q_{max}) and mean urinary flow rate (Q_{ave}) were measured before and after treatment in both groups. The NIH-CPSI was used to score the urinary symptom, pain or discomfort, and quality of life and determine the efficacy of the treatment in both groups. The total NIH-CPSI score ranged from 0 to 43, with a total score of 0 to 10 for urinary symptoms, 0 to 21 for pain or discomfort, and 0 to 12 for quality of life, with higher scores indicating more severe symptoms. Efficacy determination: Healed: > 90% reduction in total NIH-CPSI score after treatment; Significantly valid: 60–89% reduction in total NIH-CPSI score after treatment; Valid: 30–59% reduction in total NIH-CPSI score after treatment; Invalid: <30% reduction in total NIH-CPSI score after treatment [9]. The total effective rate was calculated as healed rate- + significantly valid rate + valid rate.

2.7. Statistical Methods. Data were analysed with SPSS 21.0 software. Grade data were analysed with the U test, measurement data were expressed as $x \pm s$ and compared with the t-test, and count data were analysed with the χ^2 test, with $P < 0.05$ being considered a statistically significant difference.

3. Results

3.1. Comparison of the Number of Lecithin Bodies in the EPS of the Two Groups. After treatment, the number of lecithin bodies in EPS improved significantly in both groups compared to before, and both the electrical stimulation group was better than the drug group, the difference had a statistical significance ($P < 0.05$) (Figure 1).

3.2. Comparison of the Number of White Blood Cells in the EPS of the Two Groups. After treatment, the number of white blood cells in EPS improved significantly in both groups compared to before, and both the electrical stimulation group was better than the drug group, the difference had a statistical significance ($P < 0.05$) (Figure 2).

3.3. Comparison of Urine Flow Rates of the Two Groups. After treatment, the Q_{max} and Q_{ave} were significantly higher in both groups compared to before, and both the electrical stimulation groups were higher than the drug group, the difference had a statistical significance ($P < 0.05$) (Figure 3).

3.4. Comparison of NIH-CPSI Scores of the Two Groups. After treatment, the urinary symptom scores, pain or discomfort scores, quality of life scores, and total NIH-CPSI scores were significantly lower in both groups compared to before, and all were lower in the electrical stimulation group than in the drug group, the difference had a statistical significance ($P < 0.05$) (Figure 4).

3.5. Comparison of the Efficacy of the Two Groups. After treatment, the overall efficiency of patients in the electrical stimulation group was significantly higher than that of the drug group, the difference had a statistical significance ($P < 0.05$) (Table 1).

4. Discussion

Currently, the reported prevalence of chronic prostatitis ranges from approximately 6.0 to 32.9% in China, 9.0% in the United States, and 2.0 to 10.0% worldwide [10, 11]. Although the disease is not directly life-threatening, chronic and recurrent pain and discomfort in the perineum, lower abdomen, lumbosacral area, and abnormal urination can seriously reduce the quality of life of the patient.

There are different theories on the aetiology and pathophysiology of chronic prostatitis, including occult infection, inflammation/autoimmunity, pelvic floor muscle dysfunction, voiding dysfunction, intraprostatic urinary reflux and elevated intraprostatic pressure, neuropsychological factors, adrenal axis abnormalities, genetic predisposition and oxidative stress [12–15]. Type IIIA chronic nonbacterial prostatitis, also known as chronic pelvic pain syndrome, is inflammatory prostatitis that presents with varying degrees of elevated leukocytes in both routine EPS and voided bladder three (VB3) [16]. Although routine bacterial cultures for EPS in this type of patient are negative and no pathogens have been isolated, they may still be associated with mycoplasma, chlamydia trachomatis, fungi, viruses, and certain bacterial infections, so current guidelines still recommend empirical antibiotic treatment for 2–6 weeks in combination with other medications to relieve pain and urinary tract symptoms.

In recent years, researchers have begun to more accurately diagnose prostatitis-like symptoms as pelvic floor muscle dysfunction, usually associated with pain, spasm, and pressure in the pelvic muscles. Pelvic floor spasms may lead to voiding dysfunction and pain, which in turn can increase pressure and make the condition worse [17]. Pelvic floor spasms may be the cause of the condition alone or secondary to inflammation or infection. When pelvic floor spasm is the cause alone, the painful symptoms can be resolved by relieving the muscle spasm and, in secondary cases, the painful symptoms can be also relieved to some extent as a result.

Research [18] shows that type III prostatitis is closely related to pelvic floor muscle spasms. Pelvic floor muscle spasms can cause urethral tension pain, a decrease in urinary flow rate, an increase in maximum urethral closure pressure, and an increase in the chance of urine reflux in the prostate. The pelvic biofeedback instrument can convert the pelvic floor myoelectric activity that the patient can not directly perceive into visual signals that can be directly sensed, which is conducive to the patient's selective contraction and relaxation of the pelvic floor muscle, and finally form the self-regulation response ability without the feedback instrument, which makes the pelvic floor muscle fatigue relax and tend to be coordinated, increases the synergy between the bladder detrusor and the urethral sphincter, and reduces the afferent impulse of nociceptive sensation, So as to relieve perineal pain and urination symptoms [19, 20].

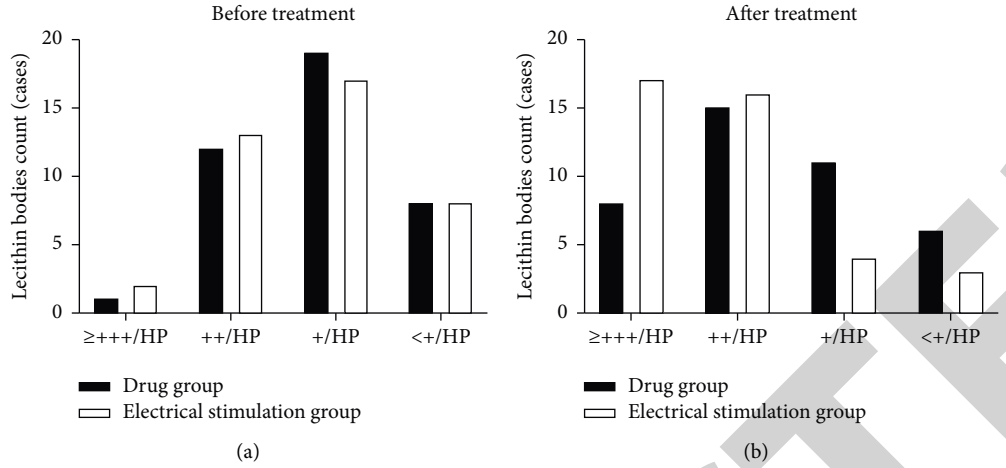

Figure 1: Comparison of the number of lecithin bodies in the EPS of the two groups. Note: (a) Number of lecithin bodies in EPS before treatment in both groups. (b) Number of lecithin bodies in EPS after treatment in both groups.

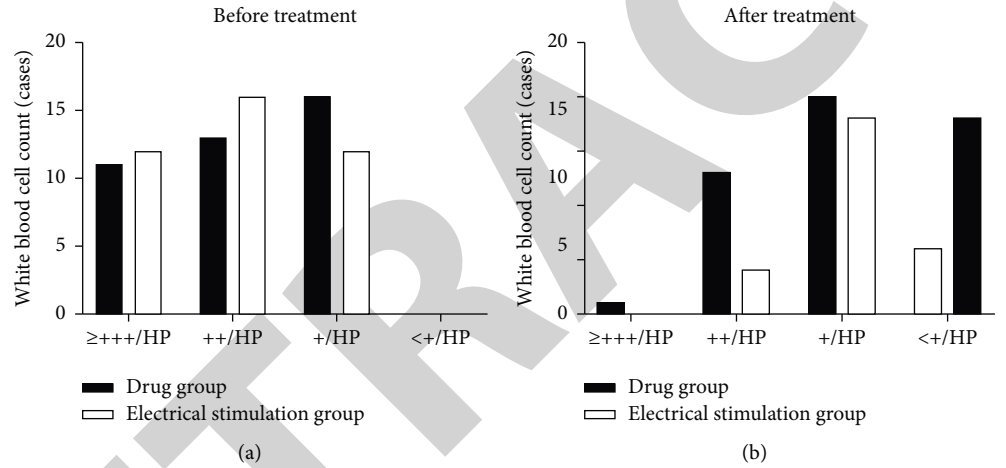

Figure 2: Comparison of the number of white blood cells in the EPS of the two groups. Note: (a) number of white blood cells in EPS before treatment in both groups. (b) The number of white blood cells in EPS after treatment in both groups.

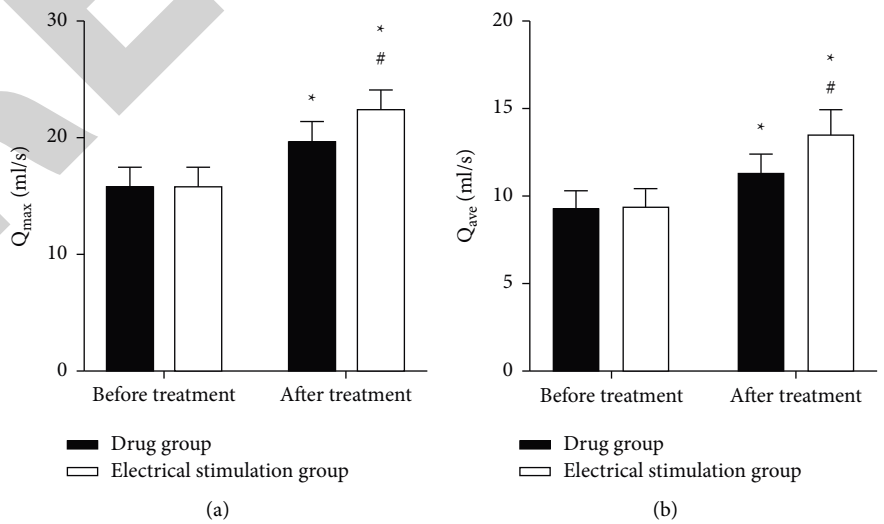

Figure 3: Comparison of urine flow rates of the two groups. Note: (a) Q_{max} before and after treatment in both groups. (b) Q_{ave} before and after treatment in both groups. Compared with the same group before treatment, $^{*}P < 0.05$; Compared with the drug group after treatment, $^{\#}P < 0.05$.

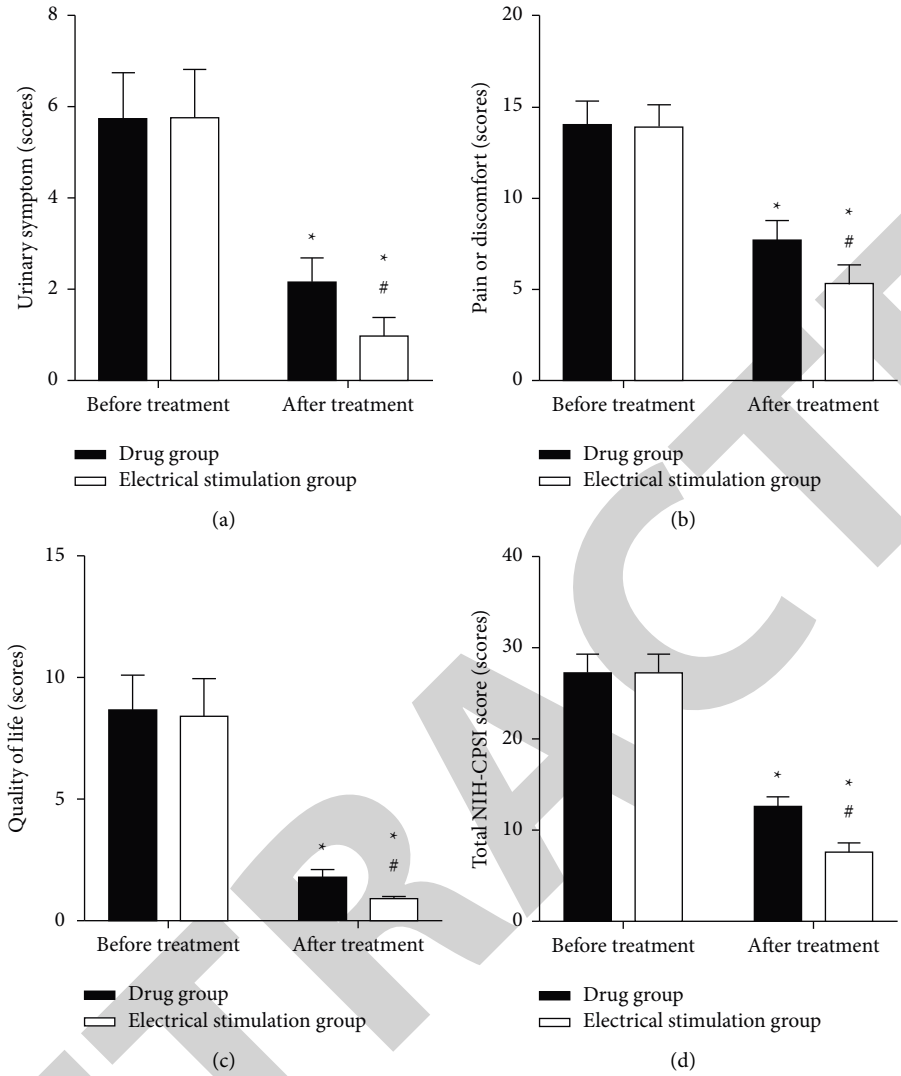

Figure 4: Comparison of NIH-CPSI scores of the two groups. Note: (a) urinary symptom scores before and after treatment in both groups. (b) Pain or discomfort scores before and after treatment in both groups. (c) Quality of life scores before and after treatment in both groups. (d) Total NIH-CPSI scores before and after treatment in both groups. Compared with the same group before treatment, $^{*}P < 0.05$; compared with the drug group after treatment, $^{\#}P < 0.05$.

Table 1: Comparison of the efficacy of the two groups (n, %).

Groups	n	Healed	Significantly valid	Valid	Invalid	Overall valid
Drug group	40	5 (12.50)	10 (25.00)	14 (35.00)	11 (27.50)	29 (72.50)
Electrical stimulation group	40	10 (25.00)	15 (37.50)	11 (27.50)	4 (10.00)	36 (90.00)
χ^2		2.051	1.455	0.524	4.021	4.021
P		0.152	0.228	0.469	0.045	0.045

In this study, we used biofeedback electrical stimulation combined with doxycycline to treat type IIIA chronic prostatitis. The results showed that both treatments with drugs and combined treatment with biofeedback electrical stimulation significantly improved lecithin bodies and white blood cells in the patients' EPS, and the improvement was greater in the electrical stimulation group, with a significant difference compared to the drug group. This suggests that the use of antibiotics combined with biofeedback electrostimulation can synergistically improve the level of inflammation in patients with type IIIA chronic prostatitis and facilitate their recovery. Antibiotics (usually quinolones, tetracyclines, and macrolides are the most common) have long been the first-line drugs used by many physicians to treat chronic prostatitis [21]. In fact, antibiotic treatment is only effective for chronic bacterial prostatitis, and frequent blind use of antibiotics may not only lead to bacterial resistance, but also cause the disease to persist, and there is still

clinical controversy as to whether there is a pathogenic infection in type IIIA chronic prostatitis, so the efficacy of antibiotic treatment cannot be guaranteed. In addition, the barrier effect of the lipid membrane of the prostatic alveolar epithelium makes it difficult for most antibiotics to concentrate in the prostate gland and therefore does not achieve an effective bactericidal effect [22]. The above causes chronic prostatitis to become one of the common refractory diseases in the urogenital system. In the current study, we combined invasive biofeedback electrical stimulation, which helps restore the pelvic floor muscles to their normal dynamic range, thereby interrupting the spasticity and pain cycle, potentially unblocking the prostatic ducts, promoting the evacuation of bacteria and necrotic material from the prostatic alveoli, improving the blood supply to the prostate, correcting urinary disturbances and accelerating the improvement of patients' symptoms, and from the limited number of cases, its recent results are reasonable.

The results also showed that the Q_{max} and Q_{ave} were significantly higher in the electrical stimulation group than in the drug group after treatment; the urinary symptom scores, pain or discomfort scores, quality of life scores, and total NIH-CPSI scores were significantly lower in the electrical stimulation group than in the drug group after treatment; and the overall effective rate was significantly higher in the electrical stimulation group than in the drug group. As seen above, the clinical efficacy of biofeedback electrical stimulation in combination with doxycycline in the treatment of type IIIA chronic prostatitis is significant compared to the use of medication alone, which is consistent with the report in the literature [23]. In addition, diet and lifestyle modification during treatment, control of the duration and intensity of treatment, as well as the patient's awareness of active participation in treatment, and compliance were also important factors influencing the efficacy of this study.

In summary, biofeedback electrostimulation combined with doxycycline in the treatment of type IIIA chronic prostatitis can synergistically improve the patient's inflammation level, urinary dysfunction, relieve pelvic floor tension myalgia and improve their quality of life, opening up new avenues for the rehabilitation of patients with type IIIA chronic prostatitis.

Data Availability

The data supporting this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Retraction

Retracted: Study on the Relationship between MMP-2, MMP-9 Gene Polymorphisms, and the Risk of Colorectal Cancer

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] S. Peng, M. Chen, C. Wang, C. Liu, K. Luo, and L. Yang, "Study on the Relationship between MMP-2, MMP-9 Gene Polymorphisms, and the Risk of Colorectal Cancer," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7357160, 7 pages, 2022.

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Research Article

Study on the Relationship between MMP-2, MMP-9 Gene Polymorphisms, and the Risk of Colorectal Cancer

Su Peng, Maoliang Chen, Chunyun Wang, Changhua Liu, Kangning Luo, and Lebin Yang

The Second Affiliated Hospital, Department of Gastrointestinal Surgery, Hengyang Medical School, University of South China, Hengyang, Hunan 421001, China

Correspondence should be addressed to Lebin Yang; lebyang@126.com

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Objective. The aim of the study is to explore the relationship between matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) gene polymorphisms and the risk of colorectal cancer. *Methods*. From January 2019 to December 2021, 308 patients with colorectal cancer in our hospital were selected to be included in the colorectal cancer group and 300 normal healthy people were included in the control group. We perform genotyping, compare the genotype frequencies between the colorectal cancer group and the control group, calculate the relationship between MMP-2 and MMP-9 gene polymorphisms and disease risk, and analyze the genotype distribution characteristics of colorectal cancer patients with different pathological stages and lymph node metastasis status. The expression levels of serum MMP-2 and MMP-9 in patients with different genotypes were compared. *Results*. The frequency of CC genotype and C gene at the MMP-2 gene−735 (C/T) locus in the colorectal cancer group was higher than that of the control group, and the frequency of TT genotype and T gene at MMP-9 gene−1562 (C/T) locus was a higher control group ($P < 0.05$). The comparison of genotype and gene frequency distribution of MMP-2 gene−1306 (C/T), −790 (T/G), and MMP-9 gene R668Q and P574R between the colorectal cancer group and the control group ($P > 0.05$); MMP-2 gene−735 (C/T) locus CC genotype and MMP-9 gene−1562 (C/T) locus TT genotype are dangerous genotypes for colorectal cancer. OR values were 1.490 (95% CI: 1.085–2.047), 1.519 (95% CI: 1.061–2.174); TNM stage III-IV, the proportion of CC genotype and TT genotype at MMP-9 gene−1562 (C/T) locus in patients with lymph node metastasis is higher than that without lymph node metastasis of TNM stage I-II patients ($P < 0.05$); MMP-2 gene in colorectal cancer patients. Serum MMP-2 levels in patients with CC genotype at 735 (C/T) locus were higher than those with CT + TT genotype, and serum MMP-9 levels in patients with TT genotype at MMP-9 gene−1562 (C/T) locus were higher CT + CC genotype patients ($P < 0.05$). *Conclusion*. The CC genotype at −735 (C/T) locus of the MMP-2 gene and the TT genotype at−1562 (C/T) locus of the MMP-9 gene are risk genotypes for the development of colorectal cancer.

1. Introduction

Colorectal cancer, also known as colorectal cancer, is one of the most common digestive tract malignant tumors in my country. The statistical results of relevant data suggest [1] that the five-year survival rate of colorectal cancer can reach 90% if it is detected early and treated early. However, many countries still lack effective means of early screening, and less than 40% of patients are diagnosed early. The occurrence, invasion, and metastasis of colorectal cancer involve multiple pathophysiological processes, such as changes in the internal environment, gene mutations, abnormal cell pathways, and immune disorders [2].

(MMPs) are a group of important enzymes that can degrade ECM and BM, which can promote the invasion and metastasis of tumor cells and the formation of new blood vessels. Twenty-six kinds of MMPs have been found to degrade almost all extracellular matrix components, and they are the research hotspots of tumor invasion and metastasis mechanisms in recent years. Matrix metalloprotein-2 (MMP-2) and matrix metalloprotein-9 (MMP-9) are members of the matrix metalloproteinases (MMPs) family, which are the main enzymes that degrade the extracellular matrix. It can promote the infiltration of tumor cells to surrounding tissues along the basement membrane and accelerate the formation and spread of tumors [3]. Due to

biological diversity, human similarities and differences, and multistage carcinogenicity, different individuals have different susceptibility to carcinogen exposure, and genetic polymorphism is an important reason for individual differences in response to environmental factors [4]. There are polymorphisms in human MMP-2 and MMP-9 genes, and their genetic variation affects the expression, structure, and function of MMP-2 and MMP-9, as well as their biological activities. Studies have found that MMP-9 is one of the proteins most closely related to colorectal malignancies in the MMP family. Its main function is to degrade collagen IV and V, gelatin, and elastic fibers in the extracellular matrix (ECM), and induce cancer cells. In the process of ECM degradation, MMP-9 releases a large amount of stored vascular endothelial growth factor (VEGF), thus inducing the formation of new blood vessels, providing nutrients for tumor cells and accelerating blood transmission. Therefore, detecting the expression of MMP-9 in tumor tissue is helpful for judging the degree of progression of colorectal cancer and has guiding significance for evaluating the prognosis. This study analyzed the relationship between MMP-2 and MMP-9 gene polymorphisms and colorectal cancer susceptibility, aiming to detect susceptible people early and take corresponding measures to reduce the risk of the disease. The report is as follows.

2. Objective and Methods

2.1. General Information. A total of 308 colorectal cancer patients in our hospital from January 2019 to December 2021 were selected and included in the colorectal cancer group. Among them, 160 were males and 148 were females; 137 cases were <60 years old and 171 cases were ≥60 years old; tumor site: 142 cases of colon, 166 cases of the rectum; degree of differentiation: 177 cases of moderate and well differentiated, 131 cases of poor differentiation; TNM Stage: 169 cases of stage I-II, 139 cases of stage III-IV, lymph node metastasis: no 186 cases, 122 cases.

The inclusion criteria were as follows: (1) primary colorectal cancer, diagnosed by pathology; (2) age ≥ 18 years old; (3) have not received radiotherapy, chemotherapy, and biological therapy before enrollment; and (4) approved by the hospital ethics committee and the patients and their families agreed to sign.

The exclusion criteria were as follows: (1) combined with other serious tumor diseases; (2) combined with autoimmune diseases; (3) combined mental illness; (4) complicated with a history of severe organic heart, liver, and lung disease; (5) received antitumor therapy such as radiotherapy and chemotherapy before enrollment; (6) pregnant and lactating women; and (7) unwilling patients. Another 300 healthy subjects were selected and included in the control group.

2.2. Methods

2.2.1. Collection of General Data. The basic clinical data of the research subjects were collected through profile questionnaires, a literature review, combined with clinical practice, and pretest corrections were performed. The survey contents included demographic characteristics, personal disease history, family history, exposure history of major risk factors in the past year (including dietary habits, physical exercise, and lifestyle), smoking (≥5 cigarettes per day and more than 1 year), alcohol consumption (>2 times/week, beer consumption >500 mL/time or rice wine consumption >250 mL/time or liquor consumption >50 mL/time), frequent consumption of spicy food (average > 3 times)/week), frequent consumption of pickled barbecued food (average > 2 times)/week), regular physical exercise (average > 4 times/week). Professionally trained and qualified investigators conduct face-to-face investigations, check in real time, and logically check the input data. If there are omissions or errors, they will be filled and corrected.

2.2.2. MMP-2 and MMP-9 Gene Polymorphism Detection. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was used to detect and detect MMP-2 (−1306 (C/T) locus, −735 (C/T) locus, −790 (T) locus/G) locus) and MMP-9 (−1562 (C/T) locus, R668Q locus, P574R locus) gene polymorphisms. (1) Specimen collection: 5 mL of fasting venous blood was drawn from the included subjects, mixed with EDTA evenly, and stored at −80°C. (2) Genomic DNA extraction: The genome was extracted using a blood genome kit (Beckman AMPurea XPDNA), DNA was extracted from leukocytes, dissolved in double distilled water, and after the purity of the samples was qualified, the samples were stored at −80°C for testing. (3) Primer design and synthesis: primer design (Sequenom, USA), primer synthesis (Chengdu Synthetic Biotechnology Co., Ltd.). Primer sequence: MMP-2: ① 1306 (C/T) locus: upstream: 5′-CTTCCTAGGCTGGTCCTTAC-3′, downstream: 5′-AGACCTGAAGAGCTAAAGACG-3′; ② -735 (C/T): Upstream: 5′-ATAGGGTAAACCTCCC-CACATT-3′, Downstream: 5′-GGTAAAATGAGGCTGAG ACCTG-3′; ③ 790 (T/G): upstream: 5′-CACTGGTGGGTG CTTCCTTTAAC-3′, downstream: 5′-TGAGATAGAAATT GGGCAAGACTGGTTTACTA-3′. MMP-9: ① 1562 (C/T): Upstream: 5′-GCCTGGCACATAGTAGGCCC-3′, Downstream: 5′-TTCCTAGCCAGCCGGCATC-3′; ② R668Q: Upstream: 5′-ACACGCACGACGTC TTCC AGTATC-3′, downstream: 5′-GGGGCATTTGT TTCCATTTCCA-3′; ③ P574R: Upstream: 5′-GCTGGACTCGGTCTTTGAGGAT C-3′, Downstream: 5′-TTGAGCCTCCTTGA CTGATGG G-3′. (4) Genotyping analysis: ① Amplification: PCR amplification reaction volume is 25 μL, including template (6 μL), upstream and downstream primers (1 μL each), 12.5 μL 2 × Taq PCR Master Mix, 4.5 μL deionized water, PCR amplification reaction parameter settings: pre-denaturation (95°C, 5 min), denaturation (95°C, 30s), annealing (62°C, 30s), extension (72°C, 1 min), 35 cycles, and final extension 72°C, 5 min. ② Genotyping and sequencing: The enzyme digestion reaction system is 20 μL, including PCR amplification products 12 μL, Hinf I endonuclease 2.0 μL, 10× restriction endonuclease buffer 2.0 μL, deionized water 4.0 μL. After 30 min in a water bath at 37°C, the digested products were electrophoresed on a 2.5% agarose gel, and their genotypes were analyzed by a gel imaging analysis system.

Table 1: Comparison of general information between the colorectal cancer group and control group.

Indexes		Number of cases (n)	Colorectal cancer group ($n = 308$)	Control group ($n = 300$)	χ^2	P
Gender	Male	310	160	150	0.231	0.631
	Female	298	148	150		
Age (year)	<60	267	137	130	0.081	0.776
	≥60	341	171	170		
BMI index (kg/m^2)	<18.5	55	30	25	0.587	0.746
	18.5–23.9	485	242	243		
	>23.9	68	36	32		
Family history of colorectal cancer	Yes	32	26	6	12.647	<0.001
	No	576	282	294		
Smoking	Yes	193	101	92	0.317	0.574
	No	415	207	208		
Drinking alcohol	Yes	107	65	42	5.289	0.022
	No	501	243	258		
Irregular diet	Yes	134	73	61	1.003	0.317
	No	474	235	239		
Regular consumption of marinated/ barbecued food	Yes	114	69	45	5.467	0.019
	No	494	239	255		
Regular consumption of spicy food	Yes	105	59	46	1.554	0.213
	No	503	249	254		
Regular physical activity	Yes	287	139	148	1.077	0.299
	No	321	169	152		

2.2.3. Detection of Serum MMP-2 and MMP-9 Levels. 4 ml of fasting venous blood was centrifuged at 3000 r/min for 10 min and the supernatant was taken. MMP-2 and MMP-9 were detected by an enzyme-linked immunosorbent assay. The microplate reader was operated according to the kit instructions.

2.3. Statistical Methods. SPSS 22.0 statistical software was used for data statistics; count data were expressed as percentages (%) and comparisons between groups were performed using the χ^2 test or Fisher's exact test. Measurement data are expressed as mean ± standard deviation. Independent sample t test comparison between groups. The logistic regression was used to analyze the risk factors for colorectal cancer. $P < 0.05$ means the difference is statistically significant.

3. Results

3.1. Comparison of General Data between the Colorectal Cancer Group and Control Group. There was no statistical difference between the colorectal cancer group and the control group in terms of gender, age, BMI index, smoking, irregular diet, and physical exercise ($P > 0.05$). The colorectal cancer group had a higher proportion of family history, drinking alcohol, and frequent consumption of pickled food than the control group ($P < 0.05$) as shown in Table 1.

3.2. Comparison of MMP-2, MMP-9 Genotype, and Frequency Distribution between the Colorectal Cancer Group and Control Group. Colorectal cancer group and control group MMP-2 and MMP-9 genes−1306 (C/T), −735 (C/T), −790 (T/G), and −1562 (C/T), R668Q, P574R. The genotype distribution of points was in accordance with the Hardy–Weinberg equilibrium ($P > 0.05$).

The CC genotype and C gene frequency of the MMP-2 gene −735 (C/T) locus in the colorectal cancer group were higher than those of the control group, and the TT genotype and T gene frequency of the MMP-9 gene −1562 (C/T) locus were higher than those of the control group. Control group ($P < 0.05$); Comparison of genotype and gene frequency distribution of MMP-2 gene −1306 (C/T), −790 (T/G) and MMP-9 gene R668Q, P574R in colorectal cancer group and control group ($P > 0.05$) as shown in Table 2.

3.3. Analysis of Risk Factors Affecting the Occurrence of Colorectal Cancer. Using a generalized model, logistic regression analysis was performed on the above items with statistically significant differences and assigned values, family history of colorectal cancer (no = 0, yes = 1), alcohol consumption (no = 0, yes = 1), frequent consumption of pickled food and grilled food (no = 0, yes = 1), MMP-2-735 (C/T) genotype (CT or TT type = 0, CC type = 1), MMP-9-1562 (C/T) genotype (CC or CT type = 0, TT type = 1). Logistic regression analysis showed that family history of colorectal cancer, alcohol consumption, frequent consumption of pickled barbecued food, MMP-2 gene −735 (C/T) locus CC genotype, and MMP-9 gene −1562 (C/T) locus TT genotype are an independent risk factors for colorectal cancer. MMP-2 gene −735 (C/T) locus CC genotype and MMP-9 gene −1562 (C/T) locus TT genotype are risk genotypes for colorectal cancer. The OR values were 1.490 (95% CI: 1.085–2.047) and 1.519 (95% CI: 1.061–2.174), respectively as shown in Table 3.

3.4. Comparison of MMP-2 and MMP-9 Genotype and Frequency Distribution in Colorectal Cancer Patients with Different Pathological Features. In TNM stage III-IV, the proportion of CC genotype at−735 (C/T) locus of MMP-2 gene and TT genotype at −1562 (C/T) locus of MMP-9 gene

Table 2: Comparison of MMP-2 and MMP-9 genotype and frequency distribution between the colorectal cancer group and control group.

Indexes	Genetic locus			*Colorectal cancer group (n = 308)*		*Control group (n = 300)*		χ^2	*P*
				Number of cases	Frequency (%)	Number of cases	Frequency (%)		
MMP-2	Genotype	−1306 (C/T)	CC	243	78.90	226	75.33	1.385	0.500
			CT	62	20.13	69	23.00		
			TT	3	0.97	5	1.67		
		−735 (C/T)	CC	206	66.88	167	55.67	9.026	0.011
			CT	86	27.92	118	39.33		
			TT	16	5.19	15	5.00		
		−790 (T/G)	TT	235	76.30	226	75.33	0.182	0.913
			TG	69	22.40	69	23.00		
			GG	4	1.30	5	1.67		
	Gene frequencies	−1306 (C/T)	C	548	88.96	521	86.83	1.295	0.255
			T	68	11.04	79	13.17		
		−735 (C/T)	C	498	80.84	452	75.33	5.401	0.020
			T	118	19.16	148	24.67		
		−790 (T/G)	T	539	87.50	521	86.83	0.121	0.728
			G	77	12.50	79	13.17		
MMP-9	Genotype	−1562 (C/T)	CC	169	54.87	205	68.33	13.764	0.001
			CT	124	40.26	90	30.00		
			TT	15	4.87	5	1.67		
		R668Q	RR	291	94.48	276	92.00	1.528	0.466
			RQ	13	4.22	19	6.33		
			QQ	4	1.30	5	1.67		
		P574R	PP	275	89.29	277	92.33	1.809	0.405
			PR	26	8.44	19	6.33		
			RR	7	2.27	4	1.33		
	Gene frequencies	−1562 (C/T)	C	452	73.38	500	83.33	13.871	<0.001
			T	154	25.00	100	16.67		
		R668Q	R	595	96.59	571	95.17	1.564	0.211
			Q	21	3.41	29	4.83		
		P574R	P	576	93.51	573	95.50	2.320	0.128
			R	40	6.49	27	4.50		

Table 3: Analysis of risk factors affecting the occurrence of colorectal cancer.

Factor	Regression coefficients (β)	Standard error	Wald χ^2 value	P value	OR value	95% CI
Family history of colorectal cancer	1.022	0.391	6.832	0.009	2.779	1.291–5.980
Drinking alcohol	0.506	0.198	6.531	0.011	1.659	1.125–2.445
Regular consumption of marinated/barbecued food	0.794	0.250	10.087	0.002	2.212	1.355–3.611
MMP-2-735 (C/T) gene type	0.399	0.162	6.066	0.014	1.490	1.085–2.047
MMP-9-1562 (C/T) gene type	0.418	0.183	5.217	0.023	1.519	1.061–2.174

Table 4: Comparison of MMP-2 and MMP-9 genotype and frequency distribution in patients with colorectal cancer with different pathological characteristics.

Clinicopathological features		Number of cases	*MMP-2* (−735(C/T))		χ^2	P	*MMP-9* (−1562(C/T))		χ^2	P
			CC ($n = 206$)	CT + TT ($n = 102$)			TT ($n = 15$)	CT + CC ($n = 293$)		
TNM Staging	Phase I-II	169	103	66	5.958	0.015	4	165	5.065	0.024
	Phase III-IV	139	103	36			11	128		
Lymph node metastasis	No	186	116	70	4.327	0.038	5	181	4.825	0.028
	Yes	122	90	32			10	112		

Table 5: Comparison of serum MMP-2 and MMP-9 levels in colorectal cancer patients with different MMP-2 and MMP-9 genotypes.

Detection indicator	*MMP-2* (−735 (C/T))		T	P	*MMP-9* (−1562 (C/T))		T	P
	CC ($n = 206$)	CT + TT ($n = 102$)			TT ($n = 15$)	CT + CC ($n = 293$)		
MMP-2	139.05 ± 32.06	119.75 ± 27.44	5.207	<0.001	—	—	—	—
MMP-9	—	—	—	—	179.18 ± 39.51	151.62 ± 31.24	3.287	0.001

in patients with lymph node metastasis was higher than that in TNM stage I-stage II patients without lymph node metastasis ($P < 0.05$) as shown in Table 4.

3.5. Comparison of Serum MMP-2 and MMP-9 Levels in Colorectal Cancer Patients with Different MMP-2 and MMP-9 Genotypes. Among 308 patients with colorectal cancer, the serum MMP-2 level in patients with CC genotype at MMP-2 gene−735 (C/T) locus was (139.05 ± 32.06) ng/mL higher than that in patients with CT + TT genotype (119.75 ± 27.44) ng/mL ($P < 0.05$). MMP-9 gene−1562 (C/T) locus patients with TT genotype serum MMP-9 level (179.18 ± 39.51) ng/mL higher than CT + CC genotype patients (151.62 ± 31.24) ng/mL ($P < 0.05$) as shown in Table 5.

4. Discussion

In the early stages of colorectal cancer, there may be no obvious clinical symptoms. With the passage of time and the continuous growth of the tumor, changes in bowel habits and symptoms of abdominal pain may occur, and further aggravation may cause systemic changes in patients [5]. With the rapid development of cellular and molecular biology research at this stage, the occurrence, development, invasion, metastasis mechanism, and treatment of malignant tumors have become a hotspot in clinical research.

MMPs are a group of zinc ion-dependent endopeptidases, which can degrade almost all extracellular matrix and vascular basement membrane, participate in embryonic development and tissue modeling, and are also proteolytic enzymes involved in tumor cell invasion and metastasis [6]. Under pathological conditions, MMPs not only break through the matrix barrier by degrading the matrix membrane and surrounding tumor matrix to promote tumor invasion and metastasis but also stimulate tumor growth and spread by promoting endothelial cell migration and angiogenesis [7]. Both MMP-2 and MMP-9 are closely related factors in the MMP family. Among them, the MMP-2 gene is located on human chromosome 16q21, secreted in the form of zymogen, and activated after hydrolysis, which can degrade the components of the intercellular matrix, and can also destroy the integrity of the basement membrane, allowing cancer cells to infiltrate the damaged extracellular space around the substrate. MMP-9 is located on chromosome 20q11.2-q13.1, can degrade extracellular matrix gelatin, various collagens, elastic fibers, etc., and plays an important role in tumor invasion and metastasis [8,9].

Sequence analysis of the MMP-2 gene showed that [10], the promoter region of the MMP-2 gene contains a variety of cis-acting elements such as AP-1, SP-1 and AP-2, suggesting that there are multiple transcription factors in the transcription process of the MMP-2 gene participation. In

this study, −1306 (C/T) and −735 (C/T) are located upstream of the MMP-2 transcriptional start point, which may alter protein expression by changing gene transcriptional activity. Studies have shown that the risk of lung cancer in Chinese people with −1306CC genotype is 1.6 times higher than that of the CT or TT genotypes, and the risk of oral squamous cell carcinoma is 2 times higher [11]. However, in this study, there was no significant difference in the genotype distribution of the −1306 (C/T) locus between the colorectal cancer group and the control group. The −1306 (C/T) locus gene polymorphism did not affect the risk of colorectal cancer. The impact mechanism of colorectal cancer is complex, and many genes are involved in the occurrence of the disease. A single gene has little effect, and different stimuli may have different effects [12]. In this study, the frequency of the CC genotype and C allele at the −735(C/T) locus in the colorectal cancer group was higher than those in the control group. Logistic regression analysis showed that the CC genotype was an independent risk factor for colorectal cancer susceptibility, and the CC gene The risk of colorectal cancer in patients with this genotype was 1.490 times that of the CT + TT genotype. To analyze the possible reasons, the T ⟶ C change at the −735 (C/T) locus in the MMP-2 promoter region destroyed the binding locus of the transcription factor Sp1, significantly reduced the promoter activity, and affected the expression level of MMP-2. This study also showed that the expression level of serum MMP-2 in individuals with CC genotype was higher than that in individuals with TT or CT genotype, further indicating that CC genotype at −735 (C/T) locus can alter gene transcriptional activity and affect MMP-2 expression, which in turn affects tumorigenesis. Some researchers found that patients with TT or CT genotype at the MMP-2 gene−735 locus in small cell lung cancer had longer survival and a lower risk of death than those with CC genotype [13]. In this study, the relationship between the −735(C/T) locus genotype and the clinicopathological characteristics of colorectal cancer was compared and analyzed. The results showed that the −735(C/T) locus had a higher proportion of patients with high clinical stage and lymph node metastasis with CC genotype. Indicating that the −735(C/T) locus CC genotype increases the risk of colorectal cancer disease development and metastasis. At the same time, this study showed that MMP-2 gene−790 (T/G) was not associated with the risk of colorectal cancer.

In addition, this study selected MMP-9 gene −1562 (C/T), Q279R, P574R, a total of 3 SNP loci, to study in the colorectal cancer group and the control group. Nascimento et al. [14] pointed out that MMP-9−1562 (C/T) gene polymorphism is associated with aortic aneurysm, colorectal cancer, lung cancer and so on. This study also showed that the TT genotype frequency and T allele frequency of the MMP-9 gene −1562 (C/T) locus in the colorectal cancer group were higher than those in the control group, which was consistent with the above research results. With genotype CC and CT as reference, the adjusted OR (95% CI) of genotype TT was 1.519 (95% CI: 1.061–2.174), which can be considered as an MMP-9 gene −1562 (C/T) locus polymorphism, which is related to the occurrence of colorectal cancer, and TT genotype may increase the risk of colorectal cancer susceptibility. Among colorectal cancer patients, the frequency of the TT genotype was higher in patients with stage III-IV than in patients with stage I-II, and it was found that TT genotype carriers were more prone to lymph node metastasis than CC + CT genotypes. The study of Walter et al. [15] showed that tumor formation, metastasis, and invasion were inhibited in MMP-9-deficient transgenic mice. After transplantation of MMP-9-expressing bone marrow cells, tumor formation and invasiveness were restored. This shows that MMP-9 contributes to tumor cell invasion and metastasis. In this study, the differences in serum MMP-9 expression levels in colorectal cancer patients with different genotypes at the −1562 (C/T) locus were compared. The results showed that the expression level of serum MMP-9 in patients with TT genotype was higher than that of CT + CC genotype, and the change of C ⟶ T at −1562 (C/T) locus could promote the expression of MMP-9 and mediate the occurrence and development of colorectal cancer. In this study, a case-control study method was used to analyze the relationship between the MMP-9 gene P574R polymorphism and R668Q polymorphism and the risk of colorectal cancer. The results showed that P574R and R668Q gene polymorphisms were not associated with the risk of colorectal cancer.

The disadvantages of this study are that race was not excluded as a confounder, the results of this study may not be generalizable to patients outside the region, and clinical data such as patient survival and sensitivity to chemoradiotherapy were not analyzed. The follow-up sample will be expanded to allow for further follow-up studies.

In conclusion, MMP-2 gene −735 (C/T) locus CC genotype and MMP-9 gene −1562 (C/T) locus TT genotype are risk genotypes for the occurrence and development of colorectal cancer. The detection of related gene polymorphisms can detect the susceptible population of colorectal cancer early and take corresponding intervention measures as soon as possible to reduce the risk of the disease.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author.

Ethical Approval

This study was approved by the ethics committee of our hospital.

Conflicts of Interest

The authors declare that they have no conflicts of Interest, financially or otherwise.

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Retraction

Retracted: Clinical Curative Effects and Influencing Factors of Uterine Artery Chemoembolization Combined with Uterine Curettage Treating with Cesarean Scar Pregnancy Patients

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] K. Yu and H. Zhou, "Clinical Curative Effects and Influencing Factors of Uterine Artery Chemoembolization Combined with Uterine Curettage Treating with Cesarean Scar Pregnancy Patients," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7785573, 6 pages, 2022.

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Research Article

Clinical Curative Effects and Influencing Factors of Uterine Artery Chemoembolization Combined with Uterine Curettage Treating with Cesarean Scar Pregnancy Patients

Kewen Yu[1] **and Haifeng Zhou**[2]

[1]*Department of Gynecology, Ningbo Women and Children's Hospital, Ningbo 315010, Zhejiang, China*
[2]*Department of Obsterics and Gynecology, Zhuji Maternal and Child Health Hospital, Zhuji 311800, Zhejiang, China*

Correspondence should be addressed to Haifeng Zhou; 13588571289@163.com

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Objective. To explore the clinical curative effects of uterine arterial chemoembolization (UACE) combined with uterine curettage treating with cesarean scar pregnancy (CSP) patients, and analyze the influencing factors of postoperative efficacy. *Methods*. A total of 86 patients with CSP from January 2019 to December 2021 in the Gynecology ward of our hospital were selected and divided into the control group ($n = 43$) and the observation group ($n = 43$) according to the random number method. The control group was treated with an injection of methotrexate (MTX) combined with uterine curettage, and the observation group was treated with UACE combined with uterine curettage. Two months after the operation, the therapeutic effect, cesarean scar mass, and β-human chorionic gonadotropin (β-HCG) level were observed and compared between the two groups. The general conditions of patients in two groups were recorded, and the influencing factors of surgical efficacy in patients were analyzed using univariate analysis and a multivariate logistic regression model. *Results*. After treatment, the total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$). The volume of intraoperative blood loss, hospitalization period, menstrual recovery time, mass disappearance time, and β-HCG recovery time of the observation group were lower than those of the control group ($P < 0.05$). Single factor analysis showed that the number of cesarean sections, gestational age, the largest diameter of the gestational sac, the thinnest muscular layer, and the type of CSP can all affect postoperative efficacy ($P < 0.05$). Multivariate logistic analysis showed that the gestational age, a maximum diameter of a gestational sac, the thinnest muscular layer, and the type of CSP were independent factors influencing the postoperative efficacy of the patients ($P < 0.05$). *Conclusion*. UACE combined with uterine curettage for CSP can significantly improve the curative effect, reduce intraoperative bleeding, and improve the recovery time of postoperative-related symptoms. The gestational age of the patient, the maximum diameter of the gestational sac, the thinnest muscular layer, and the type of CSP can independently affect the therapeutic effect of CSP patients. Fully understanding the high-risk factors that affect the efficacy of treatment of CSP, timely preventive measures, and targeted care can effectively improve the prognosis and reduce the risk of CSP.

1. Introduction

Cesarean scar pregnancy (CSP) refers to the growth and development of fertilized eggs in the scar of a previous cesarean section, which belongs to a special kind of ectopic pregnancy. With the opening of the second child and the maturity of cesarean section in China, the incidence of CSP is increasing year by year [1, 2]. Currently, the incidence of CSP accounts for about 0.5% of the total number of pregnancies. Because the myometrium of cesarean section scar is weak and the blood supply is rich, if the diagnosis and treatment of cesarean section scar pregnancy cannot be made in time, the patient will have the risk of uterine rupture and massive hemorrhage, which will seriously endanger the

life of the patient [3, 4]. Currently, the methods of treating cesarean scar pregnancy include total hysterectomy, methotrexate (MTX) combined with uterine clearance, and uterine artery chemoembolization (UACE) combined with uterine clearance. [5]. Among many methods, UACE is an interventional therapy that injects an embolic agent into a blood vessel under ultrasound, CT, or X-ray guidance to reduce massive hemorrhage in a patient [6, 7]. This study investigated the efficacy of UACE combined with uterine curettage in the treatment of cesarean scar pregnancy, and the related factors affecting the efficacy. The specific report is as follows.

2. Materials and Methods

2.1. General Information. The clinical data of 86 patients with cesarean section scar pregnancy who were hospitalized in the gynecological ward of our hospital from January 2019 to December 2021 were retrospectively collected. They were divided into the control group and the observation group by random number method, with 43 cases in each group. In the control group, the age was 20–35 years old, with an average of (26.95 ± 3.42) years old; 2^{nd} pregnancy times (1~4); 26 cases of CSP Type 1 and 17 cases of CSP Type 2. In the observation group, the age was 19–36 years old, with an average of (27.25 ± 4.01) years old; 2^{nd} pregnancy times (1~3); 24 cases of CSP Type 1 and 19 cases of CSP Type 2. There was no statistically significant difference in general data such as age and pregnancy between the two groups, and they were comparable ($P > 0.05$).

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria. Inclusion criteria were as follows: patients who meet the diagnostic criteria of CSP (the ultrasonic diagnosis showed that there was no fetal sac in the normal position of the uterine cavity, and the fetal sac appeared in the lower part of the uterine cavity, and the fetal sac locally protruded to the cesarean section scar site, or it was directly located in the cesarean section scar diverticulum) [8]; under the age of 40; patients with type I or type II CSP (both diagnosed and classified by a gynecologic three-dimensional ultrasound performed by an experienced sonographer); patients with serum β-human chorionic gonadotropin (β-HCG) ≥ 10000 mIU/mL; the vital signs are stable; the liver and kidney function and coagulation function are normal; and no history of allergy to iodinated contrast media and methotrexate.

2.2.2. Exclusion Criteria. Exclusion criteria were as follows: patients with type III CSP or type I CSP with a course of less than 8 weeks; Patients with serum β-HCG < 10000 mIU/ml; patients with vaginal bleeding, unstable vital signs, or shock before treatment; or patients with severe liver and kidney function and coagulation function; Patients with contraindications for UACE.

2.3. Research Methods. The control group was treated with MTX combined with ultrasound-guided uterine curettage. Perform ultrasound-guided intravaginal or intra-abdominal injection of MTX, 50 mg/m^2 each time, and review the blood β-HCG after 5 days. If the increase or decrease of this index is less than 15%, MTX 50 mg/m^2 is injected again on the 6^{th} day. After that, the blood β-HCG and ultrasonography were reviewed every 5 days, and the uterus was cleared under the guidance of ultrasonography after the blood β-HCG was less than 10000 mIU/ml.

The observation group was treated with UACE combined with ultrasound-guided uterine curettage. UACE was performed, and lidocaine was used to locally anesthetize the right femoral artery area. After a successful percutaneous puncture of the right femoral artery, a 5F-uterine artery catheter was placed. Under digital subtraction angiography, guided by a coaxial guide wire, selective after intubation to the uterine artery, MTX (total dose of 50 mg/m^2) was first perfused, and then gelatin sponge particles (> 560–710 μm in diameter) were used to embolize the uterine artery. Ultrasound-guided uterine curettage was performed about 24 hours after embolization (Figures 1–4).

2.4. Observation Indicators. Clinical data of all patients were collected retrospectively (including the patient's age, cesarean section times, intraoperative blood loss, postoperative hospital stay, menstrual return to normal time, mass disappearance time, β-HCG recovery time, time from the last cesarean section, gestational week, diameter, thinnest muscle layer, CSP type, initial β-HCG level, uterine fibroids, fetal heartbeat, maximum gestational sac, and other data). The size of the cesarean section scar mass and β-HCG level were checked after the operation.

CSP classification: Type I: The thinnest part of the myometrium at the scar is more than 0.3 cm; Type II: The thinnest part of the myometrium at the scar is less than 0.3 cm but > 0.1 cm, and the fetal sac or mass is not protruding or slightly convex toward the bladder. Type III: The gestational sac was completely implanted in the myometrium at the site of the uterine scar and protruded outward toward the bladder, and the myometrium between the gestational sac and the bladder was markedly thinner, or even absent, with a thickness of ≤ 3 mm.

2 months postoperative efficacy evaluation criteria. Significant effect: the cesarean scar mass disappeared, and β-HCG returned to normal without complications. Effective: the cesarean section scar mass was decreased, and β-HCG gradually returned to normal, but the patient still had complications such as bleeding (> 200 ml). Invalid: The size of cesarean scar mass and β-HCG level did not change significantly. The patient had severe complications such as hemorrhage and uterine perforation and required laparotomy, laparoscopy, or vaginal surgery. Total effective rate = (Significant effect cases + Effective cases)/Total number of cases × 100%.

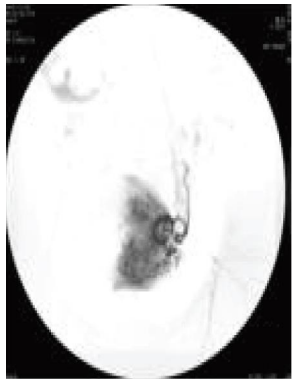

Figure 1: The left uterine artery is slightly thickened, the spiral artery can be seen extending upward, and the uterine body is congested.

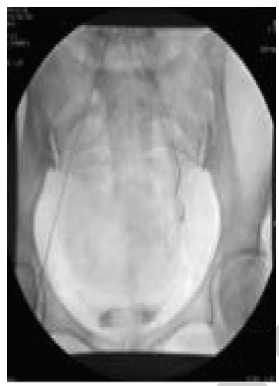

Figure 2: Complete embolization of left uterine artery.

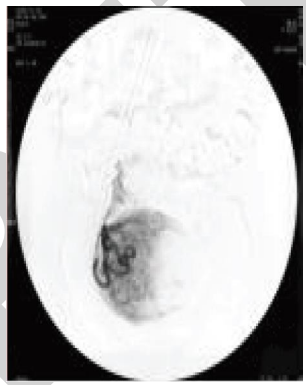

Figure 3: The right uterine artery is slightly thickened, the spiral artery can be seen extending upward, and the uterine body is congested.

2.5. Statistical Methods. We used SPSS 22.0 software to process the data analysis, and measurement data were expressed as mean ± standard deviation ($\overline{x} \pm s$). Multigroup comparisons were performed using analysis of variance, and pairwise comparisons were performed using a t-test. Enumeration data were expressed as (%), and differences between groups were compared by the χ^2 test. A logistic regression model was used for multivariate analysis. The test level was $\alpha = 0.05$, and $P < 0.05$ indicates a statistically significant difference.

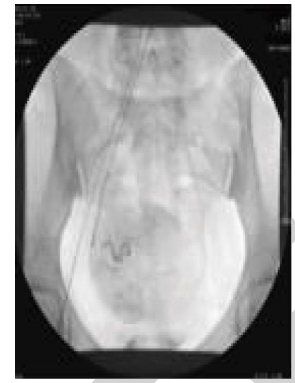

Figure 4: Right uterine artery completely embolized.

3. Results

3.1. UACE Angiography. 3.2. Comparison of Postoperative Curative Effects between the Two Groups of Patients. After the operation, the total effective rate of patients in the observation group was 95.35%, which was higher than that of the control group (74.42%), and the difference was statistically significant ($P < 0.05$), as shown in Table 1.

3.3. Comparison of Intraoperative Bleeding and Postoperative Symptom Improvement Time between the Two Groups. After the operation, the volume of intraoperative blood loss, hospitalization period, menstrual recovery time, mass disappearance time, and β-HCG recovery time in the observation group were all lower than those in the control group, and the differences were statistically significant ($P < 0.05$), as shown in Table 2.

3.4. Univariate Analysis of Postoperative Efficacy in CSP Patients. Univariate analysis showed that the number of cesarean sections, gestational age, the maximum diameter of a gestational sac, the thinnest muscle layer, and the type of CSP could affect the postoperative curative effect of patients, and the differences were statistically significant ($P < 0.05$), as shown in Table 3.

3.5. Multivariate Analysis of Postoperative Curative Effects in CSP Patients. Multivariate Logistic analysis showed that gestational age, the maximum diameter of a gestational sac, the thinnest muscle layer, and the type of CSP were independent influencing factors of postoperative efficacy ($P < 0.05$), as shown in Tables 4-5.

4. Discussion

CSP refers to the implantation of a fertilized egg in the scar formed by the uterus after cesarean section, which is a special kind of ectopic pregnancy. At present, the etiology

Table 1: Comparison of postoperative efficacy between the two groups of patients (n, %).

Group	Significant effect	Effective	Invalid	Total efficiency (%)
Control group ($n = 43$)	30	2	11	74.42 (32/43)
Observation group ($n = 43$)	38	3	2	95.35 (41/43)
χ^2 value				7.372
P Value				0.025

Table 2: Comparison of intraoperative bleeding and postoperative symptom improvement time between the two groups (n, $\overline{x} \pm s$).

Group	The volume of intraoperative blood loss (ml)	Hospitalization period (d)	Menstrual recovery time (d)	Mass disappearance time (d)	β-HCG recovery time (d)
Control group ($n = 43$)	66.42 ± 7.54	10.01 ± 4.55	40.02 ± 5.39	65.10 ± 8.45	60.35 ± 28.32
Observation group ($n = 43$)	39.26 ± 7.29	7.96 ± 1.32	36.96 ± 3.52	60.36 ± 6.11	46.88 ± 16.77
t value	16.982	2.837	3.117	2.981	2.684
P Value	0.000	0.006	0.003	0.004	0.009

Table 3: Univariate analysis of postoperative efficacy in patients with cesarean section scar pregnancy (n, %).

Influencing factors		Number of cases ($n = 86$)	Significant effect or effective ($n = 73$)	Invalid ($n = 13$)	χ^2 value	P Value
Age (year)	20~30	39	36	3	3.065	0.080
	30~40	47	37	10		
The number of cesarean sections (times)	≤1	54	50	4	5.653	0.017
	>1	32	23	9		
Time since last cesarean section (years)	≤5	39	31	8	1.620	0.203
	>5	47	42	5		
Gestational age (week)	≤8	48	45	3	6.655	0.010
	>8	38	28	10		
Maximum diameter of the gestational sac (cm)	≤3.6	61	55	6	4.560	0.033
	>3.6	25	18	7		
Thinnest muscle layer (cm)	≤0.21	36	27	9	4.714	0.030
	>0.21	50	46	4		
Type of CSP	Type 1	50	47	3	7.736	0.005
	Type 2	36	26	10		
Initial β-HCG (mIU/ml)	≤30000	37	33	4	0.938	0.333
	>30000	49	40	9		
Uterine fibroids	Yes	38	32	6	0.024	0.877
	No	48	41	7		

Table 4: Multifactor analysis assignment.

Influencing factors	Assignment
The number of cesarean sections	"≤1" = "0"; ">1" = "1"
Gestational age	"≤8" = "0"; ">8" = "1"
Maximum diameter of a gestational sac	"≤3.6" = "0"; ">3.6" = "1"
Thinnest muscle layer	"≤0.21" = "0"; ">0.21" = "1"
Type of CSP	"Type 1" = "0"; "type 2" = "1"

of CSP is still unclear, which may be related to endometrial injury or poor healing of uterine incision caused by surgical stimulation such as curettage and cesarean section [9, 10]. There was no significant difference in serum β-HCG concentration between cesarean section scar pregnancy patients and normal pregnancy, therefore, b-ultrasound is a commonly used method to check the CSP, and can also be used to evaluate the patient's postoperative recovery. The muscle layer at the cesarean section scar is weak and has poor contractility, and the gestational sac grows aggressively toward the blood vessel-rich muscle layer, which can easily damage the blood vessels and cause massive bleeding and even uterine rupture [11–13]. Therefore, early diagnosis and timely treatment of CSP are very important.

The results of this study showed that the total effective rate in the observation group was higher than that in the control group, and the intraoperative blood loss, postoperative hospital stay, menstrual recovery time, mass disappearance time, and β-HCG recovery time in the observation group were all lower than those in the control group. The reason is that UACE is an interventional therapy, and the risk of massive hemorrhage for patients is reduced by injecting an embolic agent into the uterine arteries. In

Table 5: Multivariate analysis of postoperative recovery in CSP patients (*n*, %).

Influencing factors	B	SE	Walds	Df	Sig	Exp (B)
The number of cesarean sections	0.811	0.601	1.821	1	0.177	2.250
Gestational age	0.474	0.241	3.885	1	0.049	0.622
Maximum diameter of a gestational sac	1.117	0.272	16.920	1	0.000	0.327
Thinnest muscle layer	0.553	0.242	4.830	1	0.028	1.704
Type of CSP	0.592	0.244	5.868	1	0.015	0.553

addition, UACE combined with uterine curettage has many advantages, such as simple operation, promotion of patients' postoperative recovery, and maintenance of patients' fertility. This method of treatment can greatly improve the efficacy of the treatment of CSP, effectively improve the prognosis, and is an acceptable treatment method for patients [14, 15].

The results of this study showed that the number of cesarean sections, gestational age, the largest diameter of the gestational sac, the thinnest muscle layer, and the type of CSP could affect the postoperative efficacy of the patients. It is an independent factor affecting the postoperative efficacy of patients. The reason for this is that with the increase of gestational age, the pregnant uterus of patients with CSP gradually expanded, resulting in the reduction of muscle contraction force in the scar during cesarean section, and further leading to the occurrence of vaginal bleeding in patients, which affected the therapeutic effect of patients [16]. The maximum diameter of the patient's gestational sac increases, which leads to a more abundant blood supply around the gestational sac, which affects the effect of an intervention. The uterus also increases with the increase of the maximum diameter of the gestational sac, so that the contraction ability of the muscle layer at the cesarean section scar is further improved. It increases the risk of massive bleeding and uterine rupture, which is not conducive to the treatment of CSP patients [17, 18]. The thinner the thinnest muscle layer at the cesarean section scar, the lower the uterine contractility, and the easier it is for the gestational sac to penetrate the thinnest muscle layer of the uterine scar and enter the abdominal cavity when the muscle layer invasively grows, resulting in uterine rupture, which is not conducive to the patient's health and treatment efficacy [19, 20]. There are two types of CSP patients: endogenous type (CSP Type 1) and exogenous type (CSP Type 2). The gestational sac tissue of exogenous CSP patients grows aggressively toward the deep myometrium due to insufficient blood supply at the scar, which may cause a uterine rupture in the first trimester. Because the gestational sac in exophytic CSP patients invades and grows deep into the myometrium and is closely adhered to the uterus, the gestational sac is not easily separated from the uterus, and incomplete uterine curettage is prone to occur during uterine curettage [21, 22]. In addition, all patients have observed the development of their condition 6 months after treatment, no obvious adverse reactions were found in the treatment and postoperative follow-up of the two groups of patients in this study, indicating that UACE combined with curettage had high safety.

In conclusion, UACE combined with uterine curettage in the treatment of CSP can significantly improve the curative effect, reduce intraoperative bleeding, and improve the recovery time of postoperative-related symptoms. The gestational age, the largest diameter of the gestational sac, the thinnest muscle layer, and the type of CSP can independently affect the therapeutic effect of CSP patients. Fully understanding the high-risk factors affecting the efficacy of the treatment of CSP, timely preventive measures, and targeted nursing can effectively improve the prognosis and reduce the risk of CSP.

Data Availability

The data can be obtained from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Research Article

A Comparative Study on the Clinical Efficacy of Stereotaxic Catheter Drainage and Conservative Treatment for Small and Medium Amount Intracerebral Hemorrhage in the Basal Ganglia

Junhui Yuan, Yansong Lv, Shaowei Zhang, Yongpeng Li, and Xi Jiao

Department of Neurosurgery, Sanmenxia Central Hospital, Sanmenxia, Henan 472000, China

Correspondence should be addressed to Junhui Yuan; 15238963360@163.com

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The incidence rate and fatal disability rate of cerebral hemorrhage increase year by year. At present, most patients with a hematoma volume of ≤20 mL are treated conservatively by internal medicine. With the development of the stereotactic technique, it has been widely used for the treatment of cerebral hemorrhage in clinics. This study compared the clinical differences between stereotactic surgery and conservative treatment for small- and medium-sized cerebral hemorrhages. The results show that stereotactic hematoma evacuation is more effective than conservative treatment in the treatment of medium and small intracerebral hemorrhages in the basal ganglia. It can accelerate the resolution of hematoma and improve the neurological function and quality of life of patients, which is worthy of clinical promotion and application.

1. Introduction

Spontaneous intracerebral hemorrhage (SICH) refers to intracerebral hemorrhage caused by spontaneous rupture of large and small arteries, veins, and capillaries of the brain due to various reasons under nontraumatic factors [1, 2]. Hypertension is the most common predisposing factor for SICH, and the risk of SICH disease in hypertensive patients increases with age [3]. SICH with a hematoma volume of less than 30 mL is considered to be a moderate-to-small-volume SICH. In the past, it was considered that surgery was not required for small and medium-sized SICH, and conservative medical treatment was the first treatment option for patients [4]. However, more and more data showed that although patients with small- and medium-sized SICH had low blood loss and low mortality, the neurological function of the patients will be significantly damaged, and the recovery of neurological function of patients with conservative medical treatment is poor [5, 6]. Therefore, some scholars have suggested that for small- and medium-sized SICH diseases, auxiliary surgical schemes can be adopted, such as small bone window craniotomy, craniotomy, and endoscopic surgery.

Brain stereotactic technology has been put forward for more than 100 years. It has experienced a long period from experiment to instrument setting to clinical application, and its development tends to be mature. Stereotaxic technology includes frame positioning technology, frameless brain stereotaxic technology, cube orientation technology, and neuronavigation technology. Previous studies have shown that the injury caused by open surgery might offset the efficacy of hematoma removal to varying degrees, but hematoma removal based on stereotaxic techniques may be more helpful in improving the prognosis [7, 8]. Recently, stereotaxic technology has been used in the treatment of SICH, known as stereotactic catheter drainage [9, 10]. In the present study, 146 patients with small and medium-sized cerebral hemorrhages in the basal ganglia were selected, which was designed to compare the clinical effects of stereotactic catheter drainage and conservative drug therapy in patients with small and medium amounts of intracerebral hemorrhage in the basal ganglia.

2. Methods and Materials

2.1. Patients and Grouping. A total of 146 patients with small- and medium-sized cerebral hemorrhages in the basal ganglia who were admitted to our study from January 2019 to December 2021 were included. According to different treatment protocols, the patients were divided into 2 groups, control group and research group (73 patients in each group). There was no statistically significant difference in the general data between the two groups, and they were comparable ($P > 0.05$). All studies in the present study were approved by the hospital ethics committee, and patients and their families voluntarily signed the hospital-related informed consent.

2.2. Inclusion Criteria. (1) Age ≥18 years old; (2) small and medium amount intracerebral hemorrhage in the basal ganglia by head CT; (3) no previous history of SICH; (4) no anticoagulants were taken 2 weeks before joining the group; (5) patients with hypertension history; (6) and patients admitted to hospital within 24 hours after symptoms appeared.

2.3. Exclusion Criteria. (1) Patients with other surgical contraindications such as coagulation disorders; (2) combined with other serious diseases, such as malignant tumor, liver, kidney, or other organ dysfunctions; (3) history of mental illness, intellectual disability, or communication impairment; (4) history of taking anticoagulants or immunosuppressants; (5) history of traumatic brain injury, cerebrovascular malformation, cerebral aneurysm, and stroke; (6) alcohol addiction or drug addiction; and (7) coexisting systemic diseases, such as autoimmune diseases, chronic infectious diseases, or uremia.

2.4. Treatment Protocol. Patients in the control group received conservative drug treatment, including symptomatic treatment such as oxygen inhalation, blood pressure stabilization, dehydration, and prevention of bedridden-related complications.

Patients in the research group received stereotaxic surgery. In brief, patients were placed in a supine position before the operation and given local anesthesia after disinfection of the surgical site. The headframe was installed, and then a CT examination of the head was performed. The center of the hematoma or the surgical target was determined on the computer, and the X, Y, and Z values were calculated. After the location of the surgical incision is determined, the dura is drilled and incised. An intraoperative stereotactic navigation device was installed, and the drainage tube was placed according to the procedure. During the operation, 5–15 mL of clot was slowly aspirated. After surgery, 30,000 units (5 mL) of urokinase were injected into the hematoma cavity to provide adequate drainage of the hematoma. Finally, a reexamination of the head CT is performed and the drainage tube is removed within 1 to 3 days after surgery.

2.5. Baseline Data Collection. Collect the clinical data of patients through the hospital electronic medical record system, including gender, age, course of hypertension, hematoma volume, GCS score of admission, location of hematoma, comorbidities, and degree of paralysis of the limb.

2.6. Hematoma Volume Measurement. At admission and 1, 3, 7, 14, and 30 days after treatment, all patients underwent head CT examination, and the largest high-density area of the CT section was selected to measure the longest and widest diameters of the hematoma. Brain hematoma calculation formula: hematoma volume (mL) = 1/2 × longest diameter (cm) × widest diameter (cm) × CT slice thickness (cm) x number of CT slices [11].

2.7. Observation Indicators

(1) Clinical prognosis. Length of hospital stay, number of complication cases, diseased limb muscle strength on 30th day after treatment (level 4–5 on the Lovett scale), and the Glasgow outcome scale (GOS) on 90th day after treatment [12].

(2) Neurological assessment. We used the National Institute of Health Stroke Scale (NIHSS) [13] and the modified ranking rating scale (mRS) [14] to evaluate the neural function of patients before treatment and at 7, 14, 30, and 90 days after treatment. Among them, the NHISS score ranged from 0 to 42, and the higher the score, the more serious the nerve defect was. The maximum score of mRS was 6 points, and 0 points meant no symptoms at all. A score of 1 indicates that, despite the symptoms, the insured has no obvious disability and is able to complete all the frequently engaged work and activities. 2 points mean slightly disabled, unable to complete all work and activities, but able to handle personal affairs without the help of others. 3 points indicate moderate disability and the need for help from others, but no help when walking. 4 points represent severe disability, inability to walk without the help of others, and inability to take care of oneself. A 5 indicates severe disability, bedridden, incontinence, need for continuous care, and a need to be looked after more than 24 hours a day. 6 points mean dead.

(3) Daily life recovery. Before treatment and at 7, 14, 30, and 90 days after treatment, we used the Modified Barthel Index (MBI) to evaluate the patient's functions of daily living and activities [15]. The highest score of the MBI scoring criteria was 100 points, with 61–99 points indicating mild need dependence, 41–60 points indicating moderate dependence, and ≤40 points indicating severe dependence.

2.8. Statistical Analysis. Data in the present study were analyzed by SPSS 20.0 software (SPSS Inc., Chicago, USA). The measurement data were expressed as ($\overline{x} \pm S$) and the t-test was performed. The count data were expressed as

percentage (%) using the χ^2 test, and $P < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1. Baseline Data. The baseline data including gender, age, course of hypertension, hematoma volume, GCS score of admission, location of hematoma, comorbidities, and degree of paralysis of the limb between the two groups were comparable with no significant difference (Table 1).

3.2. Clinical Outcome. During 90-dayfollow-up, there were no deaths in two groups. At the same time, the time of hematoma vanish, the number of complication cases and the time of hospital stay in the research group were significantly lower than those in the control group ($P < 0.05$), while the number of cases where the degree of paralysis of the limb on the diseased side recovered to level 5 on the 30th day and the number of GOS scores >5 on the 90th day in the research group were all significantly higher than those in the control group ($P < 0.05$) (Table 2).

3.3. Hematoma Volume. Patients in two groups were followed up with head CT at 1, 3, 7, 14, and 30 days after treatment to calculate the hematoma volume by the Tada formula. As shown, the hematoma of the patients in the research group began to drain 3 days after treatment, while that in the control group was 30 days after treatment. In conclusion, the hematoma volume in the control group was significantly higher than that in the research group on days 1, 3, 7, 14, and 30 after treatment ($P < 0.05$) (Table 3).

3.4. Neurological Score. Patients in two groups were followed up on neural function using the NIHSS scale and the mRS scale before treatment and at 7, 14, 30, and 90 days after treatment. As shown, there was no significant difference in the NIHSS score and the mRS score before treatment between the control group and the research group ($P < 0.05$), while the scores of NIHSS and mRS in the research group at 7, 14, 30, and 90 days after treatment were all significantly lower than those in the control group ($P < 0.05$) (Table 4).

3.5. Daily Life Recovery. Patients in two groups were followed up on activities of daily living and activities using the MBI scale before treatment and at 7, 14, 30, and 90 days after treatment. As shown, there was no significant difference in MBI scores before treatment between the control group and the research group ($P > 0.05$), while MBI scores in the research group at 7, 14, 30, and 90 days after treatment were all significantly higher than those in the control group ($P < 0.05$) (Table 5).

4. Discussion

Intracerebral hemorrhage has the characteristics of "high morbidity, high recurrence rate, high disability rate, and high fatality rate." The basal ganglia area is a relay station for nerve fiber conduction and is also the spontaneous brain. At present, it is considered that a hematoma volume of >30 ml is the indication for craniotomy, while for patients with a hematoma volume of ≤30 ml, conservative drug therapy is generally used [16]. However, previous studies have shown that patients with 15–30 mL of cerebral hemorrhage in the basal ganglia region may develop hemiplegia and aphasia [17]. Because the hematoma cannot be removed in time during the conservative treatment, the brain tissue and nerve fiber bundle will be compressed for a long time, leading to irreversible changes in the nerve fiber bundle [18]. At the same time, the existence of compression will also cause cell ischemia and hypoxia, secondary pathological changes and necrosis, and toxic effects on the surrounding cells. In addition, the decomposition of blood produces hemosiderin, which aggravates the edema of surrounding tissues and aggravates the compression, further aggravating the fiber bundle injury [19]. Therefore, after conservative treatment, it is difficult for such patients to restore their motor and language functions to the expected effects, which will impose a great burden on the family economy and life in the future. The persistent existence of hematoma is the starting factor of this series of vicious circles. Only when the etiology disappears will the vicious circle be broken and the prognosis of patients will be improved.

Through clinical practice, it is generally believed that the advantages of stereotactic hematoma evacuation are as follows: ① it is simple to operate and quick to operate. ② The localization is accurate, and the application range is wide. The inserted drainage tube can accurately reach any target set before surgery. ③ The patients with hypertensive intracerebral hemorrhage are mostly middle-aged and elderly people, and most of them are complicated with heart, lung, diabetes, and other diseases, which will seriously affect the life and quality of life of the patients after the operation [20]. However, this technique can be operated under local anesthesia. The preparation time and operation time are short, with no obvious contraindication. The trauma is small. Hematoma drainage is thorough when urokinase is used to dissolve hematoma. The patient has a short bed rest time, rapid recovery, and few complications. Additional brain injury caused by surgical striking and repeated traction caused by the traditional craniotomy operation can be avoided. ④ After successful stereotactic catheterization, 60% of the hematoma was suctioned out, and the disease would be relieved. In line with the diagnosis of hypertensive intracerebral hemorrhage, the hematoma should be quickly and effectively removed to reduce secondary brain injury, which is conducive to the rescue of early patients with cerebral hernia [21]. ⑤ A single catheter placement can be used for multiple drug injections, irrigation, and drainage, and the position and depth of the catheter placement can be adjusted according to the extraction of hematoma. Repeated puncture and catheterization are avoided, and the probability of intracranial infection and rebleeding is reduced. This study found that in the research group treated with stereotactic surgery, the average disappearance time of hematoma, the number of complications, and hospital stay were significantly lower than those in the control group. The

Table 1: Baseline data of two groups.

Baseline data	Control group ($n = 73$)	Research group ($n = 73$)	t/χ^2	P
Gender (n)				
Male	43	46	0.259	0.611
Female	30	27		
Age (years)	63.58 ± 9.38	65.24 ± 8.13	0.628	0.327
Course of hypertension (years)	7.03 ± 2.15	7.08 ± 2.08	1.124	0.105
Hematoma volume (mL)	18.91 ± 4.02	18.19 ± 3.34	0.956	0.297
GCS score of admission				
3–12	53	52	0.034	0.854
13–15	20	21		
Location of hematoma				
Thalamus	23	21	0.559	0.906
Outside the putamen	30	33		
Inner side of putamen	12	13		
Caudate nucleus	8	6		
Comorbidities (n)				
No	31	27	0.535	0.765
Diabetes	9	11		
Coronary heart disease	33	35		
Upper extremity muscle strength (n)				
Level 1	18	15	0.353	0.838
Level 2	20	21		
Level 3	35	37		
Lower extremity muscle strength (n)				
Level 1	15	12	0.536	0.755
Level 2	21	20		
Level 3	37	41		

Note. GCS, Glasgow Coma Scale.

Table 2: Comparison of observation indicators related to clinical outcomes between the two groups.

Observation indicators	Control group ($n = 73$)	Research group ($n = 73$)	t/χ^2	P
Hematoma vanish (days)	24.62 ± 4.35	3.36 ± 1.57	29.328	<0.001
Complication occur (n)	20	9	5.207	0.023
Hospital stay (days)	23.31 ± 3.81	17.34 ± 4.95	13.567	<0.001
Diseased limb muscle strength at 30th day (level 4–5) (n)	29	47	8.892	0.003
GOS score >5 at 90th day (n)	45	60	7.631	0.006

Note. GOS, Glasgow Outcome Scale.

Table 3: Comparison of hematoma volume at different times between the two groups ($\overline{x} \pm s$, mL).

Time	Control group ($n = 73$)	Research group ($n = 73$)	t/χ^2	P
1st day	19.65 ± 4.14	15.65 ± 3.05	5.138	0.031
3rd day	19.61 ± 4.06	5.36 ± 2.24	18.637	<0.001
7th day	19.08 ± 3.94	2.15 ± 0.69	23.157	<0.001
14th day	13.38 ± 2.15	0.00 ± 0.00	34.392	<0.001
30th day	2.95 ± 1.01	0.00 ± 0.00	10.927	<0.001

number of cases in which the degree of limb paralysis on the affected side recovered to Grade 5 on the 30th day and the GOS score >5 on the 90th day were significantly higher than those in the control group, and the edema degree and mass effect around the hematoma in patients were also significantly lower than those in patients treated with medication. This indicates that stereotactic surgery can improve the patient's disorder of consciousness, reduce the related complications, start rehabilitation treatment earlier, and increase the GOS score of the patient in 90 days.

In addition, we also found that the recovery of neurological function and daily activity after surgery in the research group receiving stereotactic therapy was significantly better than that in the control group receiving conservative treatment, which was consistent with the research results by Huang et al. [22]. This further confirmed that the

Table 4: Comparison of NIHSS score and mRS score at different times between the two groups ($\overline{x} \pm s$, score).

Observation indicators	Control group ($n = 73$)	Research group ($n = 73$)	t	P
NIHSS score				
Before treatment	9.33 ± 2.82	9.51 ± 2.35	0.698	0.301
7th day	9.08 ± 2.35	8.04 ± 2.19	4.269	0.042
14th day	7.56 ± 2.03	6.67 ± 1.82	5.638	0.021
30th day	6.87 ± 1.96	4.98 ± 1.68	10.957	<0.001
90th day	4.82 ± 1.35	3.56 ± 1.12	6.351	0.013
mRS score				
Before treatment	4.85 ± 0.92	4.90 ± 0.89	0.719	0.264
7th day	4.18 ± 0.82	3.81 ± 0.76	4.038	0.047
14th day	4.01 ± 0.86	3.14 ± 0.62	4.537	0.038
30th day	3.06 ± 0.79	1.91 ± 0.65	6.956	0.008
90th day	2.84 ± 0.97	1.25 ± 0.54	7.329	<0.001

Note. NIHSS, National Institute of Health Stroke Scale. mRS, Modified Ranking Rating Scale.

Table 5: Comparison of MBI score at different times between the two groups ($\overline{x} \pm s$, score).

Time	Control group ($n = 73$)	Research group ($n = 73$)	t	P
7th day	22.53 ± 9.56	21.86 ± 8.93	0.834	0.297
14th day	29.61 ± 13.32	38.21 ± 10.34	7.935	<0.001
30th day	47.86 ± 13.25	75.62 ± 16.82	13.628	<0.001
90th day	60.45 ± 14.57	85.67 ± 11.53	19.147	<0.001

Note. MBI, Modified Barthel Index.

postoperative neurological recovery of small- and medium-sized SICH patients treated by stereotactic surgery was significantly superior to conservative treatment. The reason is that stereotactic surgery is conducive to the rapid removal of hematoma, which can reduce the mass effect, alleviate the compression on brain tissue, and reduce the damage to neurons, the pyramidal tract, and glial cells around hematoma caused by various toxic substances released during the solidification, liquefaction, and decomposition of hematoma, thereby reducing the incidence of secondary damage to brain tissue.

However, through clinical practice, we have found some noteworthy places. The operation timing of applying stereotactic techniques to cerebral hemorrhage is controversial. Because the internal hemorrhage is not stable for 6 h after the onset of cerebral hemorrhage, the operation at this time will increase the risk of rebleeding. Therefore, it is not recommended to conduct stereotactic operations during this period.

5. Conclusion

Stereotactic hematoma evacuation is more effective than conservative treatment in the treatment of medium and small intracerebral hemorrhages in the basal ganglia. It can accelerate the resolution of hematoma and improve the neurological function and quality of life of patients, which is worthy of clinical promotion and application. However, this study is only a cohort study, the measurement indicators are highly subjective, and it fails to provide a causal conclusion. It also does not conduct in-depth research on clinical communication skills, but it provides more ideas for in-depth research on stereotactic hematoma evacuation in the future.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Retraction

Retracted: Outcome of Percutaneous Transforaminal Endoscopic Lumbar Decompression for Multisegment Lumbar Spinal Stenosis and the Effect on VAS Scores

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] C. Li and Z. Guo, "Outcome of Percutaneous Transforaminal Endoscopic Lumbar Decompression for Multisegment Lumbar Spinal Stenosis and the Effect on VAS Scores," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 9040402, 7 pages, 2022.

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Research Article

Outcome of Percutaneous Transforaminal Endoscopic Lumbar Decompression for Multisegment Lumbar Spinal Stenosis and the Effect on VAS Scores

Chi Li and Zhonghua Guo

Department of Orthopedics, People's Hospital of Dongxihu District Wuhan City, Wuhan, Hubei 430040, China

Correspondence should be addressed to Zhonghua Guo; zhonghuaguo139@sina.com

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Purpose. To investigate the efficacy of percutaneous transforaminal endoscopic lumbar decompression (PTED) in the treatment of multisegment lumbar spinal stenosis (LSS) and its effect on VAS scores. *Methods*. 126 patients with multisegment LSS admitted between August 2017 and August 2021 were selected and divided into the PTED group and the traditional open surgery group (TOS group) according to the different treatment methods. There were 70 cases in the PTED group, treated with PTED, and 56 cases in the TOS group, treated with traditional open surgery. The clinical outcomes, the preoperative and postoperative pain visual analogue scale (VAS), the Oswestry disability index (ODI), the SF-36 quality of life questionnaire scores, the perioperative indicators (operative time, days in hospital, intraoperative blood loss), the postoperative complications, and imaging data were compared between the two groups. *Results*. After the operation, the excellent and good rate in the PTED group (91.43%) was significantly higher than that in the TOS group (75.00%) ($P < 0.05$). At each time after the operation, the VAS and ODI scores of the two groups were lower than those before the operation, and the VAS scores of the PTED group at 1 day and 3 months after operation were lower than those of the TOS group, and the ODI scores of the PTED group at 3 months after operation were lower than those of the TOS group ($P < 0.05$). 3 months after the operation, the SF-36 scores in both groups were higher than those before the operation, and those in the PTED group were higher than those in the TOS group ($P < 0.05$). The operation time and days in hospital in the PTED group were shorter than those in the TOS group, and the intraoperative dominant blood loss and recessive blood loss were less than those in the TOS group ($P < 0.05$). The total incidence of complications in the PTED group (15.71%) was significantly lower than that in the TOS group (32.14%) ($P < 0.05$). *Conclusion*. Both PTED and traditional open surgery are effective in treating patients with multisegmental LSS, and both show positive postoperative changes in all indicators, but the former has more promising near -term results in improving lumbar spine pain, function and quality of life than the latter, and has the advantages of less trauma, less bleeding, and fewer complications.

1. Introduction

Lumbar spinal stenosis (LSS) mostly occurs in the elderly, aged 60–70, and more in women than in men [1]. It refers to the narrowing of the spinal canal, nerve root canal, and intervertebral foramen caused by compression of bones and soft tissues, resulting in the corresponding clinical symptoms. The pathogenesis of the disease is not completely clear. It may be that when spinal canal stenosis and nerve root compression occur, the horizontal area of the central spinal canal and nerve root canal decreases due to the stretching activity of the lumbar spine, further compressing the surrounding venules, resulting in local congestion and ischemic nerve damage [2, 3]. Surgical treatment can relieve the compression, increase the space of the diseased segments, and theoretically alleviate the symptoms. However, there is great controversy about which surgical method to choose for treatment [4]. Open posterior laminectomy, decompression of the lumbar spine, and interbody fusion are commonly used in

traditional operations. Although the decompression is complete, the surgery is more traumatic and requires prolonged postoperative bed rest. Moreover, this procedure requires stripping the paravertebral muscles and removing part or all of the lamina, which may lead to complications of medical origin such as lumbar instability and epidural scar formation, affecting the clinical outcome to a certain extent [5, 6]. Percutaneous transforaminal endoscopic lumbar decompression (PTED) is one of the most popular minimally invasive spinal techniques in recent years, with the unique advantages of being performed under local anesthesia with a small surgical incision (approximately 7 mm), short duration, minimal bleeding, no posterior ligamentous structures or muscle damage, and rapid recovery, which provides a viable treatment option for patients with underlying disease or who are too old to tolerate open surgery [7, 8]. However, due to the relatively complex causative factors of LSS, the relatively limited field of view of endoscopic surgery, and the long learning curve for the operator, there is a strong clinical need to analyse the efficacy and complications of PTED in the treatment of LSS. This study compares and analyses the efficacy of PTED versus traditional open surgery for a multisegmental LSS and the effect on VAS scores. It is reported as follows.

2. Materials and Methods

2.1. General Materials. 130 patients with multisegment LSS admitted between August 2017 and August 2021 were retrospectively analysed and divided into the PTED group and the traditional open surgery group (TOS group) according to the different treatment methods. Follow-up was carried out for 6 months via Internet questionnaires, telephone, and outpatient clinics. 3 patients failed to complete follow-up due to a change of contact and home address during this period, and 1 patient died of natural causes. 126 cases in total received complete follow-up information. There were 70 cases in the PTED group, treated with PTED, and 56 cases in the TOS group, treated with traditional open surgery.

2.2. Inclusion Criteria. ① A clear history of low back and leg pain with intermittent claudication and radiating pain in the lower limbs. ② Multiresponsible segmental LSS confirmed by CT and MRI data, consistent with the patient's symptoms and signs. ③ Those who had failed to respond to strict conservative treatment for more than 3 months. ④ Those who voluntarily accepted surgical treatment in our hospital and met the conditions for regular follow-up.

2.3. Exclusion Criteria. ① X-rays suggesting lumbar instability, lumbar spondylolisthesis, and scoliosis. ② Patients who had previous surgery on the same segment of the lumbar spine. ③ Those with lumbar spine infections, tumours, *tuberculosis*, etc. ④ Those with a single responsible segment LSS. ⑤ Those who presented with cauda equina syndrome. ⑥ Those with bleeding tendencies and organ dysfunction. ⑦ Those with missing follow-up information.

2.4. Methods

2.4.1. The PTED Group Was Treated with PTED. All patients underwent the procedure under local anesthesia without any water fasting and were instructed to urinate. Preoperative psychological counselling and routine skin preparation were performed and prophylactic intravenous antibiotics were administered half an hour before surgery. The operation was performed, in a lateral position, with the symptomatic side on the top, and the waist of the healthy side was padded up (remove the cushion after successful catheterization) to stabilize the position and expand the intervertebral foramen. The anesthetic needle entry point was determined according to the patient's body type and preoperative lumbar frontal and lateral radiographs. Local anesthesia was performed and the needle position was adjusted under intermittent fluoroscopy, with the needle tip finally placed at the tip of the superior articular process at the surgical segment. The puncture needle was replaced with a locating needle along the trajectory, and the locating needle was used to penetrate the superior articular process bone, after which the tip of the needle was gradually traveled to the posterior aspect of the superior endplate of the vertebral body below the surgical target space, keeping the tip of the locating needle close to, but not above, the posterior midline on the orthoptic image. Along the puncture needle trajectory, a 6 mm and 8 mm bone drill were shaped to enlarge the intervertebral foramen and the lateral saphenous fossa, respectively, and the trocar was then placed. After C-arm fluoroscopy had determined the position of the working trocar, endoscopic decompression was performed. The proliferative and hypertrophic ligamentum flavum and posterior longitudinal ligament were removed, the degenerative intervertebral disc was removed, and the proliferative osteophyte was removed by osteotome to complete the all-around decompression of the nerve root. During the operation under the microscope, radiofrequency hemostasis was applied, there was continuous flushing with normal saline, and patients were regularly communicated to determine their status. Surgical completion criteria are as follows: the dural sac was full and pulsating, and the ventral space was sufficient; the blood supply of the nerve root was improved; there was no bony compression in the proximal and distal nerve roots; straight leg elevation or femoral nerve traction test was negative; when the affected limb was moved, the patient felt better; under the microscope, there was no extrusion of intervertebral disc tissue, and sometimes nerve root sliding could be seen. After the operation, the drainage tube was left for 24 h, the cannula was withdrawn, and the incision was sutured.

2.4.2. TOS Group Was Treated with Traditional Open Posterior Laminectomy and Decompression of Lumbar Spine and Interbody Fusion. After general anesthetic intubation, the patient was placed prone, a posterior median incision was made with the patient's lesioned segment as the centre, the skin, subcutaneous tissue, and fascia at the edge of the

supraspinous ligament were incised in turn, the sacrospinous muscles on both sides of the spinous process were separated, and the decompression-fixed segment was fully exposed. The pedicle screw was inserted, the lower edge of the upper lamina and all the upper edges of the lower lamina were removed, the articular process around the bone window and the cohesive part of the hyperplasia of the ligamentum flavum was removed, the lateral recess was expanded sneakily, and the nerve root was exposed and released. After that, the nerve root and dura mater were pulled to the inside, the intervertebral disc and cartilage endplate were completely removed, the appropriate intervertebral fusion cage was selected for intervertebral bone grafting and fusion, and the nail rod was connected and fixed under pressure. The incision was sutured layer by layer, the wound drainage tube was placed, and the wound was bandaged after the operation. In order to avoid postoperative instability, all patients in the open group underwent interbody fusion.

2.5. Assessment Indicators

(1) Clinical outcomes: patients walking pain-free for >5 min or >200 m after the operation were regarded as excellent; patients walking pain-free for 3~5 min or 150~200 m after the operation were regarded as good; patients walking pain-free for 1-2 min or 100~149 m after the operation were regarded as moderate; patients walking pain-free for <1 min or <100 m after the operation were regarded as poor. Excellent and good rate = (excellent + good)/total number of cases × 100%.

(2) Visual analogue scale (VAS) score of pain: before the operation, 1 day after the operation, and 3 and 6 months after the operation, the pain level of both groups was assessed by VAS. The total score of 10, with higher scores indicating more severe pain.

(3) Oswestry disability index (ODI) : the ODI was used to assess the degree of functional recovery in both groups before the operation and at 3 and 6 months after the operation. It consisted of 10 aspects, such as pain intensity, lifting, walking, and social life. Each item was scored from 0 to 5, with a total score of 50. The scoring method was actual score/highest possible score × 100%. The higher the score, the worse the functional recovery.

(4) SF-36 quality of life questionnaire score: before and 3 months after the operation, the quality of life of the two groups was assessed by the SF-36 quality of life questionnaire. There were 36 entries in 8 dimensions, bodily pain (BP), general health (GH), health transition (HT), mental health (MH), physical functioning (PF), role physical (RP), social functioning (SF), and vitality (VT). The higher the score, the better the quality of life.

(5) Perioperative indicators: the operative time, days in hospital, and intraoperative blood loss were recorded for both groups.

(6) Complications: the occurrence of intraoperative dural tears, transient nerve injury, incisional infection, bone fibrous hyperplasia, deep vein embolism of the lower extremity, local swelling, refurbishment, and other complications were recorded in both groups.

2.6. Statistical Methods. The statistical software SPSS 22 was used for data analysis. The measurement data were described by the mean ± standard deviation, and a t-test was used for pairwise comparison between groups. The count data was described as (%), and comparisons were made using the χ^2 test. The two-sided test ($P < 0.05$) was statistically significant.

3. Results

3.1. Comparison of Baseline Information between the Two Groups. There was no significant difference between the two groups when comparing baseline information ($P > 0.05$). (Table 1).

3.2. Comparison of Clinical Outcomes between the Two Groups. After the operation, the excellent and good rate in the PTED group (91.43%) was significantly higher than that in the TOS group (75.00%). The difference was significant ($P < 0.05$). (Table 2).

3.3. Comparison of VAS Scores between the Two Groups. At each time after the operation, the VAS scores of the two groups were lower than those before the operation, and the VAS scores of the PTED group at 1 day and 3 months after the operation were lower than those of the TOS group. The difference was significant ($P < 0.05$). (Figure 1).

3.4. Comparison of ODI Scores between the Two Groups. At 3 and 6 months after the operation, the ODI scores of the two groups were lower than those before the operation, and the ODI scores of the PTED group at 3 months after the operation were lower than those of the TOS group. The difference was significant ($P < 0.05$). (Figure 2).

3.5. Comparison of SF-36 Scores between the Two Groups. 3 months after the operation, the SF-36 scores in both groups were higher than those before the operation, and those in the PTED group were higher than those in the TOS group. The difference was significant ($P < 0.05$). (Figure 3).

3.6. Comparison of Perioperative Indicators between the Two Groups. The operation time and days in hospital in the PTED group were shorter than those in the TOS group, and the intraoperative dominant blood loss and recessive blood loss were less than those in the TOS group. The difference was significant ($P < 0.05$). (Figure 4).

3.7. Comparison of Intraoperative and Postoperative Complications between the Two Groups. The total incidence of complications in the PTED group (15.71%) was significantly

Table 1: Comparison of baseline information between the two groups.

Items	PTED group ($n = 70$)	TOS group ($n = 56$)	t/χ^2	P
Age (years old)	65.29 ± 4.16	64.91 ± 4.43	0.495	0.622
Gender (cases)			0.058	0.810
Male	39 (55.71)	30 (53.57)		
Female	31 (44.29)	26 (46.43)		
Typology (cases)			0.191	0.909
Lateral recess stenosis	36 (51.43)	30 (53.57)		
Central spinal canal stenosis	25 (35.71)	18 (32.14)		
Intervertebral foraminal stenosis	9 (12.86)	8 (14.29)		
Narrow segments (cases)			0.014	0.904
L_{3-5}	32 (45.71)	25 (44.64)		
L_{4-5}-S_1	38 (54.29)	31 (55.36)		

Table 2: Comparison of clinical outcomes between the two groups.

Outcomes	PTED group ($n = 70$)	TOS group ($n = 56$)	χ^2	P
Excellent	40 (57.14)	24 (42.86)	2.540	0.111
Good	24 (34.29)	18 (32.14)	0.064	0.800
Moderate	5 (7.14)	11 (19.64)	4.385	0.036
Poor	1 (1.43)	3 (5.36)	1.497	0.221
Excellent + good	64 (91.43)	42 (75.00)	6.288	0.012

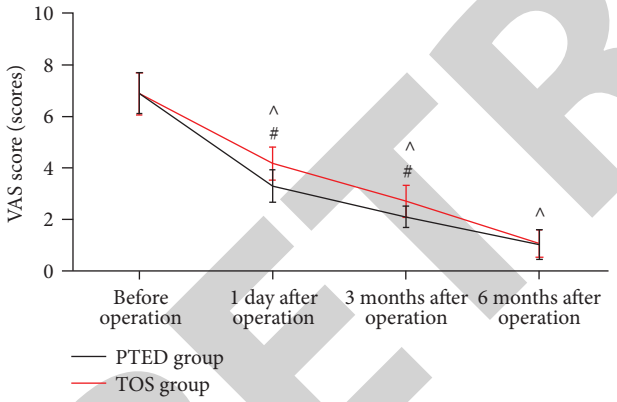

Figure 1: Comparison of the VAS scores between the two groups. *Note*: ^ is $P < 0.05$ compared with the same group preoperatively, #is $P < 0.05$ compared with the same time in the TOS group.

lower than that in the TOS group (32.14%). The difference was significant ($P < 0.05$). (Table 3).

4. Discussion

The typical symptoms of LSS are sciatica and lower back pain, which can be associated with sensory abnormalities [9]. Intermittent claudication is one of its main clinical features and is characterised by pain, numbness, and weakness during walking, which may be relieved by rest and reappear when walking again, and so on. The etiology of the disease is complex, and the nerve compression is often not a single factor. Many factors, such as intervertebral disc degeneration and bulging, small joint hyperplasia and cohesion, ossification

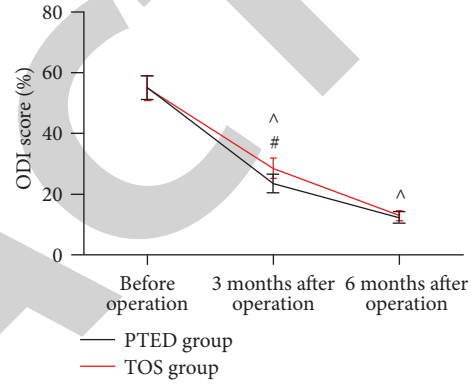

Figure 2: Comparison of the ODI scores between the two groups. *Note*: ^ is $P < 0.05$ compared with the same group preoperatively, #is $P < 0.05$ compared with the same time in the TOS group.

of the posterior longitudinal ligament, hypertrophy of the ligamentum flavum, and formation of osteophytes at the posterior edge of the vertebral body, participate in the pathological process of LSS [10–12]. For those who fail to respond to conservative treatment, surgery is the best option to maintain spinal stability, relieve nerve root compression, and relieve symptoms and signs. This study compares and analyses the effects of different surgical approaches applied to multisegment LSS on patient outcomes and VAS scores. The results showed that after the operation, the excellent and good rate of patients in the PTED group (91.43%) was significantly higher than that in the TOS group (75.00%), which was generally consistent with the excellent and good rate of 90.6% in the results of the study by Li et al. [13]. This suggests that PTED has unique advantages over traditional open procedures for the treatment of multisegment LSS.

The VAS score can be used as a quantitative reference for the painful condition of lumbar spondylosis [14]. The ODI can be used as a quantitative indicator of low back pain dysfunction and is important in reflecting functional recovery [15]. In this study, pain conditions, functional impairment, and quality of life were monitored at multiple time points for multisegment LSS. The results showed that VAS, ODI, and SF-36 scores were better than preoperative scores in both groups et al. l postoperative time points. and VAS scores were better than TOS group in the PTED group at

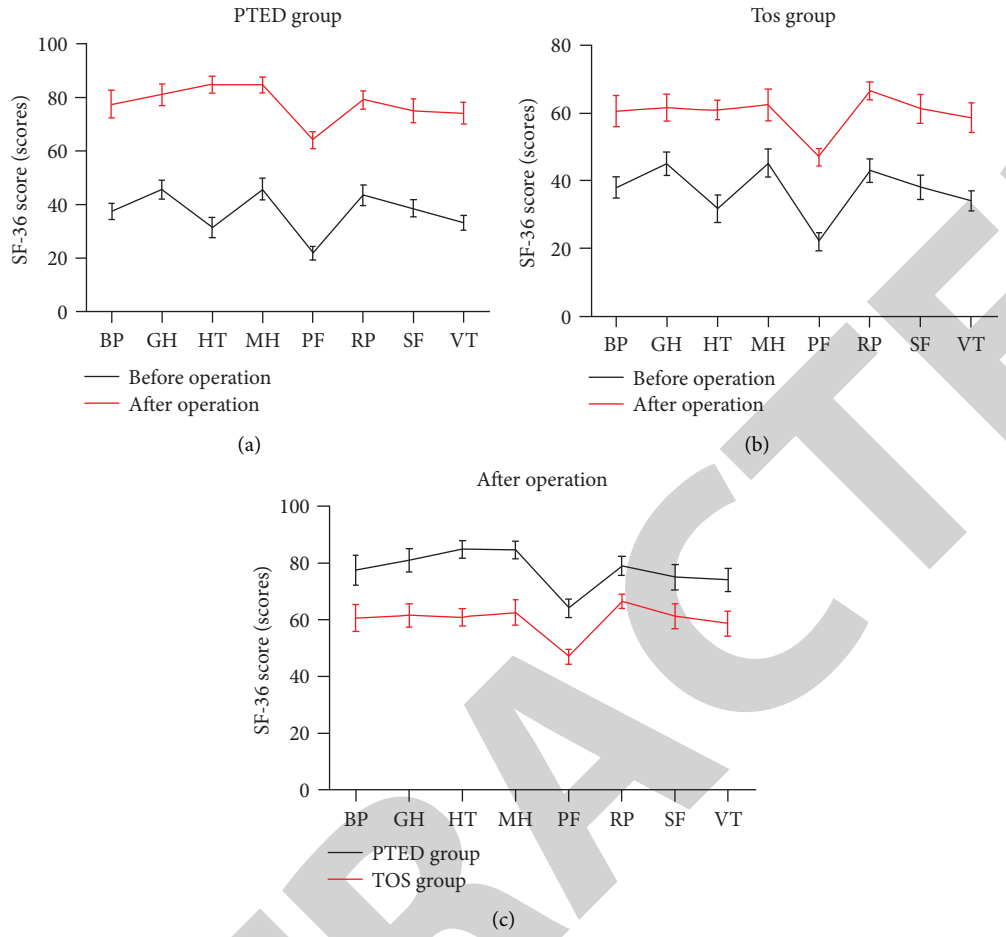

Figure 3: Comparison of the SF-36 scores between the two groups. *Note*: (a) pre and postoperative SF-36 scores in the PTED group. (b) Pre and postoperative SF-36 scores in the TOS group. (c) Postoperative SF-36 scores in the PTED and TOS groups.

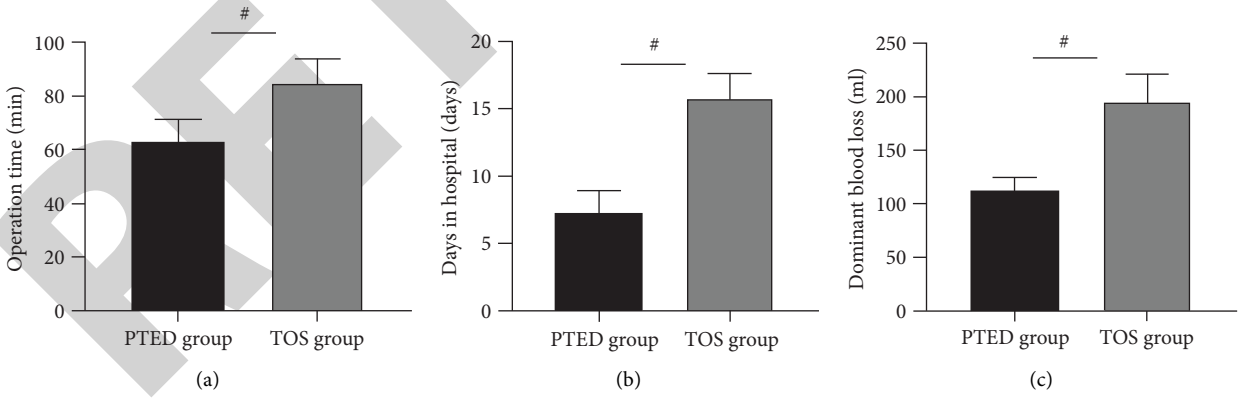

Figure 4: Continued.

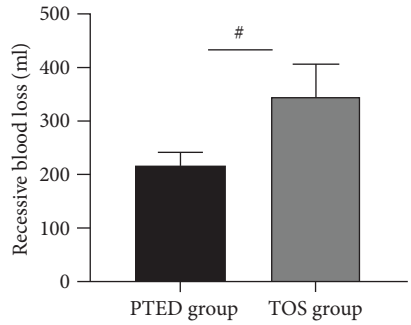

Figure 4: Comparison of perioperative indicators between the two groups. *Note*: *means the difference between groups is statistically significant.

Table 3: Comparison of intraoperative and postoperative complications between the two groups.

Complications	PTED group ($n = 70$)	TOS group ($n = 56$)	χ^2	P
Intraoperative dural tear	3 (4.29)	3 (5.36)	0.079	0.779
Transient nerve injury	2 (2.86)	1 (1.79)	0.154	0.695
Incisional infection	0 (0.00)	3 (5.36)	3.842	0.050
Bone fibrous hyperplasia	0 (0.00)	2 (3.57)	2.540	0.111
Deep vein embolism of lower extremity	0 (0.00)	2 (3.57)	2.540	0.111
Local swelling	1 (1.43)	4 (7.14)	2.666	0.103
Refurbishment	3 (4.29)	0 (0.00)	2.459	0.117
Others	2 (2.86)	3 (5.36)	0.510	0.475
Total	11 (15.71)	18 (32.14)	4.739	0.029

1 day after the operation, and VAS, ODI, and SF-36 scores were better than TOS group in the PTED group at 3 months after the operation. The above suggests that the use of PTED for multisegmental LSS can significantly reduce postoperative pain, promote functional recovery, and improve quality of life compared to traditional open surgery. The results also showed that the VAS and the ODI scores of the patients showed significant improvement as the treatment time was extended, and at 6 months after the operation, the VAS and the ODI scores of the two groups basically normalized, and the difference was not statistically significant in any comparison. This indicates that regardless of the above-mentioned procedures, the improvement in pain levels and lumbar spine dysfunction becomes more pronounced as the duration of treatment increases and that patients' index scores for each item can largely return to normal values after 6 months of surgical treatment.

Traditional open surgery is more widely used and can effectively reduce pressure on the nerve root canal and lateral saphenous fossa, while eliminating the need for allograft bone and artificial bone assistance and accelerating contact between the bone bed and the lateral ophthalmic fossa [16]. However, this procedure is more invasive, has more complications, and is slower to heal postoperatively. PTED is a minimally invasive procedure with the advantage of a clear intraoperative view, which reduces intraoperative injuries and complications. It is also possible to achieve effective decompression of the nerve root, relieving clinical symptoms, and with a rapid postoperative recovery, patients can return to work and life early [17, 18]. However, the procedure is demanding, and the operator's level of puncture positioning and microscopic manipulation can directly affect postoperative outcomes and associated complications, making the use of PTED for LSS somewhat challenging [19]. In this result, the PTED group had a shorter operative time and days in hospital than the TOS group and less intraoperative blood loss than the TOS group. The overall complication rate for patients in the PTED group was significantly lower than in the TOS group. These reaffirm the importance of PTED in the treatment of LSS, significantly reducing operative time, intraoperative bleeding, accelerating postoperative recovery, and reducing complications.

As most patients with LSS are elderly, patients have more severe bone degeneration and are prone to osteoporosis and other degenerative joint pathologies [20]. PTED treatment combines traditional surgery with endoscopic surgery, which is performed under local anesthesia. It is suitable for elderly patients with multiple system diseases who are not suitable for general anesthesia, and it can minimize the impact of surgery and anesthesia on patients. However, as an invasive procedure, there are specific complications associated with PTED for LSS. For example, 3 patients in the PTED group in this study had refurbishment due to incomplete intraoperative decompression. It is considered that this may be related to the poor intraoperative placement of the tube, which limits the scope of the microscopic view and the range of instrumentation. In addition, the residual nucleus pulposus and the pressure factors that are not easy to

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Research Article

Efficacy of Mecobalamin Tablets Combined with Troxerutin in the Treatment of NSCLC Chemotherapy-Induced Peripheral Neuropathy

Yang Li,[1] Jiufu Gu,[2] and Qiquan Yu[1]

[1]*Department of Thoracic, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 200032 Shanghai, China*
[2]*Department of Neurosurgery, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 200032 Shanghai, China*

Correspondence should be addressed to Qiquan Yu; qiquanyu1979@163.com

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Objective. To assess the efficacy of mecobalamin tablets combined with troxerutin in the treatment of nonsmall cell lung cancer (NSCLC) chemotherapy-induced peripheral neuropathy (CIPN). *Methods*. From January 2020 to December 2021, 120 NSCLC patients with CIPN treated in our institution meeting the inclusion criteria were enrolled and assigned to receive mecobalamin tablets treatment in the control group, or assigned to receive mecobalamin tablets combined with troxerutin treatment in the research group, with 60 patients in each group. All patients were evaluated for clinical efficacy, neuropathic score, patient-reported CIPN symptoms, neuropathic pain grade, and quality of life after 3 weeks of treatment. *Results*. The clinical treatment effective rate of the patients in the research group was significantly higher than that of the patients in the control group (81.7% vs. 58.3%, $P < 0.05$). Compared with before treatment, neuropathic score, numbness and tingling score, hot/coldness in hands/feet score, and peripheral neurotoxicity grade in all patients decreased significantly after treatment ($P < 0.05$). And these reductions were more considerable in the research group compared to the control group ($P < 0.05$). In addition, the quality of life scores (EORTC QLQ-C30) increased significantly in all patients after treatment, and this rise was more considerable in the research group compared to the control group ($P < 0.05$). *Conclusion*. Mecobalamin tablets combined with troxerutin in the treatment of NSCLC patients with CIPN is effective and safe, and can significantly improve the symptoms and quality of life of NSCLC patients with CIPN.

1. Introduction

Lung cancer is one of the most common malignant tumors worldwide and can be divided into nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and NSCLC accounts for about 80% of all lung cancers [1]. Treatment of patients with NSCLC should be selected according to the size of intrapulmonary lesions, the size of extrapulmonary lesions, the location and number of metastases, and the patient's own situation. Surgery, chemotherapy, and radiation are the most common treatment protocols for patients with NSCLC [2]. About 75% of NSCLC patients are in the middle and advanced stages of the disease when they are first diagnosed, so they have lost the opportunity of surgical treatment, and the clinical treatment protocol mostly chooses chemotherapy. Paclitaxel and platinum drugs are the most commonly used chemotherapy drugs for patients with NSCLC [3, 4]. Although these chemotherapy drugs are of great significance in prolonging the survival time of patients and improving the treatment effect of patients, they can also cause sensory disturbances during clinical treatment and peripheral neurotoxicity, such as numbness in the hands and feet, which seriously affect the quality of life and chemotherapy tolerance of patients, thereby reducing the therapeutic effect of chemotherapy [5, 6]. Various drugs or supplements, including vitamin B1, glutathione, duloxetine, and venlafaxine, have been tested in clinical studies as an effective means of preventing the neurotoxicity of

chemotherapy [7, 8]. However, most randomized controlled trials testing a variety of drugs with diverse mechanisms of action failed to reveal an effective treatment.

The mebendiamine tablet is a vitamin B12 preparation, and is mainly used for preventing and treating vitamin B12 deficiency, consumptive anemia, neuralgia, peripheral neuritis, and peripheral nerve paralysis.[9]. Previous studies have found that mecobalamin tablets were effective in treating disease or treatment-induced peripheral neuropathy, including diabetic peripheral neuropathy and FOLFOX4 chemotherapy-induced peripheral neuropathy (CIPN) [10, 11]. Troxerutin, also known as vitamin P4, is a derivative of the naturally occurring bioflavonoid rutin, found in tea, coffee, grains, and many vegetables and fruits [12]. Previous studies have shown that troxerutin is highly water-soluble, can be significantly absorbed by the gastrointestinal system, exerts protective effects without cytotoxic effects, and has been found to have antioxidant, anti-inflammatory, antidiabetic, and antitumor properties and other biological activities [13, 14]. Importantly, Gui et al. found that troxerutin alleviated chronic constriction injury (CCI)-induced neuropathic pain [15], but no studies have shown convincing evidence of substantial clinical benefit for troxerutin on the treatment of peripheral neuropathy. In the present study, we designed to study the efficacy of mecobalamin tablets combined with troxerutin in the treatment of NSCLC patients with CIPN.

2. Materials and Methods

2.1. Patients and Recruitment Criteria. The present study enrolled male and female adult NSCLC patients from January 2020 to December 2021, who were in remission after chemotherapy and presented with symptoms of CIPN. A total of 120 eligible patients with NSCLC were recruited to the study, and randomly divided into two groups, the control group and the research group, with 60 patients in each group. In the control group, there were 39 males and 21 females, aged from 40 to 72 years with an average age of (60.29 ± 5.38) years, 35 adenocarcinomas, and 25 squamous cell carcinomas. In the research group, there were 38 males and 22 females, aged from 40 to 70 years with an average age of (60.04 ± 6.01) years, 38 adenocarcinomas, and 22 squamous cell carcinomas. Studies involving human participants were reviewed and approved by the Ethics Committee of Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine.

Inclusion criteria: (1) According to National Cancer Institute's Common Terminology Criteria for Adverse Event 4.0, patients were diagnosed with chemotherapy-related sensory and motor abnormalities such as numbness, tingling, burning, hyperesthesia, or weakness in the hands and feet; (2) Karnofsky *P* score >60 (The patient was able to take care of himself/herself for most of his/her life, but occasionally needed help from others. A higher KPS indicated that the patient was in better physical condition.); (3) Expected survival greater than 3 months; (4) Complete clinical data, including age, gender, weight and height, comorbidities, tumor TNM stage, tumor differentiation, chemotherapy protocol, and previous treatment protocol; (5) 18–75 years old; (6) Normal language and cognitive skills; (7) The grade being evaluated by Eastern Cooperative Oncology Group (ECOG) score standard was 0–2 (The patient can at least move freely and live independently, and can get up and move at least half of the time during the day.).

Exclusion criteria: (1) Neuropathy from any type of nerve compression; (2) Any mental disorder, such as depression, suicidal ideation, and bipolar disorder; (3) Intellectual disability or inability to communicate; (4) History of alcohol or drug addiction; (5) Abnormal liver or kidney function; (6) Peripheral nerve abnormalities caused by diabetes, arthritis, peripheral paresthesia, radiotherapy, and infection.

2.2. Treatment Protocols and Clinical Efficacy. Patients in the control group were treated with oral mecobalamin tablets (0.5 mg each time, 3 times a day, Weicai (China) Pharmaceutical Co., Ltd., H20143107), a total of 3 weeks of treatment. Patients in the research group were treated with oral mecobalamin tablets (0.5 mg each time, 3 times a day, Weicai (China) Pharmaceutical Co., Ltd., H20143107), and intramuscular troxerutin injection (0.12 g each time, 2 times a day, Changchun Haiyue Pharmaceutical Co., Ltd., H20060246), a total of 3 weeks of treatment.

2.3. Clinical Efficacy. The clinical efficacy of all patients was assessed according to the WHO anticancer drug common toxicity grading standard combined with the numerical rating sacle (NRS). The scores of paresthesia and functional status of limbs from mild to severe were 0–3 points, respectively. 0 point: no uncomfortable feeling; 1 point: mild paresthesia or paroxysmal, but no dysfunction; 2 point: moderate to severe paresthesia, mild limb dysfunction; 3 points: unbearable paresthesia and obvious limb dysfunction. The clinical efficacy was evaluated after 3 weeks of treatment. Significantly effective: peripheral neurotoxicity assessment decreased by ≥2 grades, or peripheral neurotoxicity assessment was grade 0; Efficient: peripheral neurotoxicity reduced by 1 grade; Invalid: peripheral neurotoxicity was not alleviated or aggravated.

2.4. Neuropathy Score. Neuropathy scores were scored on patients by two neurologists blinded to the study. As previously described [16], the neuropathy score was 15 points according to the NRS score. The higher the score was, the severer the lesion was. The neuropathy score totally included five parts, i.e., sensory symptoms (0–3 points), needle sensitivity (0–3 points), vibration threshold (0–3 points), strength (0–3 points), and deep tendon reflex (0–3 points).

2.5. Patient-Reported CIPN Symptoms. Before treatment and after 3 weeks of treatment, we evaluated patient-reported CIPN symptoms by FACT/GOG-NTX, including numbness, tingling, and hot/coldness in hands/feet. Items are scored from 0 to 4 (0 = not at all; 4 = very much) [17].

2.6. Quality of Life. Before treatment and after 3 weeks of treatment, we used EORTC Quality of Life Questionnare-Core 30 (QLQ-C30) scale to evaluate the quality of life in the

patients. The EORTC QLQ-C30 scale includes 5 independent items and an overall health score, namely, the function of physical, role, emotional, cognitive and social, and total score [16]. The higher each score of QLQ-C30 was, the better the quality of life of patients would be.

2.7. Statistical Analysis. Data in the present study were analyzed by SPSS 20.0 software (SPSS Inc., Chicago, USA). Qualitative data are presented as counts (%), and P-values are calculated using chi-square or Fisher's exact test as appropriate. Kolmogorov–Smirnov test was used to check whether quantitative data conformed to a normal distribution, data that conformed to a normal distribution were presented as (mean ± standard deviation), and unpaired Student's t-test was used to compare differences and calculate P-values. Quantitative data that did not conform to a normal distribution are presented as the median (interquartile range), and Mann–Whitney U test was used to compare differences and calculate P-values.

3. Results

3.1. Baseline Characteristics. The baseline characteristics of patients including sex, nuclear status, age, BMI, TNM stage, tumor differentiation, tumor type, and previous treatment were not statistically different between the control and study groups ($P > 0.05$). There was comparability between the two groups of patients (Table 1).

3.2. Clinical Efficacy. After 3 weeks of treatment with different protocols in the two groups, we evaluated the clinical efficacy of all patients, and found that the clinical efficacy of patients in the control group was evaluated as significantly effective, efficient, and invalid in 10, 25, and 25 cases, respectively. Correspondingly, the clinical efficacy of patients in the research group was evaluated as significantly effective, efficient, and invalid in 15, 34, and 11 cases, respectively. The clinical treatment effective rate of the patients in the research group was significantly higher than that of the patients in the control group (81.7% vs. 58.3%, $P < 0.05$) (Table 2).

3.3. Peripheral Neurotoxicity Grade. There was no significant difference regarding peripheral neurotoxicity grade between the two groups before treatment, while significant difference was observed after treatment between the two groups with respect to peripheral neurotoxicity grade ($P < 0.05$) (Table3). In these two groups, peripheral neurotoxicity grade decreased considerably after treatment compared to before treatment. And such decrease which occurred in peripheral neurotoxicity grade in the research group was significantly stronger than that in the control group ($P < 0.05$) (Table 4).

3.4. Neuropathy Score. Before treatment, the neuropathy score of patients in the control group and the research group was (7.55 ± 2.12 points) and (7.60 ± 2.31 points), respectively, and there was no significant difference ($P > 0.05$). However, after 3 weeks of treatment with different protocols in the two groups, the neuropathy score of patients in the control group and the research group was all significantly decreased, and the neuropathy score of patients in the research group was significantly lower than that in the control group (3.05 ± 1.12 points vs. 3.53 ± 0.93 points, $P < 0.05$) (Table 5).

3.5. Patient-Reported CIPN Symptoms. Before treatment, the numbness and tingling score of patients in the control group and the research group was (2.00 ± 0.45 points) and (2.05 ± 0.52 points), respectively, and there was no significant difference ($P > 0.05$). However, after 3 weeks of treatment with different protocols in the two groups, the numbness and tingling score of patients in the control group and research group were all significantly decreased, and the numbness and tingling score of patients in the research group were significantly lower than that in the control group (1.00 ± 0.17 points vs. 1.55 ± 0.22 points, $P < 0.05$) (Table 3).

Before treatment, the hot/coldness in hands/feet score of patients in the control group and the research group was (1.95 ± 0.35 points) and (1.92 ± 0.41 points), respectively, and there was no significant difference ($P > 0.05$). However, after 3 weeks of treatment with different protocols in the two groups, the hot/coldness in hands/feet score of patients in the control group and the research group was all significantly decreased, and the hot/coldness in hands/feet score of patients in the research group was significantly lower than that in the control group (0.95 ± 0.12 points vs. 1.25 ± 0.18 points, $P < 0.05$) (Table 3).

3.6. Quality of Life. Before treatment, there was no significant difference in the quality of life between the two groups of patients being evaluated by the EORTC QLQ-C30 scale including the function of physical, role, emotional, cognitive and social, and total score ($P > 0.05$) (Table 6). After 3 weeks of treatment with different protocols, the quality of life assessed by the EORTC QLQ-C30 scale all changed in the two groups, and the score of physical, role, emotional, cognitive, and social function, and total score in the research group was all significantly higher than those in the control group ($P < 0.05$) (Table 7).

3.7. Adverse Effects. There were no treatment-related adverse reactions in both groups during the treatment period.

4. Discussion

Chemotherapy is an important protocol for the treatment of malignant tumors with remarkable curative effect, but chemotherapy drugs often indiscriminately damage normal cells in the process of destroying tumor cells. The sensory injury caused by the damage of peripheral nerves or autonomic nerves by chemotherapeutic drugs is called CIPN, and CIPN has a dose-limiting effect and is an important factor limiting the application of chemotherapeutic drugs. The toxic targets of chemotherapeutic drugs mainly include the central nervous system, peripheral nerves, and receptors,

Table 1: Baseline characteristics of the two groups in this study.

	Control group ($n = 60$)	Research group ($n = 60$)	t/χ^2	P
Gender (n)				
Male	39	38	0.036	0.749
Female	21	22		
Age (years)	60.29 ± 5.38	60.04 ± 6.01	0.614	0.427
BMI (kg/m^2)	22.67 ± 2.17	22.71 ± 2.24	0.725	0.305
Karnofsky performance status (points)	94.28 ± 7.41	94.88 ± 8.12	0.831	0.207
TNM stage (n)				
II	18	20	0.154	0.695
III–IV	42	40		
Differentiation (n)				
Low	8	9	0.170	0.918
Middle	30	31		
High	22	20		
Cancer type (n)				
Adenocarcinoma	35	38	0.315	0.575
Squamous cell carcinoma	25	22		
Previous treatment				
Previous surgery	41	39	0.150	0.699
Previous radiation therapy	6	7	0.086	0.769
Previous targeted therapy	5	4	0.120	0.729

Table 2: Comparison of clinical efficacy between the two groups of patients (n (%)).

Group	n	Significantly effective	Efficient	Invalid	Efficient rate
Control group	60	10 (16.7)	25 (41.7)	25 (41.7)	35 (58.3)
Research group	60	15 (25.0)	34 (56.7)	11 (18.3)	49 (81.7)
χ^2					7.778
P					0.005

Table 3: Comparison of neuropathic pain grade between the two groups of patients ($\overline{x} \pm s$, points).

Group	n	Numbness and tingling		Hot/coldness in hands/feet	
		Pretreatment	Posttreatment	Pretreatment	Posttreatment
Control group	60	2.00 ± 0.45	1.55 ± 0.22*	1.95 ± 0.35	1.25 ± 0.18*
Research group	60	2.05 ± 0.52	1.00 ± 0.17*	1.92 ± 0.41	0.95 ± 0.12*
t		0.625	5.328	0.779	4.265
P		0.408	0.011	0.284	0.042

Note. Compared with pretreatment, *$P < 0.05$.

Table 4: Comparison of peripheral neurotoxicity grade between the two groups of patients (n).

Group	n	Pretreatment			Posttreatment			
		1	2	3	0	1	2	3
Control group	60	18	20	22	13*	26	17	4*
Research group	60	12	24	24	23*	29	6	2*
χ^2			1.651			8.869		
P			0.438			0.031		

Note. Compared with pretreatment, *$P < 0.05$.

which are mainly manifested as symmetrical paresthesia, weakening, or loss of the extremities, and patients often feel burning, tingling, and paralysis [18, 19]. Platinum and third-generation cytotoxic drugs combined with chemotherapy are the first-line chemotherapy options for advanced NSCLC, but platinum chemotherapy drugs can easily lead to the appearance of CIPN in patients and affect the therapeutic effect. According to statistics [20, 21], the prevalence of

Table 5: Comparison of neuropathy score between the two groups of patients ($\overline{x} \pm s$, points).

Group	n	Pretreatment	Posttreatment
Control group	60	7.55 ± 2.12	$3.53 \pm 0.93^*$
Research group	60	7.60 ± 2.31	$3.05 \pm 1.12^*$
t		0.538	4.897
P		0.724	0.034

Note. Compared with pretreatment, $^*P < 0.05$.

Table 6: Comparison of EORTC QLQ-C30 score before treatment ($\overline{x} \pm s$, points).

Group	n	Physical	Role	Emotional	Cognitive	Social	Total
Control group	60	72.4 ± 20.2	58.6 ± 24.4	63.2 ± 21.5	67.5 ± 23.0	66.7 ± 25.7	58.9 ± 12.4
Research group	60	74.5 ± 19.2	58.7 ± 26.7	64.8 ± 25.1	66.9 ± 25.2	67.4 ± 19.7	59.2 ± 13.0
t		0.698	0.997	0.718	0.921	0.807	0.439
P		0.301	0.168	0.299	0.172	0.212	0.638

Table 7: Comparison of c EORTC QLQ-C30 score after treatment ($\overline{x} \pm s$, points).

Group	n	Physical	Role	Emotional	Cognitive	Social	Total
Control group	60	79.9 ± 15.6	70.8 ± 17.4	68.7 ± 13.8	73.2 ± 19.1	78.6 ± 18.2	63.3 ± 10.2
Research group	60	84.8 ± 13.2	75.8 ± 18.2	72.6 ± 15.1	76.7 ± 18.7	83.4 ± 16.9	68.8 ± 9.4
t		6.992	7.428	6.057	5.972	7.897	9.630
P		0.002	<0.001	0.006	0.009	<0.001	<0.001

CIPN was 68.1% in the first month after platinum-based chemotherapy, 60% in three months, and 30% of patients continued to suffer from peripheral neuropathy 6 months after chemotherapy.

In the present study, 120 NSCLC patients with CIPN were included in this study and divided into the control group and the research group according to their treatment methods. After 3 weeks of treatment in different ways, we found that the clinical treatment effective rate of the research group was 81.7%, which was significantly higher than the 58.3% clinical treatment effective rate of the control group. In addition, the improvement of neuropathic score, numbness and tingling score, hot/coldness in hands/feet score, and peripheral neurotoxicity grade in the research group were all significantly better than those in the control group. Therefore, these results indicated that the clinical efficacy of mecobalamin tablets combined with troxerutin in the treatment of CIPN in NSCLC patients is superior to that of mecobalamin tablets alone.

Adverse reactions of NSCLC chemotherapy patients are mainly divided into acute neurotoxicity and chronic neurotoxicity, mainly manifested as sensory loss and paralysis of peripheral nerves, with blood toxicity, neurotoxicity, hemoptysis, alopecia and other symptoms being the most common [22]. The onset of acute neurotoxicity is more rapid, mostly manifested as paresthesia and hypoesthesia, and chronic neurotoxicity is a delayed-onset peripheral neuropathy that occurs after multiple cycles of drug use, mainly manifested as deep sensory loss and psychomotor difficulties [23]. The occurrence of chronic neurotoxicity may be related to the following reasons. On the one hand, the neurotoxicity target of platinum drugs is in the spinal nerve followed by the ganglion, inhibiting ribosome synthesis in sensory neurons, blocking protein synthesis, and causing abnormal sensory neuron cell function which reacts with neurotoxicity [24]. On the other hand, oxidative stress, both calcium-magnesium mixtures and neuromodulators can be used as conventional drugs for the treatment of neurotoxic reactions, helping to restore the function of sensory nerve cells [25]. In addition, in our study, no significant adverse drug reactions were observed in the patients of the two groups, indicating that the combination of mecobalamin tablets combined with troxerutin in the treatment of peripheral neuropathy caused by NSCLC chemotherapy achieved good efficacy and high safety.

Mecobalamin is an endogenous coenzyme B12, mainly involved in the one-carbon unit cycle, and plays an important role in the transmethylation of homocysteine to methionine in the body. Modern drug research results have shown that mecobalamin can effectively promote the formation of neuronal myelin sheath and lecithin in the nervous system, thus generating a strong stimulation for axonal regeneration and nerve growth, and promoting its growth and development [26]. Therefore, mecobalamin was found to be effective in treating disease or treatment-induced peripheral neuropathy [9–11], which is consistent with the results of the present study. Troxerutin, also known as vitamin P4, has been shown to inhibit red blood cell and platelet aggregation, inhibit apoptosis, protect nerves, improve microcirculation, increase blood oxygen content, and promote angiogenesis [12, 27]. At present, troxerutin is mainly used for the treatment of edema, hemorrhoids, diabetic complications, venous thrombosis, cardiovascular, and cerebrovascular diseases, but its therapeutic efficacy in CIPN has not been studied [28, 29]. However, many studies have confirmed the neuroprotective effect of troxerutin, but the effect of troxerutin on CIPN is still unclear [30, 31].

Zhao et al. [30] found that troxerutin exerted neuroprotective effects in animal models of traumatic brain injury by regulating endothelial nitric oxide synthase coupling/uncoupling, and it can significantly reduce the nervous system damage, reduce the infarct size, and promote the integrity of the blood-brain barrier in animals with traumatic brain injury. In addition, previous studies have also revealed that trafluoretin can reduce the expression of glial fibrillary acidic protein and astrocyte DNA fragments and inhibit the loss of tyrosine hydroxylase-positive neurons in the substantia nigra, thus exerting neuroprotective effects in the mouse model of Parkinson's disease [31]. Although many studies have demonstrated neuroprotective properties of troxerutin, no studies have reported significant clinical benefit of troxerutin on the treatment of CIPN. In the present study, our results suggested that the clinical efficacy of mecobalamin tablets combined with troxerutin in the treatment of CIPN in NSCLC patients is superior to that of mecobalamin tablets alone.

5. Conclusion

Mecobalamin tablets combined with troxerutin in the treatment of NSCLC chemotherapy-induced peripheral neuropathy is effective and safe, and can significantly improve the symptoms and quality of life of NSCLC patients with CIPN. However, the present study is only a cohort study, the measurement indicators are highly subjective, and it fails to provide a causal conclusion, and does not conduct in-depth research on clinical communication skills, but it provides more ideas for in-depth research on the treatment of NSCLC chemotherapy-induced peripheral neuropathy in the future.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author.

Disclosure

Yang Li and Jiufu Gu are the co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Retraction

Retracted: Potential Molecular Mechanism of Guishen Huoxue Decoction against Intrauterine Adhesion Based on Network Pharmacology

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi, as publisher, following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of systematic manipulation of the publication and peer-review process. We cannot, therefore, vouch for the reliability or integrity of this article.

Please note that this notice is intended solely to alert readers that the peer-review process of this article has been compromised.

Wiley and Hindawi regret that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] W. Zhang, Y. Yuan, G. Huang, and J. Xiao, "Potential Molecular Mechanism of Guishen Huoxue Decoction against Intrauterine Adhesion Based on Network Pharmacology," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4049147, 9 pages, 2022.

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Research Article

Potential Molecular Mechanism of Guishen Huoxue Decoction against Intrauterine Adhesion Based on Network Pharmacology

Wenyan Zhang,[1,2] **Yuan Yuan**,[2] **Guangrong Huang**,[2] **and Jing Xiao**[3]

[1]*Department of Gynaecology, The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China*
[2]*Department of Gynaecology, Shenzhen Bao'an Chinese Medicine Hospital, Guangzhou University of Chinese Medicine, Shenzhen, China*
[3]*Department of Gynaecology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China*

Correspondence should be addressed to Jing Xiao; xiaojingson_2004@126.com

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Objective. Intrauterine adhesion (IUA) represents an endometrial repair disorder that is associated with menstrual disorders, recurrent pregnancy loss, and infertility. This study aimed to explore the underlying biological mechanisms of Guishen Huoxue decoction for the treatment of IUA based on network pharmacology. *Methods*. The selection of active compounds for Guishen Huoxue decoction and prediction of relevant targets were performed by the TCMSP and Swiss Target Prediction databases, respectively. The targets of IUA were obtained by three databases, including Online Mendelian Inheritance in Man (OMIM), DisGeNET, and GeneCards. The drug-disease regulatory network was constructed via Cytoscape software, following the acquisition of common genes of active compounds of drug Guishen Huoxue decoction and disease IUA, which was carried out through Venny software. Protein-protein interaction (PPI) network and function enrichment analyses were performed. *Results*. According to the data obtained from TCMSP, a total of 200 potential active compounds of Guishen Huoxue decoction and their related targets (1068) were screened by the Swiss Target Prediction database. 1303 disease targets and 134 common targets were identified. The drug-disease regulatory network showed that 165 active compounds were found to be involved in the treatment of IUA. Among 134 common targets, AKT1, SRC, TP53, VEGFA, and IL-6 were predicted as core genes against IUA. PI3K-Akt, Rap1, Ras, and AGE-RAGE were the main signaling pathways that participated in the treatment of Guishen Huoxue decoction for IUA. *Conclusion*. The active compounds of Guishen Huoxue decoction confer therapeutic effects against IUA by regulating fibrosis, inflammation, and oxidative stress through major signaling pathways such as PI3K-Akt and AGE-RAGE.

1. Introduction

Intrauterine adhesion (IUA), also known as endometrial fibrosis or Asherman's syndrome, was first proposed by Joseph Asherman in 1948 [1]. IUA is deemed to be the injury of the endometrial basal layer and partial or complete loss of the functional layer due to various reasons, which eventually leads to adhesion of the uterine walls and partial or even complete occlusion of the uterine cavity [2]. With the increase in abortion and intrauterine surgery, the incidence rate of IUA is increasing year by year, reaching as high as 25%–30% [3]. Endometrial trauma caused by surgery, including abdominal and hysteroscopic myomectomy, septectomy, and any other intrauterine surgery, is the leading contribution to the occurrence of IUA [4]. IUA has become a common gynecological disease and is characterized by a series of clinical manifestations such as oligomenorrhea, dysmenorrhea, amenorrhea, recurrent abortion, and infertility, posing serious damage to women's reproductive function [5, 6]. Previous studies have shown that hysteroscopic adhesiolysis was most commonly used for the clinical treatment of IUA, with the placement of anti-adhesion biological adhesive products in the intrauterine cavity and location of intrauterine devices for 2 to 3 months, or retention of the sacculus in the intrauterine cavity for 5–7 days and oral therapy of estrogen and progesterone

drugs for 3 months after surgery [7, 8]. However, the recurrence rate of IUA after hysteroscopic adhesiolysis reached 62.5% [9], and the success rate of pregnancy remained approximately 22.5%~33.3% [10, 11]. Therefore, exploring clinical adjuvant therapy for IUA is necessary.

No descriptions of IUA were found in ancient traditional Chinese medical books, but the symptoms of IUA belong to the categories of "hypomenorrhea," "amenorrhea," "abdominal pain," and "infertility" in traditional Chinese drugs. Most studies believed that this disease was caused by operations in the intrauterine, and the operations damaged the uterus and uterine vessels, resulting in kidney deficiency, insufficiency of vital energy and blood, and blockage of blood stasis [12, 13]. Modern pharmacological studies have shown that kidney tonifying herbs improved endometrial blood supply and elevated the embryo quality in the cycle of controlled ovarian hyperstimulation of assisted reproductive technique [14]. Traditional Chinese herbs provide a new clinical method for the treatment of low endometrial receptivity [15]. Bushen Huoxue decoction can favor decidual stromal cell proliferation and show therapeutic potential to manage patients with unexplained recurrent spontaneous abortion, and its effect was realized through the PI3K/AKT pathway [16]. Traditional Chinese drugs referring to blood circulation promotion and blood stasis removal are helpful to improve local microcirculation, reduce inflammatory reactions, and boost the restoration of the endometrium. Guishen Huoxue decoction, as a term for a series of traditional Chinese drug formulas, is similar to Bushen Huoxue decoction [17] and is effective in blood circulation promotion and kidney tonification. However, no direct evidence of Guishen Huoxue decoction in IUA treatment was found.

Network pharmacology is a new discipline used to analyze the network of biological systems and select specific signal nodes to design multitarget drug molecules [18]. This study was aimed at investigating the potential molecular mechanisms of Bushen Huoxue decoction on the treatment of IUA through network pharmacology and providing ideas for further experimental research and the development of new drugs for the treatment of IUA.

2. Materials and Methods

2.1. Screening of Drug-Related Active Compounds and Potential Targets. The traditional Chinese drug systems pharmacology database and analysis platform (TCMSP) (https://tcmspw.com/tcmsp.php) was performed to obtain the active compounds of Guishen Huoxue decoction, consisting of *Paeonia lactiflora*, *Ligusticum wallichii*, root of red-rooted salvia, *Angelica sinensis*, fruit of Chinese wolfberry, *Astragalus membranaceus*, Spatholobus stem, fruit of glossy privet, Chinese yam, fruit of medicinal cornel, prepared rehmannia root, seed of Chinese dodder. Oral bioavailability (OB) $\geq 30\%$ and drug-like (DL) ≥ 0.18 were considered the screening conditions of the main active compounds, and the potential targets of the screened compounds were identified using the Swiss Target Prediction (https://swisstargetprediction.ch/) database, with a prediction score greater than zero. The UniProt database (https://www.uniprot.org/) was used for converting target information into gene symbols.

2.2. Prediction of IUA Targets. Databases including Online Mendelian Inheritance in Man (OMIM) (https://omim.org/), DisGeNET (https://www.disgenet.org/), and GeneCards (https://www.genecards.org/) were carried out to obtain the disease-related targets (only "*Homo sapiens*") using "Asherman's Syndrome" and "intrauterine adhesion" as the keywords. A gene symbol was obtained with the help of the UniProt database (https://www.uniprot.org/).

2.3. Acquisition of Drug-Disease Common Targets and Drug-Targets-Disease Network Construction. The Venny 2.1 software was performed to acquire common targets of active compounds of the drug Guishen Huoxue decoction and disease IUA. Subsequently, the targeting relationship between active compounds of Guishen Huoxue decoction and common targets was presented by the drug-targets-disease network through Cytoscape 3.7.2 software.

2.4. Protein-Protein Interaction (PPI) Network Construction and Screening of Core Genes. The PPI network was constructed based on common targets of Guishen Huoxue Decoction and IUA mapping into the STRING database (https://string-db.org/), with the parameter of "*Homo sapiens*" as protein type and "moderate confidence" (>0.400) as the minimum interaction critical value. The PPI network was visualized by importing the TSV-based file to Cytoscape 3.7.2 software, and the visual analysis included a topology analysis, gene cluster analysis, and core gene screening. On the basis of the degree value obtained, the core genes were sorted out.

2.5. Gene Ontology (GO) Function and (Kyoto Encyclopedia of Genes and Genomes) KEGG Pathway Enrichment Analysis. The primary biological process and related signal pathways of Guishen Huoxue decoction in the treatment of IUA were explored by functional enrichment analysis. On the basis of R software, Bioconductor software (p value < 0.05, q value < 0.05) was applied to perform the GO and KEGG analysis of common targets of Guishen Huoxue decoction and IUA. Go enrichment analysis clarified gene function from three aspects: biological process (BP), cellular component (CC), and molecular function (MF). KEGG reflects a particular pathway of diseases with significant gene concentrations.

3. Result

3.1. Main Active Compounds and Targets of Guishen Huoxue Decoction. As listed in Table 1, with the help of TCMSP and a condition of OB $\geq 30\%$ and DL ≥ 0.18, it was observed that a total of 200 potential active compounds of Guishen Huoxue decoction (*Paeonia lactiflora*, *Ligusticum wallichii*, root of red-rooted salvia, *Angelica sinensis*, fruit of Chinese

Table 1: Drug-related active compounds and potential targets.

Drug	Numbers of active compounds	Numbers of targets
Paeonia lactiflora	13	342
Ligusticum wallichii	7	349
Salvia miltiorrhiza	65	716
Chinese angelica	2	43
Fruit of Chinese wolfberry	45	423
Astragalus membranaceus	20	429
Spatholobus stem	24	502
Fruit of glossy privet	13	231
Chinese yam	16	334
Fruit of medicinal cornel	20	358
Prepared rehmannia root	2	44
Seed of Chinese dodder	11	279

wolfberry, *Astragalus membranaceus*, Spatholobus stem, fruit of glossy privet, Chinese yam, fruit of medicinal cornel, prepared rehmannia root, seed of Chinese dodder) were found following duplicate removal. A total of 1169 targets related to potential active compounds were screened using the Swiss Target Prediction database.

3.2. Identification of IUA Targets. Using "Asherman syndrome" and "intrauterine adhesions" as the searching keywords, the results of three databases, including OMIM, DisGeNET, and GeneCards, indicated that 1303 disease-related records were obtained after duplicate removal.

3.3. Drug-Disease Common Targets and Drug-Targets-Disease Network Construction. The Wayne diagram was mapped using 1169 targets associated with potential active compounds of Guishen Huoxue decoction and 934 disease-related IUA targets via Venny 2.1 software. A total of 134 common target genes were shown in the Wayne diagram (Figure 1). The drug-targets-disease network was established through Cytoscape 3.7.2 software, with the use of 200 potential active compounds and 134 common targets obtained from Guishen Huoxue decoction and IUA, and in the absence of those active compounds that do not intersect with these targets (Figure 2). In Figure 2, the symbols in purple color represented drugs. The green color indicated active compounds of Guishen Huoxue decoction, of which 35 active compounds were deleted due to no commonality with the 134 targets expressed in blue color, and the red color represented disease IUA.

3.4. PPI Network Construction and Core Genes Selection. The PPI network (Figure 3), containing 134 common genes in Guishen Huoxue decoction and IUA, was constructed through the STRING database, and then the visualization analysis of PPI was carried out via Cytoscape software, with the confidence score not less than (Figure 4). In the PPI network, the size and color of the nodes were associated with degree values, and the edges indicated the interaction.

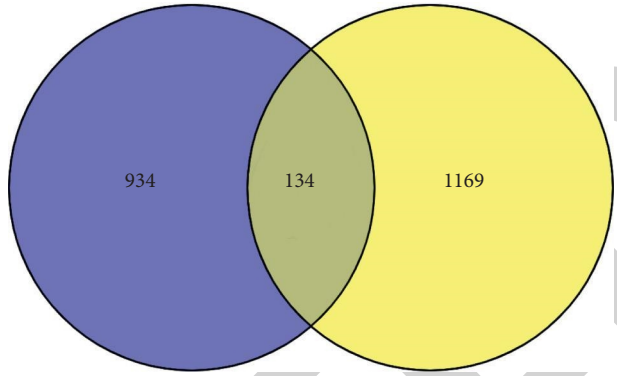

Figure 1: Screening of common targets existing in Guishen Huoxue decoction and disease IUA. The circle in purple means targets of active compounds in Guishen Huoxue decoction, and the circle in yellow represents targets of disease in IUA.

"Network Analyzer" in Cytoscape software was used for topology analysis of the PPI network. The target proteins whose degree values were greater than the average values were selected as the core proteins, and the first 30 proteins, were plotted using R 3.6.1 software (Figure 5). Among the 30 proteins, 5 proteins were predicted to be core proteins which were screened by the "MCODE tool" in Cytoscape software, and the corresponding gene symbols were AKT1, SRC, TP53, VEGFA, and IL-6.

3.5. Enrichment Analysis of Drug-Disease Common Targets. The GO enrichment analysis was conducted following the performance of the R language on 134 common genes. Go analysis indicated that the common genes were enriched in 2291 BP terms, mainly including peptidyl-tyrosine phosphorylation, peptidyl-tyrosine modification, and positive regulation of cell adhesion (Figure 6(a)). In terms of CC, the common genes were associated with 69 terms, such as membrane raft, membrane microdomain, and membrane region (Figure 6(b)). The common genes were mostly enriched in 138 MF terms, such as protein tyrosine kinase activity, transmembrane receptor protein tyrosine kinase activity, and phosphatase binding (Figure 6(c)). After KEGG pathway analysis, the first 20 significant enrichment signal pathways were screened and associated with drug-disease common targets (Figure 7).

4. Discussion

IUA is mainly characterized by hypomenorrhea or amenorrhea [6]. The purpose of IUA treatment is to control relevant symptoms, promote endometrial repair and regeneration, and reduce the incidence of readhesion as well as complications such as recurrent abortion and secondary infertility. Although hysteroscopic adhesiolysis as the main treatment is able to restore anatomical morphology of the uterine cavity and uterine cavity volume, it is not an ideal intervention for IUA due to poor recovery of menstruation

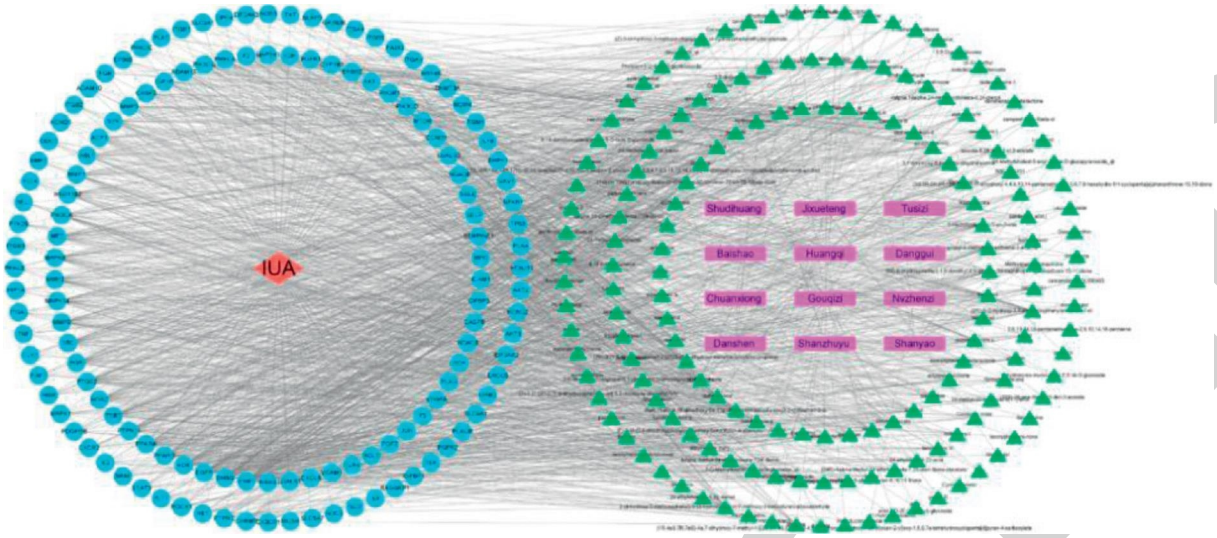

Figure 2: Regulatory networks between Guishen Huoxue decoction and IUA. The symbols in purple color represent drugs. The green color indicates active compounds in the Guishen Huoxue decoction. Common targets are expressed in the blue color. The red color meant disease IUA.

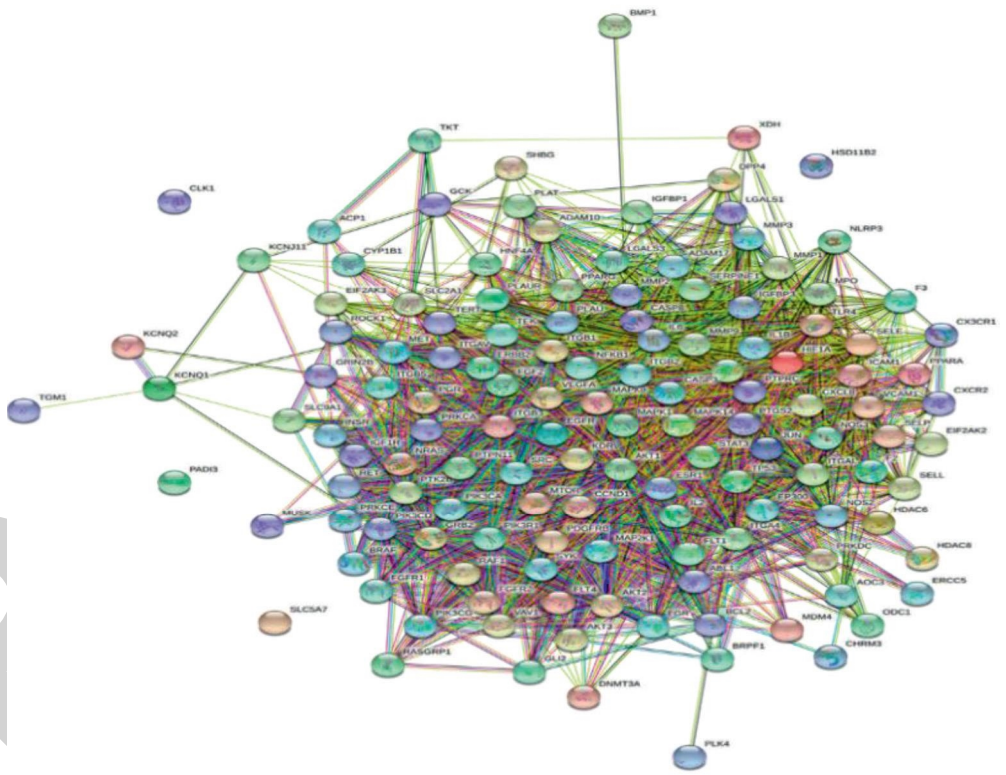

Figure 3: PPI network constructions.

and fertility, especially an extremely high recurrence rate in the presence of various approaches to prevent recurrent adhesion [19, 20]. Hence, exploring effective adjutant approaches following hysteroscopic adhesiolysis contributes to women's health.

In recent years, traditional Chinese drugs have enriched the development of therapy for uterus-related diseases. Ding et al. revealed that as a classic traditional prescription, Bushen Huoxue Huatan decoction improved polycystic ovary syndrome through regulating hormones, reversing insulin resistance, and alleviating inflammation reactions, resulting in fertility improvement [21]. Feng et al. also proved that Bushen Huoxue decoction was effective in the treatment of unexplained recurrent spontaneous abortion via activation of the PI3K/AKT pathway [16]. The traditional Chinese drug Tiaoshen Tongluo, which contained

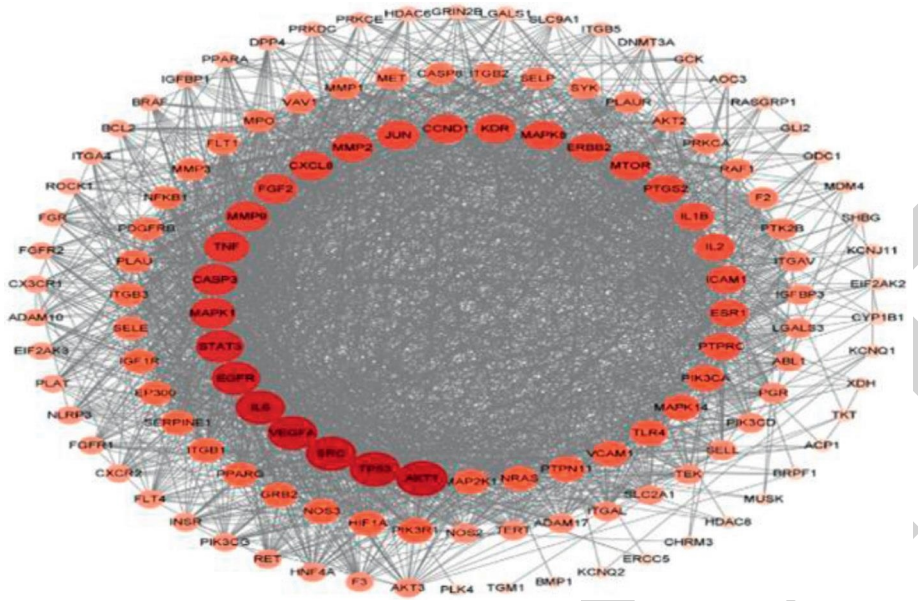

Figure 4: PPI network visualization analyses. The nodes represent the targets, and the size and color shades show their degree in the network.

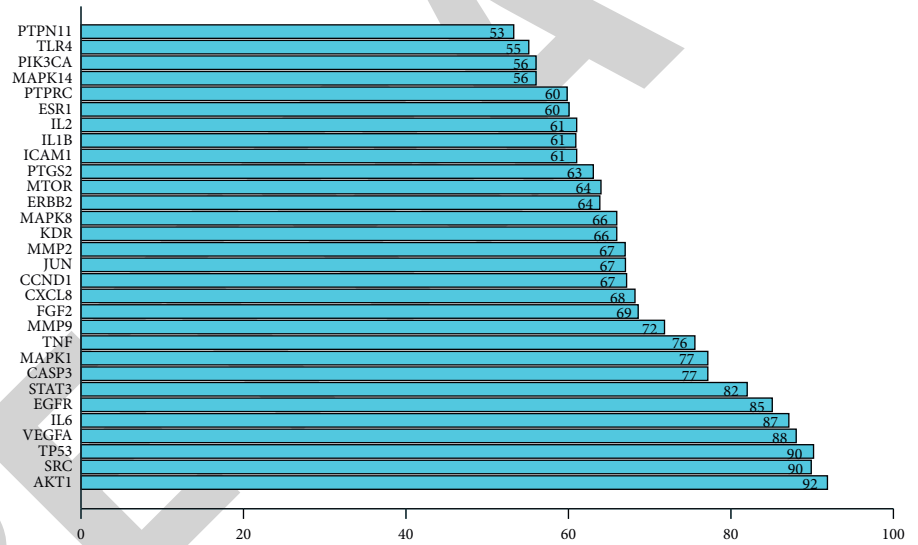

Figure 5: Screening of the top 30 genes based on the PPI topology analysis.

ingredients associated with the alleviation of fibrosis, was confirmed to attenuate endometrial fibrosis in a rat with IUA through TGF-β1/Smad Pathway [22]. Similarly to Bushen Huoxue decoction, Guishen Huoxue decoction is a traditional drug formulation, consisting of *Paeonia lactiflora*, *Ligusticum wallichii*, the root of red-rooted salvia, *Angelica sinensis*, fruit of Chinese wolfberry, *Astragalus membranaceus*, Spatholobus stem, fruit of glossy privet, Chinese yam, fruit of medicinal cornel, prepared rehmannia root, seed of Chinese seed of Chinese dodder, improves renal function and promotes blood circulation [23, 24].

In this study, we performed drug-disease regulatory network construction and the PPI network construction to obtain the core genes of Guishen Huoxue decoction for the treatment of IUA, and the core genes were analyzed by GO function enrichment and KEGG pathway enrichment to explore their potential molecular mechanisms. A total of 134 common targets were obtained from Guishen Huoxue decoction and IUA, and five core genes, including AKT1, SRC, TP53, VEGFA, and IL-6, were mainly enriched in PI3K/Akt, Rap1, Ras, and AGE-RAGE signaling pathways. IUA is a fibrotic disease, that is, the serious damage of the endometrial basal layer promotes a large number of fibrocyte proliferations and excessive deposition of extracellular matrix, leading to the partial or complete replacement of endometrial tissue by fibrous tissue [25]. VEGF is the major inducer of angiogenesis in a variety of in vivo models and plays an essential role in numerous physiological and

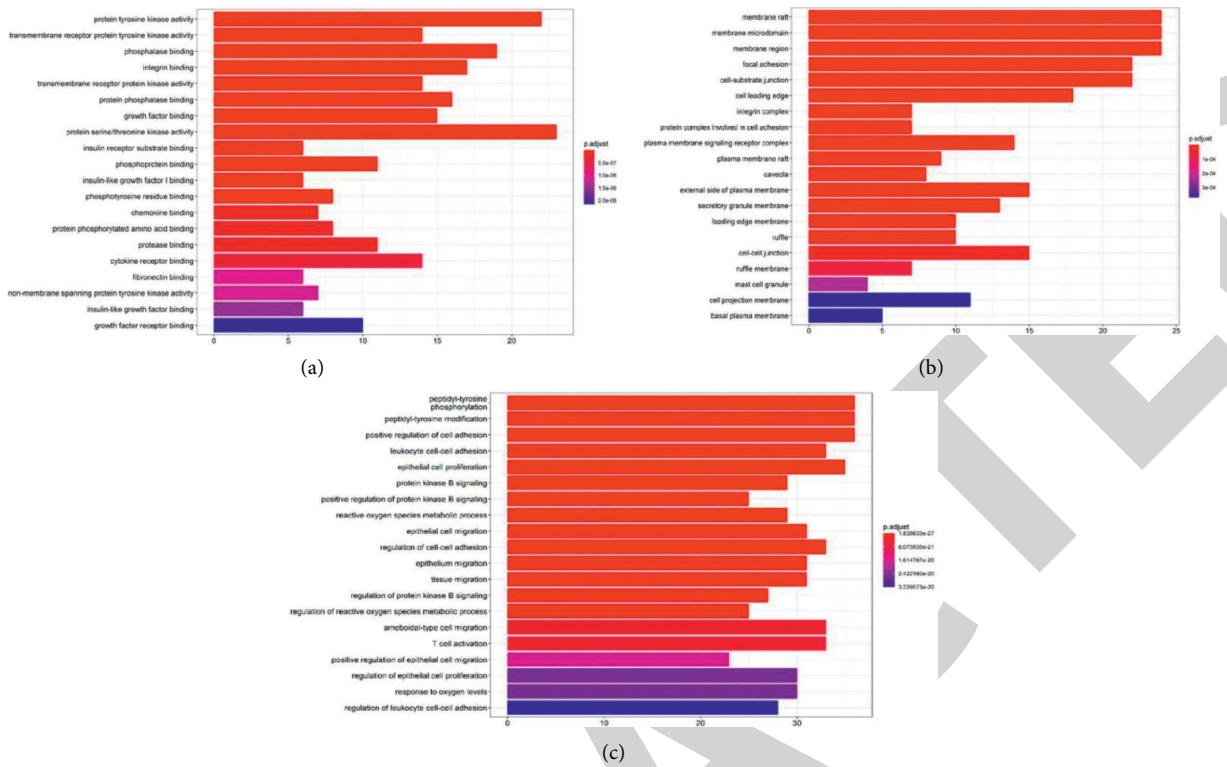

Figure 6: GO functional enrichment analyses of common genes. Significant enrichment of common genes in MF (molecular function) category (a), CC (cellular component) category (b), and BP (biological process) category (c) (the top 20 GO terms for each category are listed).

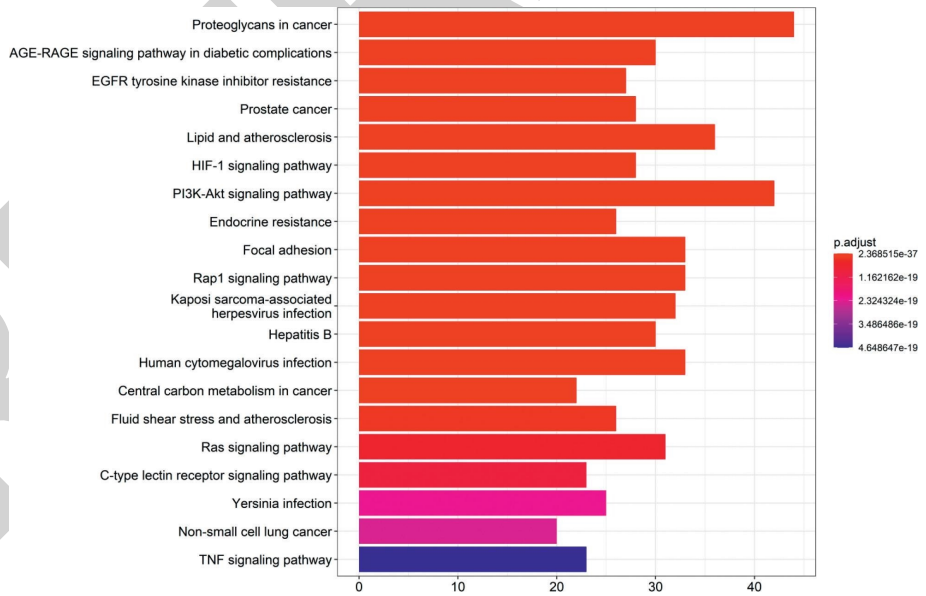

Figure 7: KEGG pathway enrichment analysis of common genes. The red color indicates a small p value and the blue color indicates a large p value; the size of the bars represents the degree of enrichment, and larger bars reflect a larger gene ratio.

pathological processes, including angiogenesis and immune response [26, 27]. Increased expression of VEGF has been reported to alleviate endometrium injury in a wounded rat uterus [28]. The patients with IUA showed vascular closure in endometrial tissues and had significantly increased VEGF expression after therapy, suggesting angiogenesis in the endometrial tissues may affect the endometrial repair [29]. A series of abnormal inflammatory cells and inflammatory responses in the uterine cavity promote the development of fibrosis. A in vivo experiment described by Ai et al. [30]

demonstrated that alleviation of the inflammatory response and epithelial-to-mesenchymal transition process enhanced endometrium regeneration rats. IL-6 is a typical cytokine that maintains homeostasis and contributes to host defense by activating acute phase responses and hematopoietic and immune responses [31]. IL-6 and IL-10 levels were associated with endometrial lesions in equines, which can be considered as inflammatory indexes to evaluate the pathological progress of the equine endometrium [32]. The role of AGE-RAGE signaling has been demonstrated in the progression of various diseases such as diabetes, cardiovascular diseases, neurodegenerative disorders, and cancer [33]. Studies have found that increased levels of AGE and its receptor RAGE are associated with ovarian senescence and induce inflammatory responses [34].

AKT1 plays a key role in cell growth and survival in various diseases. Nie et al. manifested that [35] AKT1 mediated the progression of idiopathic pulmonary fibrosis by inducing macrophages to produce IL-13. PI3K/Akt mediates cell apoptosis, proliferation, and differentiation of bone marrow stem cells and endothelial progenitor cells and was involved in IUA pathogenesis [36]. Rap1 and Ras regulate cell development and participate in the growth and survival of normal and cancer cells[37]. The Rap1 signaling pathway is involved in the cAMP-mediated decidualization of human endometrial stromal cells [38]. The Ras signaling pathway medicates the pathogenesis of RIF induced by endometrial receptivity insufficiency and regulates Talin1 expression (a local adhesion complex protein) in the endometrium. Steroid hormones, including estrogen and progesterone, are involved in mammalian reproduction and regulate the development and function of the uterus by mediating the transcription of specific genes in the uterus [39]. As the largest nonreceptor tyrosine kinases, SRC and SRC family kinases are proto-oncogenes that play vital roles in cell proliferation, invasion and metastasis, angiogenesis, and bone metabolism [40]. Furthermore, SRC family kinases have been identified to be related to the function of steroid responses [41], and SRC activation is critical for decidualization, maintaining remodeling, and differentiation of the estradiol-primed endometrium [42]. It was reported that the TP53 gene, as a tumor suppressor, has mutated in more than 45,000 single cell and germline mutations, accounting for more than 50% of human tumor gene mutations [43], including endometrial cancer [44]. TP53 function loss leads to endometrial hyperplasia and promotes aggressive or metastatic endometrial cancers [45].

In summary, our study based on network pharmacology shows that AKT1, SRC, TP53, VEGFA, and IL-6 in Guishen Huoxue decoction might be potential biomarkers for the treatment of IUA, and Guishen Huoxue decoction regulates fibrosis, inflammatory response, and oxidative stress response through several main signaling pathways including PI3K-Akt, Rap1, Ras, and AGE-RAGE. This study has conducted a preliminary theoretical discussion on the use of Guishen Huoxue decoction in the treatment of IUA. In the future, we need to verify our results through molecular docking analysis of drug-disease targets and active chemical compounds as well as experimental validation in cell and animal models.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Study on the Relationship between the Use of Bisphosphonates for Antiosteoporosis and Vertebral Re-Fracture after Vertebroplasty

Li Qian, Qian Chen, Dashou Wang, Qi Pan, Qianhong Jian, and Yinghong Ma

Department of Pain Medicine, Orthopedic Hospital of Guizhou Province, Guiyang 550002, Guizhou, China

Correspondence should be addressed to Li Qian; wsql-bio@163.com

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Objective. To explore the effect of bisphosphonates after vertebroplasty in patients with osteoporotic vertebral compression fractures (OVCF), and to analyze the relationship between the use of bisphosphonates and vertebral refracture. *Methods*. A total of 150 patients with OVCF were selected from the pain department of our hospital from January 2018 to May 2020. All patients received vertebroplasty after admission, and were divided into the surgery group (62 cases) and combined with the bisphosphonates group (combined group, 88 cases) according to whether patients had used bisphosphonates after surgery. Before surgery, 1 month, 3 months, 6 months, and 1 year after surgery, visual analogue scale (VAS), Oswestry disability index (ODI), vertebral body and femoral neck bone mineral density (BMD), and Cobb Angle were collected, and the differences among groups were compared to analyze the treatment effect. After the follow-up, patients were divided into two groups according to whether vertebral refracture occurred during the follow-up period. Clinical characteristics, general information, and surgical indicators of patients in the two groups were collected, and related factors of postoperative vertebral refracture were analyzed. *Results*. There were no significant differences in preoperative VAS score, ODI index, BMD value, and Cobb angle between the two groups ($P > 0.05$). At 12 months after surgery, VAS score, ODI index, and Cobb angle decreased, while BMD value increased in both groups. The VAS score, ODI index, and Cobb angle in the combined group were lower than those in the operation group, while the BMD value was higher than that in the operation group, and the difference was significant ($P < 0.05$). The results of multivariate regression analysis showed that in BMD, no postoperative antiosteoporosis treatment, bone cement leakage, and poor cement diffusion were independent risk factors for vertebral refracture after vertebroplasty in patients with vertebral compression fractures. *Conclusion*. In order to avoid recurrent fractures in OVCF patients, attention should be paid to BMD, whether patients take antiosteoporosis drugs, whether bone cement permeation occurs and the diffusion of bone cement, etc. The above factors are the main influencing factors leading to recurrent fractures after PKP and PVP in the clinic.

1. Introduction

Osteoporotic fractures are the most common bone diseases in middle-aged and elderly people, among which the spine is the most common site of osteoporotic fractures [1]. Osteoporotic vertebral compression fracture (OVCF) is one of the most common and serious complications of osteoporosis. It mostly occurs in the lower thoracic and upper lumbar segments, and the main symptoms of patients with OVCF are severe pain in the lower back, especially when changing body position [2, 3]. The treatment of OVCF varies, and most patients can obtain good clinical results with conservative treatment, while a small proportion of patients have poor results with conservative treatment and require surgical intervention. Percutaneous vertebro plasty (PVP) or percutanouskyphoplasty (PKP) are the main procedures for the current clinical treatment of OVCF. [4]. PVP and PKP, as relatively mature minimally invasive surgeries for elderly OVCF, have been widely applied in clinical practice with their advantages such as rapid relief of patients' pain symptoms, improvement of vertebral stability, reduction of bed time and early return to normal activities compared with conservative treatment [5, 6].

Although vertebral plasty in the treatment of vertebral compression fractures, but not fundamentally in the treatment of osteoporosis, in clinical practice, so there will be

a part of after surgery in patients with osteoporosis will still appear the symptom of back pain, and vertebral bone cement injection, as a result of the surgery stiffness enhancement, it will lead to increased risk of vertebral fracture again [7]. At present, according to literature research findings [8, 9], most of the vertebral fractures that occur after vertebroplasty occur in the adjacent vertebrae near the operating vertebrae. At present there is no large-scale clinical study to reduce PKP holds the vertebral fractures of postoperative recurrence of related research, and the specific reasons for nonsurgical vertebral fractures also has no unified conclusion, but for postmenopausal women with osteoporosis, measures for preventing nonoperative vertebral fracture again hair, to reduce the risk of vertebral fracture again hair is of great significance. Bisphosphonates are currently the first-line drugs for the treatment of osteoporosis, which can inhibit the function of osteoclasts and induce apoptosis of osteoclasts, reduce bone resorption and thus improve bone mineral density and reduce the incidence of fractures [10–12]. There are only studies on the efficacy of vertebroplasty combined with bisphosphonate use in the treatment of OVCF, but no studies on the correlation between antiosteoporosis treatment with bisphosphonates and refracture. Therefore, this project aims to investigate the correlation between the use of bisphosphonates against osteoporosis in patients with osteoporosis after vertebroplasty on the reoccurrence of new vertebral fractures, to understand whether the use of bisphosphonates is effective in reducing the reoccurrence of vertebral fractures and to provide more definite scientific evidence to the clinic.

2. Clinical Data

2.1. Subjects. In this study, OVCF patients admitted to the Department of Pain (Guizhou Orthopedic Hospital) of our hospital from January 2018 to May 2020 with concurrent surgical treatment were collected. The clinical data of 150 patients who met the inclusion criteria were retrospectively analyzed during 2 years of postoperative follow-up. Patients were divided into the operation group and the combined group according to whether they were treated with zoledronic acid after operation.

2.2. Diagnostic Criteria of OVCF. Diagnosis of OVCF [13] required the combination of patient history, clinical manifestations, and imaging evidence as the judgment criteria, of which imaging examination was the main means of diagnosis and the gold standard. The diagnosis should meet the following conditions: (1) low back pain, accompanied by limited movement, the pain was aggravated when changing the body position, and the symptoms were relieved when braking rest and bed rest; (2) Typical physical examination: patients were often passive because of pain, the corresponding vertebral spinous process, and paravertebral tenderness; (3) Anteroposterial-lateral radiographs of thoracolumbar spine or CT could suggest vertebral compression and wedge degeneration, MRI of thoracolumbar spine could suggest corresponding vertebral edema, and *T* value of orthotopic spine or femoral neck BMD was less than −2.5.

2.3. Inclusion Criteria. OVCF patients were admitted to our hospital and emergency department. In the first diagnosis and discovery of vertebral compression fracture, vertebral compression was not more than 2 segments. The clinical data, imaging data, and follow-up data of the patients were complete.

2.4. Exclusion Criteria. Abnormal coagulation function; infection of the intended puncture site; vertebral compression fractures of more than 2 segments; vertebral bone protrusion into the spinal canal leads to spinal canal stenosis; spinal tumor, spinal *tuberculosis*; serious heart and lung diseases, liver and kidney dysfunction; severe gastrointestinal diseases, mental diseases; illiterate; and patients who had been treated with bisphosphonates for osteoporosis.

2.5. Shedding or Rejection Criteria. Duration of hospitalization in pain department <7 days; lost to follow-up after discharge; automatically discharged from hospital during treatment; serious complications occurred during hospitalization (malignant arrhythmia, myocardial infarction, cardiac arrest, local anesthetic poisoning, drug allergy, severe decline in muscle strength, etc.); those who were assessed to need surgery; and reject the experimenter midway.

2.6. Criteria for Loss of Follow-Up. Those who left the hospital automatically and did not have telephone contact information, those who refused to follow-up by telephone, or those who could not receive follow-up visits during the follow-up period due to death or other force majeure factors.

3. Treatment Process

3.1. Basic Treatment. The patient rested in bed, wore a belt, could be given nonsteroidal drugs to control symptoms, and daily routine pain department treatment, i.e., the appropriate phase of posterior spinal nerve block, was performed to observe the changes in the patient's pain.

3.2. Surgical Treatment. 250 ml of 0.9% sodium chloride + 5 mg of dexamethasone intravenous drops were routinely given before surgery to prevent intraoperative adverse reactions, and SPO_2, BP, and ECG were continuously monitored intraoperatively. The patient was placed prone on the operating table with conventional disinfection cloth, and the body surface projection of bilateral vertebral pedicle was taken under the guidance of C-arm fluoroscopy, i.e., (Bull's eye sign) as the puncture point. 3 ml of 2% lidocaine was given at the puncture point. After the effect of local layer by layer anesthesia, a bone cement puncture needle (2.5 mm) was inserted at the puncture point on both sides, and the needle was directly pierced to the pedicle of the vertebral body under c-arm anteroposition and lateral fluoroscopy

monitoring. After the tip was broken, it was estimated that the tip could enter the vertebral body through the pedicle under C-arm anteroposial fluoroscopy monitoring, so the tip was slowly advanced under the guidance of C-arm anteroposial fluoroscopy to adjust the tip direction and straight into the middle 1/3 of the anterior vertebral body. C-arm anteroposial fluoroscopy suggested that the tip was in a good position. The bone cement paste was injected with a bone cement injector under the guidance of C-arm fluoroscopy, and the amount of bone cement injected into each side of each vertebral body was about 2.0 ml. Dynamic observation showed no external leakage of bone cement. The film was saved before and after needle extraction, followed by a band-aid to protect the puncture site.

3.3. Drug Therapy. Antiosteoporosis drugs were bisphosphonates, 70 mg of alendronate was given orally once a week or 5 mg of zoledronate was given intravenously once a year, combined with oral calcium as the basic treatment of antiosteoporosis.

4. Observation Methods

Outpatient follow-up or telephone follow-up were performed at 1, 3, 6, 12, and 24 months after Plo to observe the patients' recovery and recurrence of vertebral fractures. The evaluation criteria for recurrence fractures were based on the diagnosis, inclusion, and exclusion criteria of the enrolled patients, all of which were due to fracture recurrence caused by osteoporosis. The assessment measures included Oswestry disability index (ODI), bone mineral density (BMD), Visual Analogue Scale (VAS), and imaging. After the follow-up, patients were divided into two groups according to whether vertebral refracture occurred during the follow-up period. Clinical characteristics (site of initial fracture, standardized antiosteoporosis treatment), general information (age, gender, and BMI), and surgical indicators (preoperative BMD, bone cement injection amount, bone cement leakage, bone cement diffusion, etc.) of patients in the two groups were collected, and related factors of postoperative vertebral refracture were analyzed.

4.1. ODI. The [14] method was composed of 10 questions, including pain intensity, self-care, lifting, walking, sitting, standing, sleep interference, sexual life, social life, and travel. Each question consists of six choices. Each question consisted of 6 options, each question consisted of 5 questions with a score of 0 for the first option selected and 5 questions with a score of 5 for the 5^{th} option selected in order. If all 10 questions were answered, ODI = actual score/50(highest possible score)×100%, and 2 questions were not answered, ODI = actual score/40 × 100%. The lower the score, the less severe the dysfunction, and vice versa, the higher the score.

4.2. VAS Score. The [15] ruler with pain score scale was turned away from the patient, and the position representing pain degree was marked on the ruler. According to the position score, 0~2 was classified as excellent, 3~5 as good, 6~8 as acceptable, and above 8 as poor. VAS score can make objective evaluation of pain, simple and easy to operate.

4.3. BMD Measurement. The BMD of L2–L4 vertebral body was measured and the corresponding T value was calculated by the osteocore-3two-dimensional cone flash full digital dual energy X-ray (DEXA) osteometer (MEDILINK Company). T value ≥ -1 was normal, between -2.5 and -1.0 for bone loss, and ≤ -2.5 for osteoporosis.

4.4. Measurement of the Vertebral Kyphosis Angle (Cobb angle) at the Sagittal Position of the Fractured Vertebral Body. The vertebral body with compression fracture was confirmed on the thoracolumbar lateral X-ray film, and a horizontal line was drawn along the lower edge of the upper vertebral body and the upper edge of the lower vertebral body, respectively. The angle included by the vertical line of the two horizontal lines was the Cobb angle.

5. Statistical Methods

The data were input into SPSS L 6.0 for statistical analysis. Comparison was performed by T test, measurement data were expressed by mean soil standard deviation (Mean ± SD), count data were expressed by rate (%) using χ^2 tests, and grade data were compared by rank sum test (Wilcoxon two-sample comparison method). $P < 0.05$ indicated statistically significant differences between the sample groups.

6. The Results

6.1. Comparison of General Data at Diagnosis between the Surgery Group and the Combined Group. Comparison of the general data of patients at diagnosis showed that there were no statistically significant differences between the surgery group and the combined group in the general data at diagnosis, including gender, age, BMI, BMD value, VAS score, and fracture site ($P > 0.05$). The results are shown in Table 1:

6.2. Comparison of Clinical Efficacy between the Operation Group and the Combined Group. There were no significant differences in preoperative VAS score, ODI index, BMD value, and Cobb angle between the two groups ($P > 0.05$). At 12 months after surgery, VAS score, ODI index, and Cobb angle decreased, while BMD value increased in both the groups. The VAS score, ODI index, and Cobb angle in the combined group were lower than those in the operation group, while BMD value was higher than that in the operation group, and the difference was significant ($P < 0.05$). According to the differences in VAS score, ODI index, BMD value, and Cobb angle between the two groups one year before and after surgery, the combined use of bisphosphonates had a better promoting effect on pain relief, symptom improvement, and BMD improvement in OVCF patients, as shown in Figure 1:

Table 1: Comparison of general data at diagnosis between the surgery group and the combined group.

Factors		Operation group ($n = 75$)	Combined group ($n = 75$)	t/χ^2)	P
Gender	Male	15 (20.00)	17 (22.67)	0.159	0.690
	Female	60 (80.00)	58 (77.33)		
Age (years)		71.80 ± 8.59	72.53 ± 8.41	0.526	0.600
BMI (kg/m^2)		23.31 ± 4.22	22.89 ± 4.16	0.614	0.540
BMD (T)		−3.62 ± 0.74	−3.59 ± 0.80	0.238	0.812
VAS (分)		8.05 ± 0.74	8.09 ± 0.69	0.342	0.733
Fracture site	≤T10	14 (18.67)	16 (21.33)	0.187	0.911
	T10~L2	49 (65.33)	48 (64.00)		
	L3~L5	12 (16.00)	11 (14.67)		

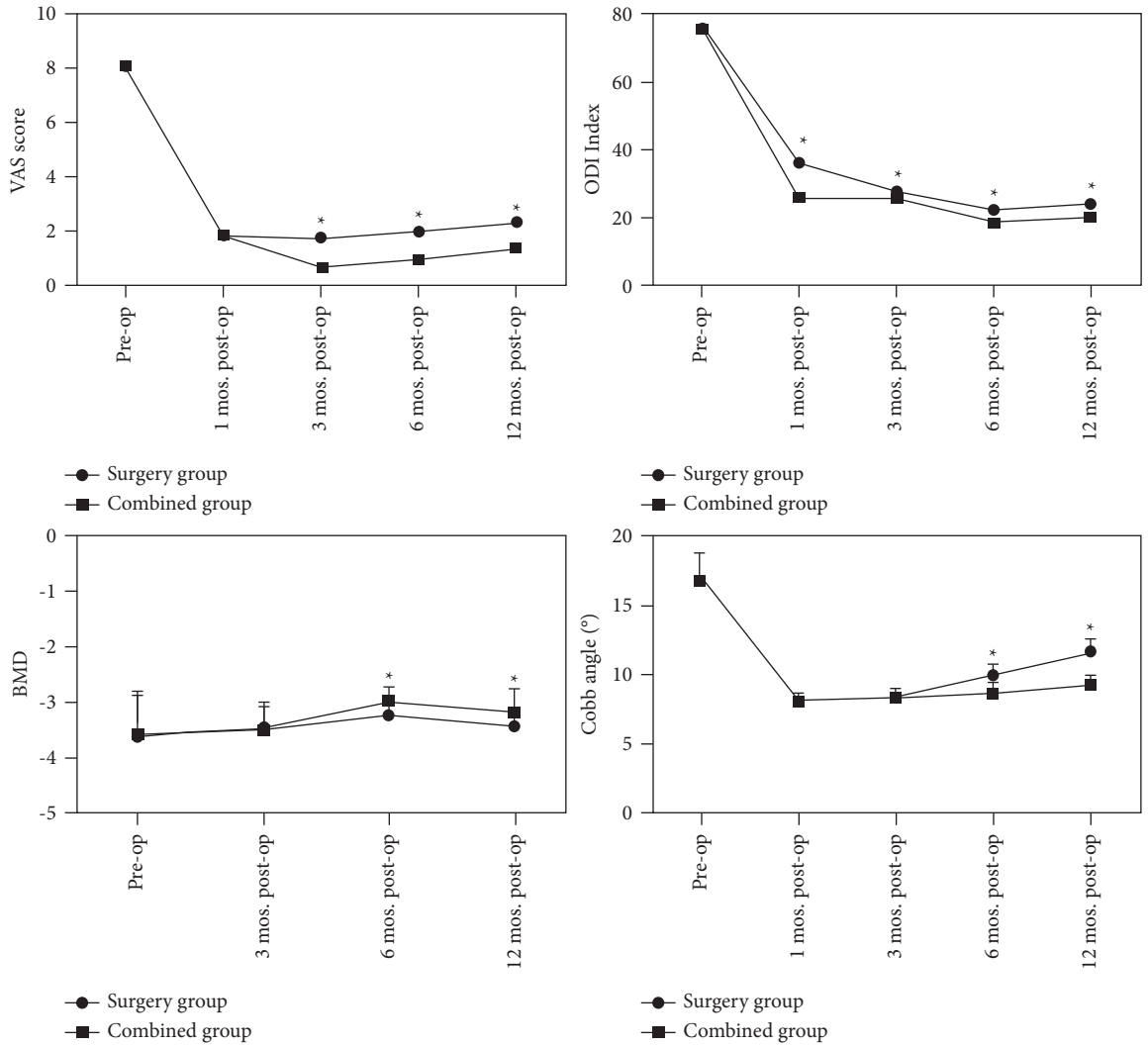

Figure 1: Comparison of clinical efficacy between the operation group and the combined group. Note: * in the figure indicates that at this time point, the difference between the two groups is statistically significant, $P < 0.05$.

6.3. Comparison of Clinical Data between the Refracture Group and the Nonrefracture Group. Univariate analysis of the clinical data of patients in the refracture group and the nonrefracture group showed that there was no significant difference in the basic data of the two groups, including gender, BMI, and initial fracture site ($P > 0.05$). There were significant differences in age, BMD value, VAS score, and postoperative antiosteoporosis treatment between the two groups, suggesting that age, BMD value, VAS score, and postoperative antiosteoporosis treatment may be related to the occurrence of refracture after vertebroplasty ($P < 0.05$), and the results are shown in Table 2:

Table 2: Comparison of clinical data between the refracture group and the nonrefracture group.

Factors		Refracture group ($n = 29$)	Nonrefracture group ($n = 121$)	t/χ^2	P
Gender	Male	6 (20.69)	26 (21.49)	0.009	0.925
	Female	23 (79.31)	95 (78.51)		
Age (years)		68.10 ± 10.86	73.14 ± 7.54	3.586	0.001
BMI (kg/m^2)		21.92 ± 5.69	23.38 ± 3.71	1.698	0.092
BMD (T)		−3.97 ± 0.94	−3.52 ± 0.70	2.897	0.004
VAS (points)		7.82 ± 0.97	9.13 ± 0.71	8.273	0.001
Initial fracture site	≤T10	8 (27.58)	22 (18.18)	1.621	0.445
	T10~L2	16 (55.17)	81 (66.94)		
	L3~L5	5 (17.24)	18 (14.88)		
Postoperative antiosteoporosis therapy	Yes	12 (41.38)	88 (72.73)	10.345	0.001
	No	17 (58.62)	33 (27.27)		

6.4. Comparison of Surgical Factors between the Refracture Group and the Nonrefracture Group. A single factor analysis was conducted on the operative indicators of the refracture group and the nonrefracture group, and the results showed that there was no statistical significance in the operative indicators, including the amount of bone cement injection, surgical method, and puncture method, between the two groups ($P > 0.05$). The proportion of bone cement diffusion and cement leakage in the refracture group was significantly higher than that in the nonrefracture group, suggesting that poor bone cement diffusion and cement leakage may be related to the occurrence of refracture after vertebroplasty ($P < 0.05$), and the results are shown in Table 3:

6.5. Analysis of Influencing Factors of Refracture after Vertebroplasty. The indicators with significant differences in the univariate analysis were used as independent variables (assigned as in the univariate analysis), and the patients were entered into a multifactorial logistic regression analysis with the occurrence of postoperative refracture as the dependent variable. The results showed that BMD, failure of postoperative antiosteoporosis treatment, cement leakage, and poor cement dispersion were independent risk factors for the occurrence of refracture after vertebroplasty in patients with vertebral compression fractures ($P < 0.05$), and the results are shown in Table 4:

7. Discussion

Patients with senile and postmenopausal osteoporosis are prone to OVCF due to slight external force due to the loss of vertebral bone mass and significant decline in vertebral strength and bearing capacity. It is the most common complication of postmenopausal osteoporosis (PMOP) and senile osteoporosis, and the main clinical manifestations are pain at the fracture site, limited movement, and kyphotic shape of the spine; Severe cases can lead to disability [16, 17]. Vertebroplasty (PVP/PKP) is an effective minimally invasive procedure for the treatment of OVCF, providing significant pain relief, reducing the incidence of postoperative complications, and allowing patients to get out of bed early and facilitate postoperative recovery [18]. There is no clear understanding of the causes and mechanisms of vertebral refracture after vertebroplasty in patients with OVCF, and it is still controversial whether vertebroplasty causes vertebral refracture.

In this study, 29 of 150 patients with OVCF had secondary vertebral fractures, with a prevalence of 19.33%, a result similar to that reported by Dai et al. [19] reported similar results. At present, the factors affecting secondary vertebral fractures after OVCF vertebroplasty are often divided into two categories: first, the patient's own factors, such as advanced age and preoperative complications of osteoporosis; second, the factors of local biomechanical changes due to vertebral body strengthening, such as the puncture method, cement dispersion, distribution, and leakage in the vertebral body. MA et al. [20] reported no statistically significant difference in the incidence of postoperative secondary vertebral fractures in the conservative treatment group compared with the PVP surgery group, and therefore attributed it to the natural course of osteoporosis, whereas the present study found that patient age was not an independent risk factor for refracture after vertebroplasty, which does not yet support the above conclusion. BMD is an important index for diagnosing osteoporosis and reflecting the efficacy of antiosteoporosis treatment. Low BMD reflects a higher degree of osteoporosis, and the more osteoporotic the vertebral body is, the more likely it is to refracture, which is a risk factor for nonoperative vertebral refracture, and some scholars found that the main risk factor for refracture after vertebroplasty is low BMD through comparative analysis [21]. The BMD of the refractured group in this study was lower than that of the nonrefractured group, and the difference was statistically significant, in line with the above findings, and low BMD was found to be an independent risk factor for vertebral refracture after logistic multifactor analysis. Bone cement leakage is a common complication after vertebroplasty, and a study [22] found that the irreversible damage to soft tissues and bone at the site of cement leakage due to heat setting of bone cement may be a risk factor for refracture after vertebroplasty, and in this study, bone cement leakage was used as an observation index to confirm that bone cement leakage is an associated risk factor for refracture. It was found that good cement dispersion significantly reduced the risk of secondary vertebral fracture after surgery. The results of this study showed that the incidence of refracture was significantly higher in patients with

Table 3: Comparison of surgical factors between the refracture group and the nonrefracture group.

Factors		Refracture group ($n = 29$)	Nonrefracture group ($n = 121$)	t/χ^2	P
Bone cement injection volume (mL)		6.02 ± 2.13	5.52 ± 2.76	0.912	0.363
Bone cement leakage	Yes	10 (34.48)	21 (18.36)	4.088	0.043
	No	19 (65.52)	99 (81.82)		
Bone cement	Bad	18 (62.07)	36 (29.75)	10.604	0.001
	Good	11 (37.93)	85 (70.25)		
Surgical method	PVP	18 (62.07)	68 (56.20)	0.330	0.566
	PKP	11 (37.92)	53 (43.80)		
Puncture mode	Unilateral	23 (79.31)	98 (80.99)	0.042	0.837
	Bilateral	6 (20.39)	23 (19.01)		

Table 4: Analysis of influencing factors of refracture after vertebroplasty.

Indicators	B	SE	Walds	OR	95% CI	P
Age	0.312	0.308	1.518	1.366	0.747~2.498	0.273
BMD	0.511	0.230	11.312	1.667	1.062~2.616	0.001
Postoperative antiosteoporosis therapy (yes vs. no)	0.078	0.016	19.330	1.081	1.048~1.116	<0.001
Bone cement leakage (yes vs. no)	0.036	0.008	6.136	1.037	1.021~1.053	0.009
Bone cement dispersion (good vs. bad)	0.416	0.122	5.246	1.516	1.193~1.925	0.021

poor cement dispersion than in those with good cement dispersion, and the results of multifactorial analysis showed that poor cement dispersion was an independent risk factor for the occurrence of refracture. This may be related to poor cement dispersion resulting in inadequate axial weight-bearing stresses in the unreinforced region, secondary to recollapse fractures and progressive kyphosis of the reinforced vertebrae, as well as uneven support between the reinforced and unreinforced regions, inconsistent stiffness and postoperative stress concentration transfer to adjacent vertebrae, and overall spinal biomechanical changes [23].

Bisphosphonates are currently the first-line drugs for the clinical treatment of osteoporosis, with long-term clinical data demonstrating their safety and reliability [24, 25]. In this study, we observed the changes of pain, limb function, BMD, and Cobb angle in patients with OVCF after vertebroplasty and standardized antiosteoporosis treatment with bisphosphonates. The results showed that the improvement of ODI index and BMD values at 12 months after surgery were significantly better in the combined group than in the surgical group, indicating that the combined standardized antiosteoporosis drug treatment after surgery can promote the improvement of BMD, relieve pain, and improve quality. We also used whether postoperative antiosteoporosis treatment was standardized as an observation indicator for postoperative refracture in OVCF patients, and the results confirmed that failure to standardize postoperative antiosteoporosis treatment was an independent risk factor for the occurrence of refracture.

In conclusion, in order to avoid recurrent fractures in OVCF patients after surgery, attention should be paid to BMD, whether the patient is taking antiosteoporosis drugs, whether bone cement infiltration occurs, and the dispersion of bone cement. The above factors are the main factors that cause recurrent fractures after PKP and PVP in clinical practice, and should be strictly noted and prevented during the clinical treatment with PKP and PVP in order to improve the clinical prognosis of patients and reduce the occurrence of recurrent fractures.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Retraction

Retracted: Analysis of Immunotherapy Combined with Radiotherapy in Patients with Brain Metastasis of Driver Gene-Negative Non-Small-Cell Lung Cancer

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] Q. Zhang, S. Zhou, H. Yin, C. Zhu, D. Li, and X. Li, "Analysis of Immunotherapy Combined with Radiotherapy in Patients with Brain Metastasis of Driver Gene-Negative Non-Small-Cell Lung Cancer," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 1193075, 7 pages, 2022.

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Research Article

Analysis of Immunotherapy Combined with Radiotherapy in Patients with Brain Metastasis of Driver Gene-Negative Non-Small-Cell Lung Cancer

Qun Zhang,[1,2,3] Shixiang Zhou,[2] Hongmei Yin,[2] Chaomang Zhu,[2] Duojie Li,[2] and Xianming Li[1,4]

[1]*Jinan University, Guangzhou 510632, Guangdong, China*
[2]*Department of Radiotherapy, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233000, Anhui, China*
[3]*Anhui Province Key Laboratory of Translational Cancer Research, Bengbu Medical College, Bengbu 233030, Anhui, China*
[4]*Department of Radiation Oncology, The 2nd Clinical Medical College (Shenzhen People's Hospital) of Jinan University, Shenzhen 518020, Guangdong, China*

Correspondence should be addressed to Xianming Li; lixianming126@126.com

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Purpose. To observe the remission rate and side effects of immunotherapy combined with radiotherapy in patients with brain metastasis of driver gene-negative non-small-cell lung cancer (NSCLC). *Methods*. 152 patients with NSCLC brain metastasis admitted to our hospital from January 2019 to December 2021 were selected as the research objects. Patients were divided into a single group (85 cases) and a combined group (67 cases) according to treatment methods. The therapeutic effects and side effects of the single group and combined group were compared. In addition, the patients who received immunotherapy combined with radiotherapy were divided into three subgroups: A, B, and C, and the therapeutic effects and side effects of different radiotherapy modes were compared among group A [whole brain radiotherapy (WBRT)], group B (WBRT combined with local radiotherapy) and group C (local radiotherapy). *Results*. The objective response rate (ORR) and disease control rate (DCR) in the combined group were higher than those in the single group ($P < 0.05$). The incidence of reactive capillary hyperplasia and immune-related pneumonia in the combined group were higher than that in the single group ($P < 0.05$). There was no significant difference in the incidence of other side effects between the two groups ($P > 0.05$). ORR and DCR in group B were higher than those in group A ($P < 0.05$). There was no significant difference in the incidence of side effects among the three groups ($P > 0.05$). *Conclusion*. Immunotherapy combined with radiotherapy is effective in patients with brain metastasis of driver gene-negative NSCLC, which can improve the disease control rate without increasing the side effects. In addition, WBRT combined with local push radiotherapy is effective and safe. *Clinical Study Registration Number*. The Clinical study registration number is K2019086.

1. Introduction

It is reported that in 2020, the number of lung cancer cases worldwide is 2.2 million, ranking second among all cancers. The worldwide death toll of lung cancer is 1.8 million, ranking first among all cancers [1]. As the most common type of lung cancer, non-small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancers [2]. Brain metastasis is one of the distant metastasis sites of NSCLC, which can cause various neurological symptoms, making the patient's condition worse. At the same time, the treatment is difficult. Brain metastases occur in 10% to 15% of patients with NSCLC at the time of the first diagnosis and in 24% to 44% of patients with advanced NSCLC [3]. For NSCLC patients with brain metastasis, about 20% of them have negative driving genes, most of which are single, and the number of metastatic foci is small [4]. The so-called driver gene-negative NSCLC is, under the existing molecular detection conditions, unable to identify the driver gene, or although there are rare mutation sites, but there is no

targeted therapy plan (including relevant clinical research plan) at this stage of the patient population, can be defined as negative gene-driver NSCLC. Because NSCLC brain metastasis has no typical clinical manifestations in the early stage, patients tend to ignore the occurrence and progress of the disease, resulting in some patients being in the terminal stage of the tumor at the time of diagnosis and missing the opportunity for radical surgery [5]. Therefore, it is of great significance to explore an effective treatment mode for NSCLC patients with brain metastasis.

At present, chemotherapy and radiotherapy are usually used to treat NSCLC brain metastasis clinically, which is helpful to delay tumor progression and improve the quality of life of patients. However, for patients with brain metastasis of driver gene-negative NSCLC, only radiotherapy and chemotherapy may have some limitations.[6]. With the continuous improvement of medical technology, in recent years, immunotherapy, represented by immune checkpoint inhibitors, has been widely favored in the treatment of NSCLC. Immunotherapy can control brain metastases and prolong the survival time of patients with advanced lung cancer [7]. Camrelizumab is a programmed death receptor 1(PD-1) immune checkpoint inhibitor independently developed by China, which can inhibit the activation of *T* lymphocytes through the PD-1 pathway and produce a sustained antitumor effect. In addition, immunotherapy has made a new breakthrough in the treatment of advanced lung cancer, liver cancer, and esophageal cancer [8, 9].

For patients with brain metastasis of driver gene-negative NSCLC, it is still inconclusive whether combined immunotherapy is needed at the same time as radiotherapy. By applying immunotherapy combined with radiotherapy to patients with brain metastasis of NSCLC with a negative driving gene, we observed the remission rate and side effects of this treatment mode and discussed the benefits of different radiotherapy modes in order to improve the quality of life of patients.

2. Materials and Methods

2.1. Research Object. 152 patients with brain metastasis of driver gene-negative NSCLC admitted to our hospital from January 2019 to December 2021 were selected as the research objects. Patients were divided into a single group (85 cases) and a combined group (67 cases) according to treatment methods.

Inclusion criteria were as follows: (1) conforming to the diagnosis of NSCLC, combined with pathological biopsy; (2) brain metastasis of lung cancer was diagnosed by chest CT and cranial MRI, accompanied by symptoms of brain metastasis, and there was at least one measurable lesion in the brain; (3) 8 items of wax block high-throughput sequencing of lung lesions showed negative driving genes; (4) PD-1/PD-L1 was positive; (5) Karnofsky (KPS score) score > 60 points (The patient can take care of himself/herself for the most part, but occasionally needs help from others. The higher the KPS score, the better the patient's health.); (6) estimated survival time > 3 months; (7) patients have indications for immunotherapy and radiotherapy, but no indications for surgery.

Exclusion criteria were as follows: (1) history of brain therapy; (2) there are contraindications to radiotherapy; (3) metastasis of the bone, abdomen, and other parts; (4) other malignant tumors; (5) combined with other important organ diseases; (6) treatment with immunosuppressant in the past 1 month; (7) those who are allergic to research drugs; (8) incomplete clinical data.

2.2. Research Methods

The combined group was treated with immunotherapy combined with radiotherapy.

Immunotherapy: patients were given camrelizumab for injection (Suzhou Shengdiya Biomedical Co., Ltd., specification: 200 mg/ bottle, national medicine standard word: S20190027), intravenous injection, 200 mg/time, once every 3 weeks, until the disease progressed or the patient could not tolerate it.

Radiotherapy: the patients were divided into group A (whole brain radiotherapy (WBRT)), group B (WBRT combined with local radiotherapy group), and group C (local radiotherapy group) by different radiotherapy modes. All patients lie on their backs on the treatment bed, and the head and face are fixed with a special mask, which is close to the patient's skin and positioned by laser. The scanning range is from the skull top to the skull base, with a thickness of 1.5 mm–3 mm. Images were obtained, and the target area was delineated by MRI. The radiotherapy techniques include 6MV-X-ray 3D CRT (three-dimensional conformal radiotherapy) or IMRT (intensity-modulated radiotherapy). Group A was treated with WBRT: clinical target volume (CTV) was the whole brain, and planning tumor volume (PTV) was 0.5 cm outside the skull. The total dose is 30–40 Gy/10–20 times. Group B was treated with WBRT combined with local push radiotherapy, push synchronously with WBRT or partial push of shrink field after WBRT, and the radiotherapy technique (3DCRT local push irradiation or IMRT local push irradiation) was selected according to the different locations, number, size of intracranial lesions, and histological types of primary lesions. Gross tumor volume (GTV) is the brain metastasis seen in the image, CTV is 0.3 cm outside GTV and PTV is 0.5 cm outside CTV. The total dose of brain metastases was 40–60 Gy/10–30 times. Group C was treated with local radiotherapy: radiotherapy technology (3DCRT radiotherapy or IMRT radiotherapy) was selected according to the location, number, size, and histological type of intracranial lesions. GTV is the brain metastasis seen in images, CTV is 0.3 cm for GTV and PTV is 0.5 cm for CTV. The total dose of brain metastases was 40–60 Gy/10–30 times. All patients were treated with dehydration, diuresis, hormone, and other methods according to their condition.

(2) The single group was treated with WBRT combined with local radiotherapy. Radiotherapy operation is consistent with the combination group.

2.3. Observation Index. Collect the clinical data and case information of all patients. The therapeutic effects and side effects of the single group and combined group were compared. In addition, the patients who received immunotherapy combined with radiotherapy were selected as subgroups for analysis, and the therapeutic effects and side effects of groups A, B, and C under different radiotherapy modes were compared.

Clinical data: including gender, age, body mass index (BMI), smoking history, course of the disease, pathological type, and the number of brain metastases.

Evaluation criteria of curative effect: 1 month after treatment, the curative effect was evaluated according to the response evaluation criteria in solid tumors (RECIST) version 1.1 [10]. It can be divided into complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), objective response rate (ORR) = (CR + PR) cases/total cases × 100%, disease control rate (DCR) = (CR + PR + SD) cases/total cases × 100%.

Toxic and side effects: 1 month after the treatment, the toxic and side effects of patients were counted. The severity of toxic and side effects is divided into 1–5 grades. According to the severity, they are reactive capillary hyperplasia, leukopenia, radiation brain injury, and immune-related pneumonia.

2.4. Follow-Up. All patients were followed up after three months of treatment. The follow-up time was six months, and the patients' condition was known through follow-up or telephone every month. In addition, the data on progression-free survival (PFS) and overall survival (OS) were collected 6 months after the treatment, and no cases were lost to follow-up.

2.5. Statistical Methods. SPSS 22.0 was used for statistical analysis. The data were expressed in percentages, and the χ^2-test was used for comparison between groups. $P < 0.05$ indicates that the difference was significant.

3. Results

3.1. Comparison of Clinical Data between Two Groups. There was no significant difference between the two groups in terms of gender, age, BMI, smoking history, course of NSCLC pathological type, and the number of brain metastases ($P > 0.05$). (Table 1).

3.2. Comparison of Short-Term Curative Effect between Two Groups. The combined group ORR (56.72%) was higher than that of the single group (37.65%), and the combined group DCR (80.60%) was higher than that of the single group (64.71%) ($P < 0.05$). The PFS rate was 58.82% (50/85), the OS rate was 74.12% (63/85) in the single group; the PFS rate was 68.66% (46/67), OS rate was 80.59% (54/67) in the combined group. The PFS rate and OS rate of the combined group were higher than those of the single group, but there was no significant difference between the two groups ($P > 0.05$). (Table 2, Figure 1).

3.3. Comparison of Toxic and Side Effects between Two Groups. The incidence of reactive capillary hyperplasia and immune-related pneumonia in the combined group were higher than that in the single group ($P < 0.05$). There was no significant difference in the incidence of other side effects between the two groups ($P > 0.05$). (Table 3).

3.4. Comparison of Short-Term Curative Effect of Three Groups under Different Radiotherapy Modes. There were significant differences in ORR and DCR among the three groups ($P < 0.05$). ORR and DCR in group B were higher than those in group A ($P < 0.05$). There was no significant difference in ORR and DCR between group B and group C ($P > 0.05$). The PFS rate was 50.00% (10/20), OS rate was 70.00% (14/20) in group A; the PFS rate was 80.00% (20/25), OS rate was 84.00% (21/25) in group B; the PFS rate was 72.73% (16/22), OS rate was 86.36% (19/22) in group C. The PFS rate and OS rate of groups B and C were higher than those of group A, but there was no significant difference between the three groups ($P > 0.05$). (Table 4, Figure 2).

3.5. Comparison of Toxic and Side Effects of Three Groups in Different Radiotherapy Modes. There was no significant difference in the incidence of side effects among the three groups ($P > 0.05$). (Table 5).

4. Discussion

At present, patients with brain metastasis of driver gene-negative NSCLC have a poor prognosis, short survival time, and poor tolerance to conventional therapy [11]. Traditional chemotherapy drugs are often difficult to exert their efficacy because of the existence of the blood-brain barrier and tumor self-protection mechanism. Conventional radiotherapy has a low therapeutic effect due to insufficient local radiotherapy dose [12]. Therefore, there is an urgent need for new clinical treatments to control the progress of tumors. In recent years, immunotherapy has provided new therapeutic hope for NSCLC patients with brain metastasis. Immune checkpoint inhibitors can activate the immune system and enhance antitumor activity, and have made rapid progress in many fields of tumor treatment. [13].

Radiotherapy can directly or indirectly destroy the DNA of tumor cells to induce tumor cells to become immunogenic cells during apoptosis. $CD8^+$T cells recognize the tumor antigen presented in MHC-I class and then activate it, thus producing an antitumor effect on nonradiation areas [14]. At the same time, radiotherapy can strengthen the immune response by regulating the tumor immune

Table 1: Comparison of clinical data between two groups (n, %).

Group	Single group ($n = 85$)	Combined group ($n = 67$)	χ^2 value	P value
Gender				
Male	46 (54.12%)	34 (50.75%)	0.171	0.679
Female	39 (45.88%)	33 (49.25%)		
Age (years)				
< 60	37 (43.53%)	28 (41.79%)	0.012	0.913
≥ 60	48 (56.47%)	39 (58.21%)		
BMI (kg/m^2)				
< 24	45 (52.94%)	49 (63.64%)	1.897	0.168
≥ 24	40 (47.06%)	28 (36.36%)		
Smoking history				
With	51 (60.00%)	37 (55.22%)	0.351	0.554
Without	34 (40.00%)	30 (44.78%)		
Course of NSCLC (months)				
< 5	66 (77.65%)	53 (79.10%)	0.047	0.829
≥ 5	19 (22.35%)	14 (20.90%)		
Pathological type				
Adenocarcinoma	78 (91.76%)	59 (88.06%)	0.578	0.447
Nonadenocarcinoma	7 (8.24%)	8 (11.94%)		
Number of brain metastases				
	50 (58.82%)	36 (53.73%)	0.395	0.529
> 3	35 (41.18%)	31 (46.27%)		

Table 2: Comparison of short-term curative effect between two groups (n, %).

Group	CR	PR	SD	PD	ORR	DCR
Single group ($n = 85$)	0 (0.00%)	32 (37.65%)	23 (27.06%)	30 (35.29%)	32 (37.65%)	55 (64.71%)
Combined group ($n = 67$)	3 (4.48%)	35 (52.24%)	16 (23.88%)	13 (19.40%)	38 (56.72%)	54 (80.60%)
χ^2 value					5.484	4.664
P value					0.019	0.031

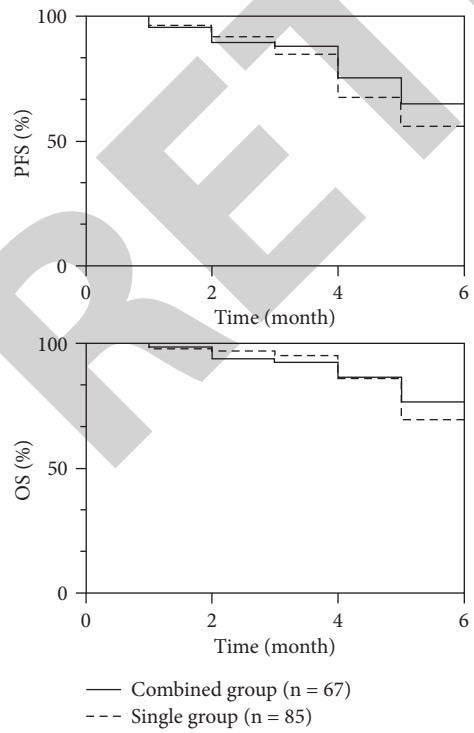

Figure 1: Comparison of survival between two groups.

microenvironment, and achieve the synergistic effect of antitumor. Radiotherapy can up-regulate the expression level of PD-L1 on the surface of tumor cells, promote the expression of inflammatory cytokines, normalize abnormal blood vessels, activate endothelial cells, and promote the infiltration of T cells in tumors [15]. Studies have shown that the occurrence of brain metastasis in advanced NSCLC is related to the immune escape of tumors. [16]. Tumors can interact with the immune system. When the proliferation rate of tumor cells exceeds the immune response ability of the body, tumor cells can gradually gain the ability of immune escape through immune editing and then invade and migrate [17]. PD-1, a type I transmembrane protein that plays an important role in tumor immune escape, is also a coinhibitory surface molecule of the CD28 immunoglobulin superfamily. It is encoded by the human programmed cell death protein 1 gene and is mainly expressed on the surface of activated T cells, B cells, and natural killer cells. PD-1 binds to programmed death protein ligand-1(PD-L1) or programmed death protein ligand-2(PD-L2), which inhibits the activation of T cells and makes T cells lose their antitumor activity, thus changing the tumor microenvironment and inhibiting immune response [18, 19].

Carrilizumab is a humanized PD-1 antibody, which can bind to PD-1 and block the PD-1/PD-L1 pathway, inhibit the activation and proliferation of T lymphocytes, mediate

Table 3: Comparison of toxic and side effects between two groups (n, %).

Group	Single group ($n = 85$)	Combined group ($n = 67$)	χ^2 value	P value
Reactive capillary hyperplasia	0 (0.00%)	33 (49.25%)	53.475	<0.001
Leukopenia	24 (28.24%)	21 (31.34%)	0.174	0.677
Radiation brain injury	3 (3.53%)	4 (5.97%)	0.508	0.476
Immune-related pneumonia	0 (0.00%)	3 (4.48%)	3.883	0.049

Table 4: Comparison of short-term curative effect of three groups under different radiotherapy modes (n, %).

Group	CR	PR	SD	PD	ORR	DCR
Group A ($n = 20$)	0 (0.00%)	6 (30.00%)	6 (30.00%)	8 (40.00%)	6 (30.00%)	12 (60.00%)
Group B ($n = 25$)	2 (8.00%)	16 (64.00%)	5 (20.00%)	2 (8.00%)	18 (72.00%)*	23 (92.00%)*
Group C ($n = 22$)	1 (4.54%)	13 (59.09%)	5 (22.73%)	3 (13.64%)	14 (63.63%)*	19 (86.36%)
χ^2 value					8.623	7.972
P value					0.013	0.019

Note. Compared with group A, $_P * < 0.05$.

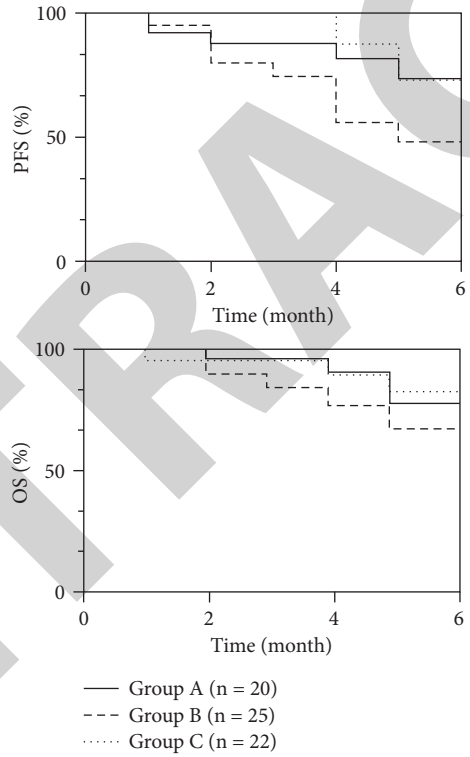

Figure 2: Comparison of survival among the three groups.

Table 5: Comparison of toxic and side effects of three groups in different radiotherapy modes (n,%).

Group	Group A ($n = 20$)	Group B ($n = 25$)	Group C ($n = 22$)	χ^2 value	P value
Reactive capillary hyperplasia	11 (55.00%)	12 (48.00%)	10 (45.45%)	0.407	0.816
Leukopenia	7 (35.00%)	10 (40.00%)	4 (18.18%)	2.766	0.251
Radiation brain injury	0 (0.00%)	2 (8.00%)	2 (9.09%)	1.835	0.400
Immune-related pneumonia	1 (5.00%)	1 (4.00%)	1 (4.55%)	0.026	0.987

the negative immune regulation process, and then play an antitumor role [20]. In this study, the ORR, the DCR, the PFS rate, and OS rate of the combined group were higher than those of the single group, and there was no significant difference in the incidence of toxic and side effects such as leucocytopenia and radiation brain injury between the two groups. The results show that immunotherapy combined with radiotherapy has a good effect in patients with brain

metastasis of NSCLC with a negative driver gene, which can improve the disease control rate without increasing the side effects. Immunotherapy can not only enhance the antitumor effect of cellular immunity but also enhance the normal immune response of the body to avoid the imbalance of immune tolerance and immune-related reactions in tumor patients. Among the subjects in our combined group, those with toxic side effects such as reactive capillary hyperplasia and immune-related pneumonia have been partially relieved after symptomatic treatment, and no serious death cases have occurred. This shows that immunotherapy combined with radiotherapy is safe and controllable.

The results showed that the ORR and DCR of group B were higher than those of group A under different radiotherapy modes, and there was no significant difference between group B and group C. The PFS rate and OS rate of groups B and C were higher than those of group A. There was no significant difference in the incidence of side effects among the three groups. This shows that compared with WBRT alone, the effective rate of WBRT combined with local push radiotherapy is higher, which can obviously improve the effective rate and disease control rate of intracranial lesions, without significantly increasing the related toxic and side effects. WBRT is the main treatment for brain metastasis, which can promote the entry of systemic therapeutic drugs by opening the blood-brain barrier. However, due to dose limitation and the patient's organ tolerance, WBRT still has the risk of treatment failure or local recurrence [21]. In addition, WBRT can lead to irreversible neurological complications, which will affect patients' neurocognitive function, and has certain limitations [22]. In addition, local radiotherapy alone can achieve a high local control rate, but it cannot eliminate small metastases, and new brain metastases are easy to occur, with poor prognosis [23]. In WBRT combined with local radiotherapy, WBRT can eliminate micrometastases, reduce recurrence and prevent new brain metastases, etc. Local radiotherapy can control large micrometastases and improve the tumor control rate. This therapy can increase the local irradiation dose of the lesion as much as possible and reduce the irradiation dose to the surrounding normal tissues, thereby avoiding the occurrence of side effects of radiotherapy. [24]. After WBRT, local radiotherapy for NSCLC patients with brain metastasis can reduce the treatment target volume, improve the tumor control rate, reduce local recurrence and the occurrence of intracranial new tumors, and relieve the clinical symptoms of patients to some extent [25].

5. Conclusion

To sum up, immunotherapy combined with radiotherapy is effective in patients with brain metastasis of driver gene-negative NSCLC, which can improve the disease control rate without increasing the side effects. In addition, WBRT combined with local radiotherapy is effective and safe. It is still necessary to further explore the timing of immunotherapy combined with radiotherapy and the best choice of radiotherapy dose.

Data Availability

The data used during the current study are available from the corresponding author.

Disclosure

Qun Zhang and Shixiang Zhou are the co-first authors.

Conflicts of Interest

To the best of our knowledge, the authors declare that they have no conflicts of interest, financial or otherwise.

Acknowledgments

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Research Article

Effects of Drug-Coated Balloon Therapy on CT Imaging Results and Levels of Vascular Inflammatory Cytokines in Patients with Arteriosclerosis Obliterans Lesions

Yanlin Yang

Department of Interventional Radiology, Harrison International Peace Hospital, Hengshui, Hebei 053000, China

Correspondence should be addressed to Yanlin Yang; yyl13315835537@163.com

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Objective. The aim of the study is to explore the effects of drug-coated balloon (DCB) therapy on computed tomography (CT) imaging results and levels of vascular inflammatory cytokines in patients with arteriosclerosis obliterans (ASO) lesions. *Methods*. A total of 200 patients with ASO lesions admitted to our hospital from January 2021 to December 2021 were enrolled. According to the random number table method, they were divided into observation groups ($n = 100$) and control groups ($n = 100$). The observation group was treated with DCB, while the control group was treated with ordinary balloon. At 1 month after surgery, the clinical curative effect was evaluated by ankle-brachial index (ABI). The image quality was compared and vascular patency was evaluated by arterial ultrasound and CT angiography. The minimum luminal diameter (MLD) and late luminal loss (LLL) were recorded. Before and at 1 month after surgery, the severity of disease was assessed by Rutherford grading of lower limb ischemia. Before, at 7 d and 1 month after surgery, inflammatory factors [serum matrix metalloproteinase-9 (MMP-9), monocyte chemoattractant protein-1 (MCP-1), high sensitivity C-reactive protein (hs-CRP), interleukin-4 (IL-4), interleukin-6 (IL-6)] were compared between the two groups. The occurrence of postoperative complications was recorded. *Results*. The clinical response rate in the observation group was significantly higher than that in the control group (97.00% *vs* 89.00%) ($P < 0.05$). The restenosis rate in the observation group was significantly lower than that in the control group (1.00% *vs* 7.00%) ($P < 0.05$). The MLD in the observation group was significantly longer than that in the control group, and the LLL was significantly lower than that in the control group ($P < 0.05$). There was no significant difference in image quality between the two groups ($P > 0.05$). After surgery, disease severity in both groups was relieved, which was milder in the observation group than in the control group ($P < 0.05$). At 7 d and 1 month after surgery, levels of MMP-9, MCP-1, hs-CRP, IL-4, and IL-6 in both groups were decreased, which were lower in the observation group than in the control group ($P < 0.05$). There was no significant difference in the incidence of complications between the two groups (6.00% *vs* 7.00%) ($P > 0.05$). *Conclusion*. The curative effect of DCB is good on patients with ASO lesions, which can reduce the restenosis rate, control luminal loss, relieve inflammatory response, and improve disease severity.

1. Introduction

Arteriosclerosis obliterans (ASO) refers to arteriosclerosis in the lower body. Common symptoms include lower extremity pain, chills, and inability to move. If the disease cannot be treated in time, the symptoms of lower extremity ulceration will also occur. In severe cases, it may lead to amputation, which is harmful to the patient's physical and mental health [1]. In the past, an open surgical bypass was used for treatment, but due to the large trauma and risk of surgery, coupled with the influence of anesthesia and other factors, the patient's inflammatory factors changed greatly and the prognosis was poor [2]. A large number of released inflammatory factors cause the body to show a high inflammatory state, which will aggravate the damage to vascular function and more easily lead to the occurrence of postoperative restenosis in patients. Therefore, it is of great significance for ASO patients to take effective measures to reduce the inflammatory reaction caused by surgical trauma. In recent years, minimally invasive treatment represented by endovascular interventional therapy

has become the dominant method for ASO. Drug-coated balloons (DCB) have become a new clinical treatment trend because of their minimally invasive, repeatable, limb preservation, and other characteristics [3]. Studies have shown [4] that DCB has a significant advantage in reducing postoperative restenosis rates in patients with ASO due to its surface covering with antiangiogenic drugs. However, there are few reports on the effect of this procedure on inflammatory factors in patients with ASO. Therefore, this study explored the effect of DCB treatment on CT imaging results and levels of vascular inflammatory cytokines in patients with ASO, in order to guide clinical medication and improve postoperative vascular flow rate.

2. Materials and Methods

2.1. General Information. A total of 200 patients with ASO lesions who were admitted to our hospital from January 2021 to December 2021 were selected. The inclusion criteria were as follows: ① meet the relevant diagnostic criteria of ASO [5]; ② have surgical indications; and ③ patients and their family members understand and agree to this study. The exclusion criteria were as follows: ① severe hepatic and renal insufficiency (hepatic function grade C, renal function stage 4, or above); ② severe cardiac insufficiency (cardiac function grade 3 or above); ③ iodine allergy; ④ the patient's condition deteriorated rapidly in the preoperative preparation stage; and ⑤ no contraindication to surgery. The enrolled patients were divided into an observation group ($n = 100$) and control group ($n = 100$) by the 1 : 1 random number table method. In the observation group, there were 54 males and 46 females aged 52–74 years, with an average of (63.27 ± 4.64) years; 57 cases of hypertension, 36 cases of diabetes mellitus, and 14 cases of coronary heart disease; the lesion length was 10–17 cm, with an average of (13.57 ± 1.26) cm. In the control group, there were 61 males and 39 females, aged 52–74 years, with an average of (63.32 ± 4.43) years; 51 cases of hypertension, 38 cases of diabetes mellitus, and 19 cases of coronary heart disease; the lesion length was 10–17 cm, with an average of (13.48 ± 1.30) cm. There was no significant difference in the general data between the two groups ($P > 0.05$).

2.2. Methods. Surgical method: The patient is placed in the supine position, after routine draping and disinfection, local anesthesia is applied, and then puncture is performed (anterograde ipsilateral femoral artery or retrograde lateral femoral artery). A 4-F vascular sheath was placed, heparin sodium was injected intravenously, heparin was added according to the operation time, and angiography was performed to understand the lesion location and the location of the patient. If there are stenotic and occluded arteries in all limbs, conventional catheter and guide wire techniques should be used to pass through the stenotic lesions, and SIA technology should be used to pre-dilate the occlusive lesions with a balloon with a smaller diameter. Then, we use balloon dilatation. The observation group was expanded with DCB (surface-coated paclitaxel, Beijing Kangtai Huizhong Technology Co., Ltd.) with the same diameter as the original stent inner diameter for 2–3 minutes (10–12 atmospheres); the control group was expanded with ordinary balloons (10–12 atmospheres). If the residual stenosis after expansion is ≥ 30% or there is a dissection that affects blood flow, a stent is implanted.

Postoperative intervention: we routinely subcutaneously inject low molecular weight heparin sodium (manufacturer: Italian Alfa Wassermann SpA, approval number: registration number H20140282) 0.1 mL/kg, 2 times/d; alprostadil injection (manufacturer: Harbin Pharmaceutical Group Bioengineering Co., Ltd., approval number: Guoyao Zhunzi H20084565) intravenous drip, 10 μg/time, 2 times/d, continuous medication for 3 days. After discharge from the hospital, we continue to use dual antibodies (aspirin and clopidogrel) for more than 6 months.

Examination method: Philips 256-slice spiral CT was used, the patient was in the supine position, and the scanning range: 2 cm above the bifurcation of the abdominal aorta to the toes of both lower extremities. The setting parameters are 120 kw, 180 mA, the layer thickness is 10 mm, and the building layer thickness is 10 mm. After the scan, the data were transferred to the GE 4.0 workstation for multislice reconstruction, maximum density projection, and volume reconstruction, and then combined with plain scan and enhanced axial images for analysis.

2.3. Observation Indicator

2.3.1. Clinical Efficacy and Imaging Indicators. One month after the operation, an ankle-brachial index (ABI) examination [6] was used to evaluate the clinical efficacy. The calculation method of ABI: The systolic blood pressure ratio of the posterior tibial artery to the brachial artery was measured once bilaterally and the mean value was taken (normal values range from 0.9 to 1.3). Effective: ABI increased by more than 0.2, the ASO site was safely opened or residual stenosis was less than 30%, distal arterial pulsation resumed, and clinical symptoms and signs improved or disappeared. Effective rate = Effective cases/total cases × 100%. Lower extremity arterial Doppler ultrasonography was used to measure and calculate the restenosis rate (the stenosis rate ≥50% is the vascular restenosis [4]) and record the minimum luminal diameter (MLD) and target vessel late luminal loss (LLL).

2.3.2. Image Quality. CT examination was performed 1 month after the operation, and the image quality was analyzed by two or more senior radiologists [7]. Level 1: artery are clearly visible without artifact. Level 2: arteries are clearly displayed, and peripheral veins can be slightly displayed. Level 3: arteries can be clearly displayed, but peripheral veins are clearly visualized. Level 4: arterial vessels are not visualized. The higher the grade, the worse the CT contrast image quality.

2.3.3. Severity of Illness. At 1 day before surgery and 1 month after surgery, the Rutherford classification of lower extremity ischemia [8] was used to evaluate the

severity of the patient's condition. Level 0: Asymptomatic. Level 1: Mild intermittent claudication, treadmill test can be completed. Level 2: Moderate intermittent claudication. Level 3: Severe intermittent claudication, unable to complete the treadmill test. Level 4: Pain at rest may occur due to replacement of the position above the foot. Level 5: Slight tissue defect. Level 6: Tissue ulceration, gangrene. The lower the grade, the better the patient's condition is controlled.

2.3.4. Inflammatory Factors. At 1 day before surgery and 7 days and 1 month after surgery, 3–4 ml of fasting blood was drawn from the patient with a vacuum blood collection tube containing a coagulant on an empty stomach in the morning, and the samples were stored in a refrigerator at −20°C Matrix metalloproteinase -9 (MMP-9), monocyte-macrophage chemoattractant factor -1 (MCP-1), and high-sensitivity C-reactive protein (hs-CRP) were all detected by enzyme-linked immunosorbent assay (Reagents and kits were provided by Shanghai Yaji Biotechnology Co., Ltd.), and serum interleukin-4 (IL-4) and interleukin-6 (IL-6) levels were detected by chemiluminescence detection (reagents and kits were provided by Beijing Soleibo Technology Co., Ltd.); all tests were performed by the same physician in strict accordance with the test instructions.

2.3.5. Complications. All patients were followed up for one month after the operation. Postoperative complications such as infection, puncture site hematoma, renal function impairment, and thrombosis were recorded in the two groups of patients.

2.4. Statistical Processing. The clinical data of patients with ASO lesions in this study were analyzed by SPSS 22.0 software, and the measurement data that met normal distribution and homogeneity of variance, such as MLD, LLL, and inflammatory factor indicators, were expressed as (mean ± sd). The differences between the observation group and the control group without time points were compared using a two-sample independent t test, and the differences between groups with time points were compared with repeated measures analysis of variance. Before and after the operation, the differences between the observation group and the control group were compared by paired t test, the count data were expressed by case (%), the χ^2 test was performed, and the rank data were subjected to the rank sum test, suggesting statistical significance.

3. Results

3.1. Comparison of Clinical Efficacy and Vascular Patency between the Two Groups. The clinical efficacy rate of patients in the observation group was 97.00%, which was significantly higher than that in the control group (89.00%) ($P < 0.05$); the restenosis rate was 1.00%, which was significantly lower than 7.00% in the control group ($P < 0.05$) as shown in Table 1.

Table 1: Comparison of clinical efficacy and vascular patency between the two groups (n (%)).

Groups	Effective rate	Vascular restenosis rate
Observation group ($n = 100$)	97 (97.00)	1 (1.00)
Control group ($n = 100$)	89 (89.00)	7 (7.00)
χ^2	4.916	4.688
P	0.027	0.030

3.2. Comparison of Imaging Indexes between the Two Groups. The MLD in the observation group was significantly higher than that in the control group and the LLL was significantly lower than that in the control group ($P < 0.05$), as shown in Figure 1.

3.3. Comparison of Image Quality between the Two Groups. There was no significant difference in image quality between the two groups ($P > 0.05$). See Table 2 for details.

3.4. Comparison of Disease Severity between the Two Groups. Before surgery, there was no significant difference in the severity of illness between the two groups ($P > 0.05$); after the operation, the severity of patients in both groups decreased, and the observation group was lower than the control group ($P < 0.05$). See Table 3 for details.

3.5. Comparison of Inflammatory Factor Levels between the Two Groups. Before the operation, there was no significant difference in MMP-9, MCP-1, hs-CRP, IL-4, and IL-6 between the two groups ($P > 0.05$). After the operation, the levels of MMP-9, MCP-1, hs-CRP, IL-4 and IL-6 in two groups were decreased as compared with those before the operation; the decrease was more significant 1 month after the operation as compared with that 7 days after the operation; and the observation group was lower than the control group ($P < 0.05$). See Figure 2 for details.

3.6. Comparison of the Incidence of Complications between the Two Groups. At follow-up within 1 month after the operation, there was no significant difference in the incidence of complications between the two groups (6.00% vs 7.00%) ($P > 0.05$). See Table 4 for details.

4. Discussion

In recent years, with the increase of risk factors such as hypertension and diabetes, the incidence of ASO lesions has also increased significantly, mainly manifested as a series of symptoms and signs such as intermittent claudication, weakened or disappeared arterial pulse, and nutritional supply disorder of limb tissue. At present, there are many clinical treatment methods for patients with ASO lesions, including drug therapy, balloon dilation, and stent implantation. However, studies have pointed out [9] that such treatment methods are not effective. Therefore, the search

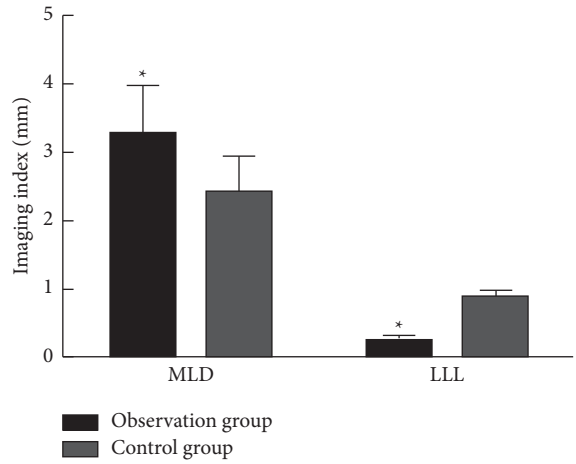

Figure 1: Comparison of imaging indicators between the two groups. Compared with the control group, $^*P < 0.05$.

Table 2: Comparison of image quality between the two groups (n (%)).

Groups	Level 1	Level 2	Level 3	Level 4
Observation group ($n = 100$)	86 (86.00)	12 (12.00)	2 (2.00)	0 (0.00)
Control group ($n = 100$)	81 (81.00)	11 (11.00)	5 (5.00)	3 (3.00)
Z		1.210		
P		0.272		

for safer and more effective treatment methods has become a focus of clinical attention. This article will discuss the application value of DCB therapy in patients with ASO lesions from the aspects of imaging indicators, efficacy, inflammatory factors, severity, and complications, in order to provide an evidence-based basis for the selection of clinical treatment methods.

The clinical efficacy of the observation group was significantly higher than that of the control group, and the restenosis rate and disease severity were significantly lower than those of the control group, which was consistent with previous research results [10], suggesting that DCB has a higher clinical efficacy in the treatment of patients with ASO lesions and can improve the patient's condition and reduce postoperative restenosis rate. Analysis of the reasons may be because DCB is coated with paclitaxel, which can inhibit intimal hyperplasia, on the surface of the traditional balloon, which can not only play a role in expanding the lesion but also release paclitaxel into the local vascular intima, so that the paclitaxel can interact with the lesion and the blood vessel wall is fully contacted, and the drug penetrates into the arterial wall through antiproliferation and anti-inflammatory effects, inhibiting and delaying the migration and proliferation of smooth muscle cells, thereby achieving the purpose of continuously inhibiting the mitosis of smooth muscle cells and inhibiting intimal hyperplasia [11, 12]. So, DCB can increase the long-term patency rate of blood vessels, reduce the restenosis rate, effectively improve the patient's condition, relieve clinical symptoms, and improve the curative effect. In this study, the MLD of the observation group was significantly higher than that of the control group, and the LLL was significantly lower than that of the control group, indicating that DCB treatment is beneficial to control lumen loss and effectively maintain adequate vascular lumen in patients. Because DCB combines the balloon with the drug elution technology, the balloon shows that the drug paclitaxel, which inhibits cell proliferation, is attached to the balloon, which hinders the promotion of smooth muscle cells to a certain extent, and can ensure sufficient lumen diameter and avoid lumen loss.

The imbalance of vascular endothelial cell function leads to an increase in the levels of inflammatory mediators and cytokines secreted and released by the vascular endothelial cells, resulting in a long-term microinflammatory response in the blood vessels. The most important part of atherosclerosis is chronic inflammation, which is significantly related to the pathological changes of vascular disease. Therefore, the imbalance of vascular endothelial cell function leads to a long-term microinflammatory reaction in blood vessels, which is the pathological basis of the ASO. MMP-9 is an important factor promoting the development of atherosclerosis, and its level reflects the formation of atherosclerosis and plaque stability; IL-4 and IL-6 act as proinflammatory factors, and their elevated levels reflect the progression of atherosclerosis to a certain extent; hs-CRP is a nonspecific inflammatory factor secreted by the liver, and studies have pointed out [13] that its elevated level is related to the occurrence, development, and prognosis of acute coronary syndrome, and is an important inflammatory factor in the development of atherosclerosis. As an initiating factor and marker of inflammation, MCP-1 has chemotaxis and activation effects on monocytes, which can expand the inflammatory response and participate in the progression of atherosclerosis [14]. In this study, after seven days and one month of treatment, the levels of MMP-9, MCP-1, hs-CRP, IL-4, and IL-6 in the observation group were significantly lower than those in the control group, indicating that DCB

Table 3: Comparison of disease severity between the two groups (n (%)).

Groups	*Preoperation*						*Postoperation*					
	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Observation group ($n = 100$)	5 (5.00)	34 (34.00)	27 (27.00)	21 (21.00)	13 (13.00)	0 (0.00)	37 (37.00)	31 (31.00)	26 (26.00)	5 (5.00)	1 (1.00)	0 (0.00)
Control group ($n = 100$)	7 (7.00)	29 (29.00)	33 (33.00)	21 (21.00)	10 (10.00)	0 (0.00)	29 (29.00)	27 (27.00)	29 (29.00)	9 (9.00)	6 (6.00)	0 (0.00)
Z	0.030						3.870					
P	0.858						0.049					

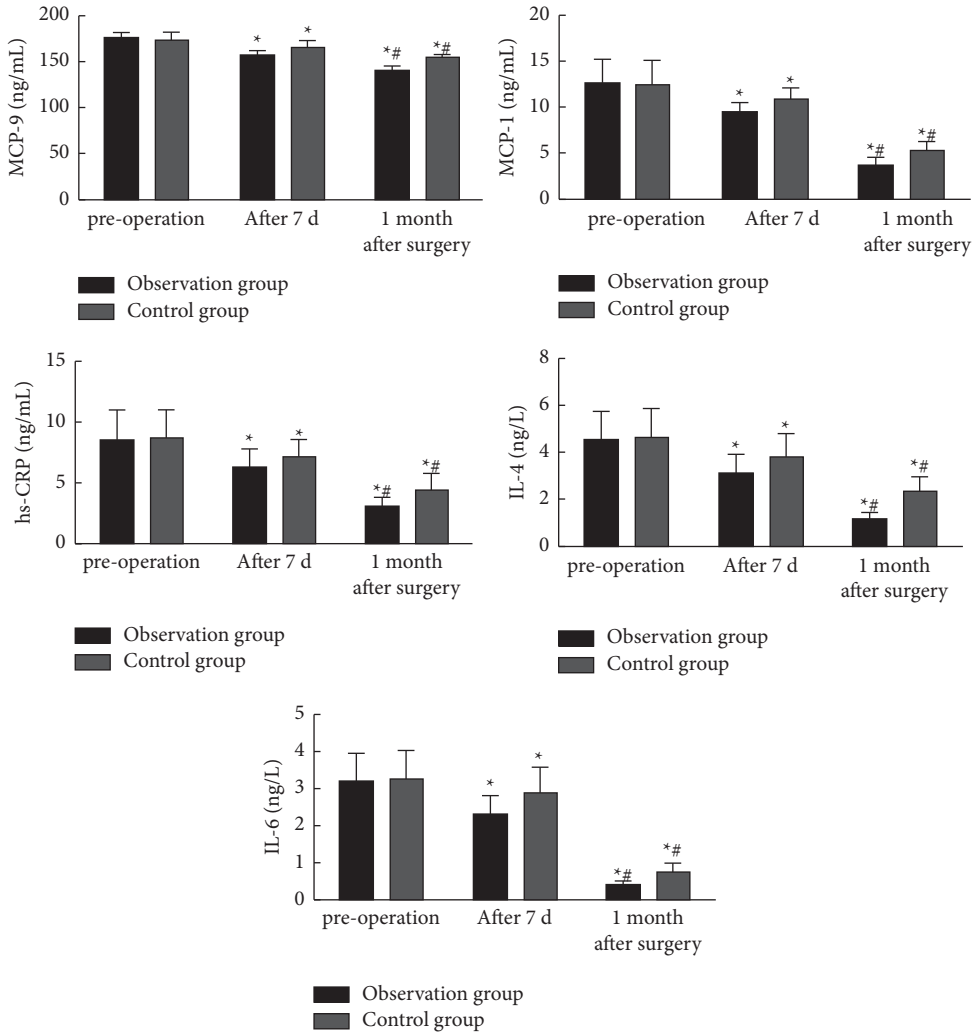

Figure 2: Comparison of inflammatory factor levels between the two groups. Compared with preoperative, $^{*}P < 0.05$; Compared with postoperative 7d, $^{\#}P < 0.05$.

Table 4: Comparison of the incidence of complications between the two groups (n (%)).

Groups	Postoperative infection	Hematoma at puncture site	Impaired renal function	Thrombogenesis	Complication rate
Observation group ($n = 100$)	2 (2.00)	1 (1.00)	1 (1.00)	2 (2.00)	6 (6.00)
Control group ($n = 100$)	3 (3.00)	2 (2.00)	3 (3.00)	1 (1.00)	9 (9.00)
χ^2					0.649
P					0.421

treatment for patients with ASO lesions was conducive to reducing inflammatory factors, which might be related to the anti-cell proliferation and inhibition of vascular endothelial injury by paclitaxel, a DCB surface coating drug.

In conclusion, DCB has good safety and efficacy in the treatment of patients with ASO lesions, which is helpful to control the lumen loss of patients, maintain the vascular lumen, reduce the restenosis rate and the level of inflammatory factors, and achieve the purpose of improving the disease. However, the sample size included in this study was relatively small and it lacked long-term efficacy and comprehensiveness. Therefore, the specific clinical benefit should be confirmed by expanding the sample size.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest, financially or otherwise.

Acknowledgments

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Volume 2023, Article ID 9769745, 1 page
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Retraction

Retracted: Analysis on Value of Continuous Nursing Based on WeChat in Improving Healthy Quality of Life and Self-Management Behavior of Patients with Diabetic Nephropathy

Evidence-Based Complementary and Alternative Medicine

Received 26 September 2023; Accepted 26 September 2023; Published 27 September 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] L. Li, H. Chen, C. Peng, and L. Yang, "Analysis on Value of Continuous Nursing Based on WeChat in Improving Healthy Quality of Life and Self-Management Behavior of Patients with Diabetic Nephropathy," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 5131830, 8 pages, 2022.

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Research Article

Analysis on Value of Continuous Nursing Based on WeChat in Improving Healthy Quality of Life and Self-Management Behavior of Patients with Diabetic Nephropathy

Liu Li,[1] Haiyan Chen,[2] Can Peng,[2] and Li Yang [2]

[1]*Second Department of Breast and Nail Surgery, Hunan Provincial People's Hospital (The First-Affiliated Hospital of Hunan Normal University), Changsha, Hunan 410005, China*
[2]*Second Department of Endocrinology, Hunan Provincial People's Hospital (The First-Affiliated Hospital of Hunan Normal University), Changsha, Hunan 410005, China*

Correspondence should be addressed to Li Yang; zyj20171006@163.com

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Objective. To explore the value of continuous nursing (CN) based on WeChat in improving healthy quality of life and self-management behavior of patients with diabetic nephropathy (DN). *Methods*. A total of 100 patients with DN who were treated in our hospital from November 2019 to January 2020 were selected. Thereinto, 54 patients who received CN based on WeChat were considered as the research group, and 46 patients who received the routine nursing intervention were considered as the control group. Peripheral blood samples were collected before nursing intervention ($T0$), 1 month after intervention ($T1$), and 2 months after intervention ($T2$) to test blood glucose, blood lipid, and renal function. Exercise of self-care agency (ESCA) scale and general self-efficacy scale (GSES) was conducted to evaluate patients' self-management ability, and a short-form 36-item health survey (SF-36) was conducted to evaluate their quality of life. Finally, the treatment compliance and satisfaction of patients were investigated. *Results*. There was no marked difference in blood glucose, blood lipid, and renal function between groups at $T0$ ($P > 0.05$), but the research group was better than the control group at $T1$ and $T2$ ($P < 0.05$). After the nursing intervention, the scores of ESCA, GSES, and SF-36 in the research group were higher ($P < 0.05$). In addition, the treatment compliance rate and satisfaction of the research group were also higher. *Conclusion*. CN based on WeChat can effectively improve the self-management behavior and quality of life of DN patients, which is extremely suitable for such chronic diseases with extremely long treatment cycles and can provide a more effective guarantee for their recovery.

1. Introduction

Diabetes is a kind of metabolic disease characterized by a chronic increase in blood glucose levels, and its prevalence and incidence are now increasing rapidly worldwide. It has developed into the most common kind of chronic disease [1]. With the improvement of people's living standards and changing lifestyles, the age of onset of diabetes is getting younger [2]. Typical clinical manifestations of diabetes are polydipsia, polyuria, polyphagia, and weight loss, which can lead to multisystem damage as the course of the disease increases and is an important risk factor for the development of many major diseases such as cardiovascular disease and heart failure [3]. At present, there is no complete cure for diabetes in a clinic, and the main intervention method is to realize maintenance hypoglycemia treatment through long-term medication [4]. Diabetes itself is not more harmful, but it is highly susceptible to a series of complications that pose a serious threat to the safety of patients who are ill [5]. For example, diabetic nephropathy (DN) is a common chronic microvascular complication of diabetes with the main clinical manifestations of proteinuria, decreased glomerular

filtration rate, increased blood pressure, and renal failure [6]. The current clinical treatment for DN is blood pressure and glucose control, lipid reduction, a low-protein diet, etc. Because its treatment needs to be long-term, patient compliance and self-management ability have a close and important correlation with prognosis [7].

Continuous nursing (CN) is a new and comprehensive approach clinically, the core of which is to provide a continuum of care, quality assurance, and therapeutic services to patients, addressing the health problems and needs they face in their lives through interventions in their daily lives and behavioral habits [8]. Therefore, CN is an essential factor in improving the long-term prognosis of DN patients. With the rapid development of the information age, the Internet has become an important part of clinical treatment, in addition to assisting doctors to manage and analyze patients' condition information; it can also be used as a bridge to spread information between doctors and patients. In China, WeChat is the most important communication tool with the significant advantages of efficiency, convenience, and timeliness. Based on these characteristics, WeChat is very helpful for doctors to understand the details of patients' life in real time, so as to achieve timely medical help [9]. Thus, we will analyze the value of CN based on WeChat to DN patients' healthy life quality and self-management behavior, in order to provide effective reference and guidance for DN patients' nursing treatment and promote the formation of a more scientific nursing service system.

2. Data and Methods

2.1. Research Data. A total of 100 patients with DN who were treated in our hospital from November 2019 to January 2020 were selected. Thereinto, 54 patients who received CN based on WeChat were considered as the research group, and 46 patients who received the routine nursing intervention were considered as the control group.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria were as follows: (1) patient has a history of type 2 diabetes and is diagnosed as DN [10]; (2) age > 18; (3) patients can communicate with others normally; (4) the information is complete; (5) Mogensen staging belongs to stage I or II; (6) know the operation of WeChat and use WeChat as the main online chat tool. Exclusion criteria were as follows: (1) patients with abnormal function of the heart, liver, and kidney; (2) patients with other chronic diseases; (3) those who suffer from hematological and immune diseases; (4) those who cannot receive complete treatment for various reasons.

2.3. Methods

2.3.1. Routine Nursing Intervention. Patients were given basic health guidance after admission, and routine checkups, and medical and nursing staff followed medical advice to assist patients in treatment. Before discharge, patients were informed of the need for caution and follow-up visits after discharge and biweekly telephone follow-up visits were made to understand patients' conditions, addressing rehabilitation problems encountered by patients, and give them some psychological guidance.

2.3.2. CN Based on WeChat. Firstly, a nursing team was established within the department including attending physicians, head nurses, and experienced nurses. A WeChat group was set up to learn about DN-related knowledge, review past data, summarize the experience and establish a complete intervention plan. CN based on WeChat was then carried out. After that, we assessed patients' needs based on physical information and develop a plan of care accordingly. Through diet management, medication management, exercise management, emotional management, and other general directions combined with each patient's situation into a graphic form sent to the WeChat group, to facilitate the daily self-management of patients, family members can also play a supervisory role based on guidance, and to inform the prevention and treatment of common problems, so that patients and family members can face the unexpected situation can be timely response to reduce the risk. WeChat groups were used to pass on treatment cases of previous patients, antidisease tips, etc., to form a correct and positive attitude towards cooperating with treatment, and to provide support and encouragement. We interact with patients through WeChat and other online platforms to eliminate their anxiety and address their actual needs and implement a combination of phased family self-management and regular follow-ups to help patients recover their health in a more comprehensive, rigorous, and efficient manner.

Both groups were intervened continuously for 2 months.

2.4. Sample Collection and Detection. The related indexes of patients were detected before nursing intervention ($T0$), one month after intervention ($T1$), and two months after intervention ($T2$). Peripheral blood was drawn in a procoagulant tube and sent to the laboratory department of our hospital for routine examination of blood glucose, lipids, and renal function.

2.5. Outcome Measures. Blood glucose function: Fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (2 h PG). Blood lipid function: Triglyceride (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C). Renal function: Serum creatinine (Scr), cystatin C (CysC), blood urea nitrogen (BUN). Self-management ability: The out-of-hospital self-care ability was evaluated by the exercise of the self-care agency (ESCA) scale [11], including four items self-concept, self-care responsibility, health knowledge awareness, and self-care skills, with lower scores indicating poorer self-care ability. The self-efficacy before and after care was assessed via the general self-efficacy scale (GSES) [12], with lower scores indicating poorer self-efficacy. Treatment compliance are as follows: Excellent: Patients follow the medical advice, take medication on time, pay attention to diet, hygiene, etc.; Good: Patients basically follow the doctor's prescription, but the diet was not controlled properly.

General: Patients occasionally follow the doctor's advice and do not pay attention to diet and hygiene. Poor: Patients don't follow the doctor's advice. Compliance rate = (excellent + good)/total × 100%. Quality of life: The quality of life was assessed using the short-form 36-item health survey (SF-36) [13], including 8 dimensions (emotional function, social function, bodily pain, general health, vitality, mental health, physical function, physical role, with a total score of 100 for each dimension, and higher scores indicating better quality of life). Nursing satisfaction: Nursing satisfaction was assessed via the self-made nursing satisfaction scale [14]: Including 22 items, with a total score of 110. 22–43 were very dissatisfied, 44–65 were dissatisfied, 66–87 were average, 88–109 were satisfied and 110 were very satisfied; satisfaction = (very satisfied + satisfied)/total × 100%.

2.6. Statistical Method. The data were processed via SPSS23.0. The counting data were expressed as (%) and compared through a chi-square test. The measurement data were represented as $(\overline{X} \pm s)$, and the statistical analysis includes independent sample t-test, paired t-test, one-way analysis of variance, and LSD post-test. $P < 0.05$ was considered that the difference was statistically marked.

3. Results

3.1. Comparison of Clinical Data. There was no statistical difference between the two groups in comparison to clinical baseline data, ($P > 0.05$), suggesting that both groups were comparable (Table 1).

3.2. Comparison of Blood Glucose Levels. First, we counted the changes in blood glucose during the nursing intervention in both groups. The differences in FPG and 2 h PG were not statistically obvious at $T0$ ($P > 0.05$), while at $T1$ and $T2$, the FPG and 2 h PG in the research group were lower than those in the control group ($P < 0.05$). The blood glucose level of both groups was the highest at $T0$, decreased at $T1$, and the lowest at $T2$ ($P < 0.05$) (Figure 1).

3.3. Comparison of Blood Lipid Levels. Subsequently, both groups also denoted no difference in TG, LDL-C, and HDL-C between groups at $T0$ ($P > 0.05$), and TG, LDL-C was lower in the research group than those in the control group at $T1$ and $T2$, HDL-C was higher in the research group than that in the control group ($P < 0.05$). Compared with $T0$, TG and LDL-C in the two groups were significantly lower at $T1$, and the lowest at $T2$ and HDL-C showed the opposite trend ($P < 0.05$) (Figure 2).

3.4. Comparison of Renal Function. Similarly, there was no difference in renal function test results between groups at $T0$ ($P > 0.05$). At $T1$ and $T2$, Scr, CysC, and BUN in the research group were lower than those in the control group ($P < 0.05$). In addition, renal function in both groups began to decrease at $T1$ and was lower at $T2$ ($P < 0.05$) (Figure 3).

3.5. Comparison of Self-Management Ability. First, ESCA scores revealed no difference between groups in the scores of self-concept, self-care responsibility, health cognitive behaviors, and self-care skills before care ($P > 0.05$), while the scores were higher in the research group than in the control group aftercare ($P < 0.05$). Besides, there was no difference in GSES scores between groups before nursing ($P > 0.05$), but it increased after nursing, and the research group was higher than the control group ($P < 0.05$) (Figure 4).

3.6. Comparison of Quality of Life. SF-36 score results manifested that the scores of patients in the research group were higher than those in the control group ($P < 0.05$), which indicated that the quality of life of patients in the former after nursing was better (Figure 5).

3.7. Compliance Rate Comparison. The compliance rate of the research group was 87.04%, which was higher than that of the control group (56.52%) ($P < 0.05$) (Table 2).

3.8. Comparison of Nursing Satisfaction. In the end, the nursing satisfaction of the research group was 85.19%, which was 58.70% higher than that of the control group ($P < 0.05$) (Table 3).

4. Discussion

As a chronic disease, the pathogenesis of DN is not yet fully understood. It is believed that a variety of factors such as genetics, hyperglycemia, hypertension, and renal hemodynamics may cause the occurrence of DN in clinical practice. As DN develops, it will eventually lead to the development of end-stage renal failure, endangering patients' lives [15]. Currently, the treatment of DN is usually prolonged and conservative, with the aim of controlling the stability of blood glucose and mitigating the pathological progression [16]. Thus, how to ensure that patients receive stable and professional medical guidance during treatment becomes a vital factor in determining the progression of DN. Although the traditional medical service model can provide timely and professional medical services during admission, it is limited by the location and cannot achieve timely and accurate medical follow-up once patients leave the hospital [17]. The best solution to this situation is to provide patients with adequate medical support even during nonadmission periods by extending the cycle of medical care. Hence, how to effectively implement this protocol is the focus of modern clinical research.

Traditional CN services are usually provided only through regular patient review or telephone follow-up, which is less effective and not ideal for care delivery [18]. With the development of the mobile Internet, WeChat has built an important communication platform for social intercourse, allowing real-time text, voice, and video communication with others, and sharing articles, pictures, and videos, which greatly facilitates people's lives [19]. CN based on WeChat, on the other hand, can not only compensate for

Table 1: Comparison of clinical data [n (%)].

	Control group ($n = 46$)	Research group ($n = 54$)	t or χ^2	P
Age (year)	56.20 ± 9.72	54.58 ± 8.18	0.905	0.368
Gender			0.100	0.752
Male	27 (58.70)	30 (55.56)		
Female	19 (41.30)	24 (44.44)		
BMI (kg/m^2)	27.82 ± 4.88	26.64 ± 3.01	0.389	0.866
Course of diabetes (years)	9.03 ± 2.84	8.95 ± 3.01	0.433	0.825
Level of education				
High school or below	32	35	0.136	0.257
University or above	14	19		
Living environment			0.047	0.828
Town	34 (73.91)	37 (68.52)		
Rural	12 (26.09)	17 (31.48)		
Family history of illness			0.150	0.698
Have	18 (39.13)	18 (33.33)		
None	28 (60.87)	36 (66.67)		
Nationality			0.216	0.642
Han nationality	42 (91.30)	50 (92.59)		
Minority	4 (8.70)	4 (7.41)		

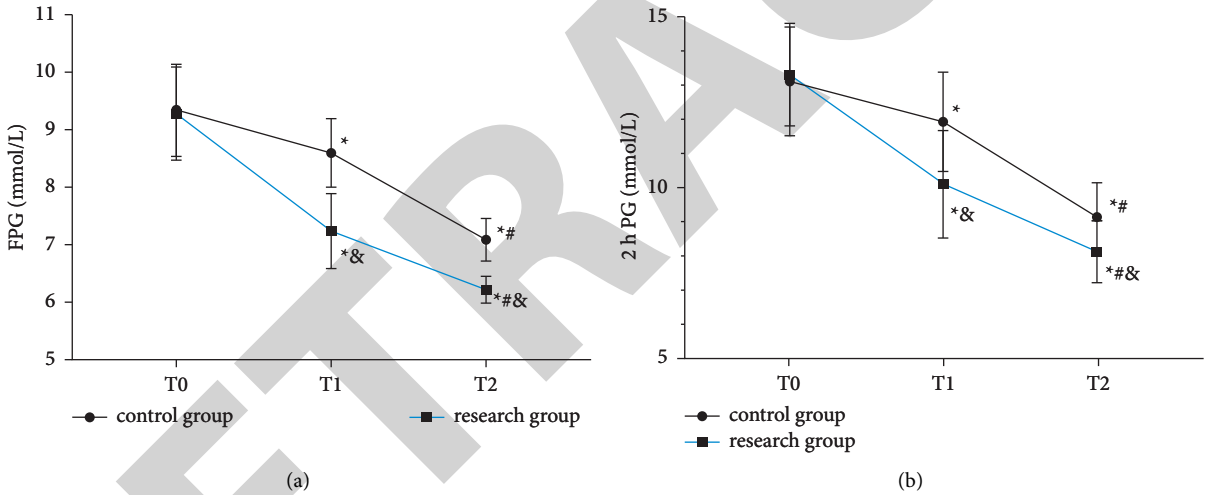

Figure 1: Comparison of blood glucose levels. (a) Comparison of FPG levels between the two groups. (b) Comparison of 2 h PG levels between the two groups. *means $P < 0.05$ compared with the same group at $T0$, #means $P < 0.05$ compared with the same group at $T1$, &means $P < 0.05$ compared with the control group.

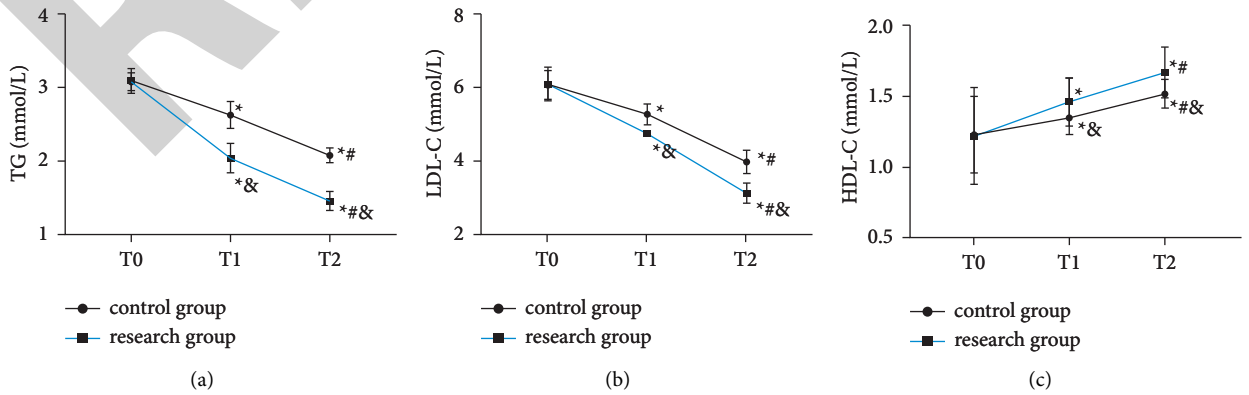

Figure 2: Comparison of blood lipid levels. (a) Comparison of TG levels between the two groups. (b) Comparison of LDL-C levels between the two groups. (c) Comparison of HDL-C levels between the two groups. *means $P < 0.05$ compared with the same group at $T0$, #means $P < 0.05$ compared with the same group at $T1$, &7485means $P < 0.05$ compared with the control group.

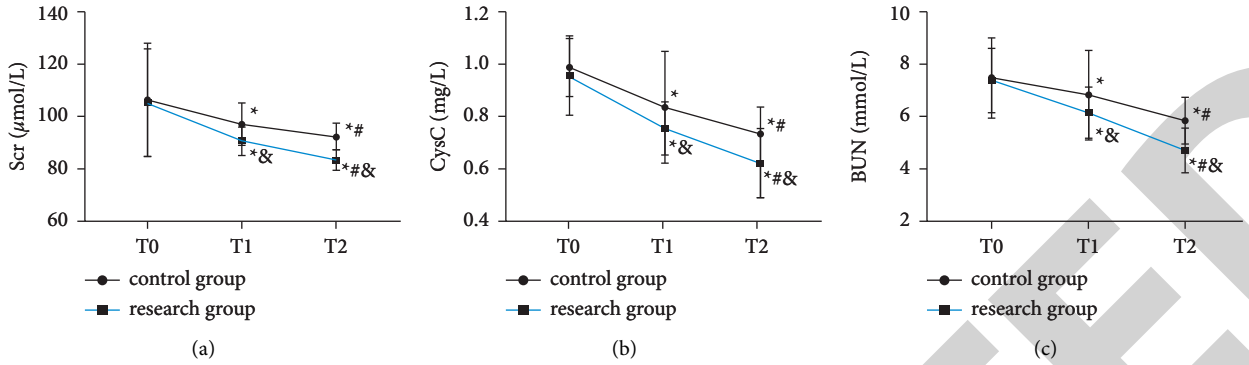

Figure 3: Comparison of renal function. (a) Comparison of Scr levels between the two groups. (b) Comparison of CysC levels between the two groups. (c) Comparison of BUN levels between the two groups. *means $P < 0.05$ compared with the same group at $T0$, #means $P < 0.05$ compared with the same group at $T1$, &means $P < 0.05$ compared with the control group.

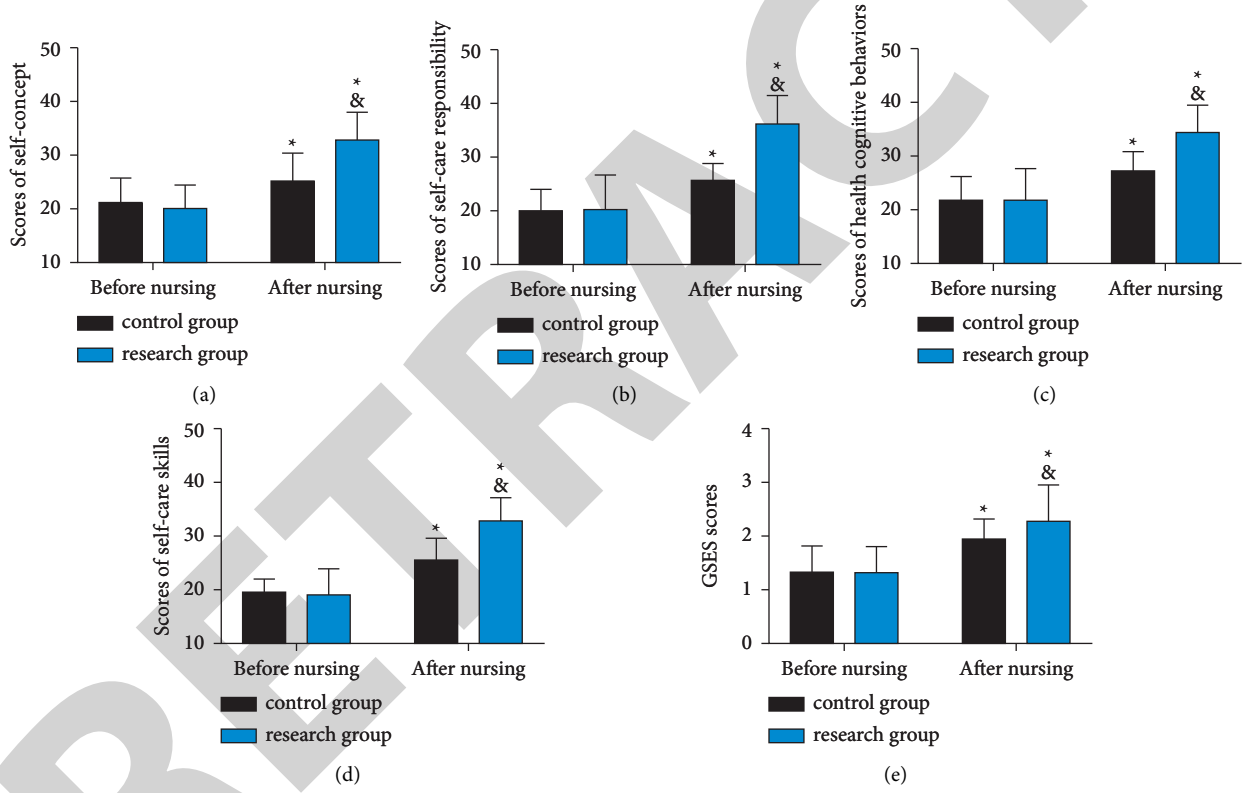

Figure 4: Comparison of self-management ability. (a) Scores of self-concept. (b) Scores of self-care responsibility. (c) Scores of health cognitive behaviors. (d) Scores of self-care skills. (e) GSES scores. *meUYJ7ans $P < 0.05$ compared with the before nursing, &means $P < 0.05$ compared with the control group.

the lack of effectiveness of traditional CN by carrying out nursing services with WeChat, the most popularly used cell phone software in modern Chinese society but also improve the quality of nursing services through more diverse and richer ways of delivering confidence [20]. As DN is extremely long and requires strict adherence to medical treatment, CN is highly applicable in it. Although several studies have confirmed the significant advantages of CN based on WeChat in providing long-term care services for patients with hypertension and coronary artery disease [21, 22], studies on DN are still relatively rare. Therefore, this research is a crucial reference for future clinical development of DN consultation and treatment services.

We first followed up on the blood glucose, blood lipid, and renal function of patients during the nursing intervention. It revealed that the improvement of blood glucose, blood lipid, and renal function of patients in the research group were better than those in the control group after the nursing intervention, suggesting that the pathological control effect of CN based on WeChat on DN patients is better. In previous studies, we found that CN based on WeChat can be more effective in improving the pathological

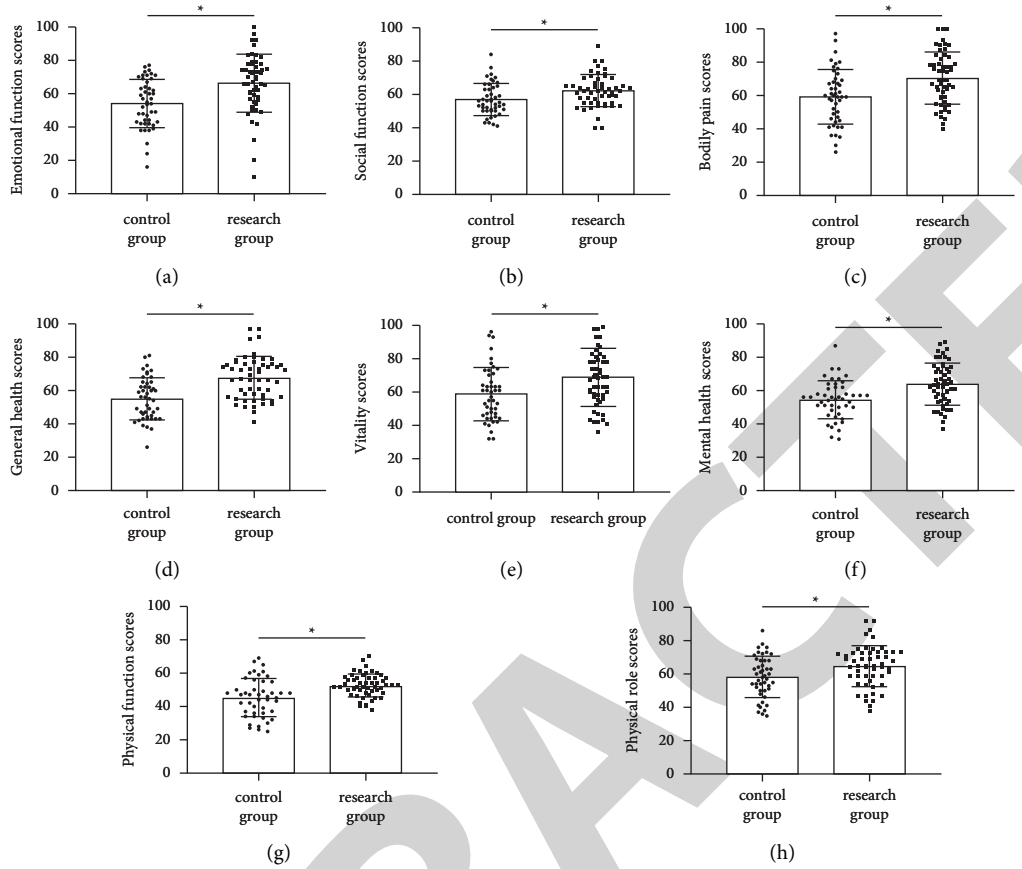

Figure 5: Comparison of quality of life. (a) Comparison of emotional function scores. (b) Comparison of social function scores. (c) Comparison of bodily pain scores. (d) Comparison of general health scores. (e) Comparison of vitality scores. (f) Comparison of mental health scores. (g) Comparison of physical function scores. (h) Comparison of physical role scores. *indicates $P < 0.05$ the comparison between the two groups.

Table 2: Compliance rate comparison [n (%)].

	Excellent	Good	General	Poor	Compliance rate (%)
Control group ($n = 46$)	11 (23.91)	15 (32.61)	12 (26.09)	8 (17.39)	56.52
Research group ($n = 54$)	29 (53.70)	18 (33.33)	5 (9.26)	2 (3.70)	87.04
χ^2					11.740
P					<0.001

Table 3: Comparison of nursing satisfaction [n (%)].

	Very dissatisfied	Dissatisfied	Average	Satisfied	Very satisfied	Satisfaction (%)
Control group ($n = 46$)	4 (8.70)	9 (19.57)	6 (13.04)	16 (34.78)	11 (23.91)	58.70
Research group ($n = 54$)	1 (1.85)	2 (3.70)	5 (9.26)	20 (37.04)	26 (48.15)	85.19
χ^2						8.843
P						0.003

process of diseases such as chronic obstructive pulmonary disease and heart failure [23, 24], which can also testify to the results of this experiment and once again validate the excellent application of CN based on WeChat in the provision of long-term care services. We believe that this is due to the higher effectiveness of CN based on WeChat. For healthcare professionals, the CN based on WeChat allows them to upload medical records to the WeChat Cloud, providing them with a timely, comprehensive, and detailed view of patients' conditions at any time. As for patients, medical staff can release videos and pictures of related diseases to upload to WeChat groups and explain to patients through voice and video, which is not only convenient for them to view information at any time, but also can further help them understand the knowledge of related diseases, which is very helpful for their own disease recovery. Because of this,

patients in the research group will have a fuller and more comprehensive understanding of DN and will have improved self-management and self-care abilities, which can be fully illustrated by the increased ESCA and GSES scores of patients. We believe that through the CN based on WeChat, we can make DN patients form a whole outside the hospital. On the one hand, we can teach patients about the disease in rich ways. On the other hand, we can allow patients to exchange their experiences related to disease treatment with each other, and continuously strengthen their knowledge and understanding of DN and thus enhance their self-management and self-care ability. Finally, adherence to treatment during the long treatment cycle is also an indicator that deserves our attention. Our survey also revealed higher adherence to treatment in the research group, which also has important positive implications for DN. The quality-of-life scores of patients in the research group were all higher than those of the control group, which can also fully illustrate the positive significance of the CN based on WeChat. Finally, the elevated satisfaction of care in the research group also fully illustrates the higher acceptance and applicability of CN based on WeChat for DN treatment.

Nevertheless, there are still many limitations. First, the limited number of cases in our study and the short follow-up period does not yet allow us to assess the impact of CN based on WeChat on the long-term prognosis of DN patients. Second, there is still a lack of uniform clinical guidelines for CN based on WeChat. Hence, the specific details of implementation still require continuous refinement and improvement in order to provide the best possible care for our patients.

In summary, CN based on WeChat can effectively improve the self-management behavior and quality of life of DN patients, which is extremely suitable for such chronic diseases with extremely long treatment cycles and can provide a more effective guarantee for their recovery.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest, financial or otherwise.

Acknowledgments

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Retraction

Retracted: Analysis of Anti-Infective Treatment of 9 Neonates with *Raoultella ornithinolytica* Sepsis

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] J. Li, Y. Zhuang, D. Xiao, H. Zhang, F. Luo, and J. He, "Analysis of Anti-Infective Treatment of 9 Neonates with *Raoultella ornithinolytica* Sepsis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2424011, 8 pages, 2022.

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Research Article

Analysis of Anti-Infective Treatment of 9 Neonates with *Raoultella ornithinolytica* Sepsis

Jing Li,[1] **Yan Zhuang**,[2] **Dingliang Xiao**,[2] **Haixia Zhang**,[1] **Fangmei Luo**,[1] **and Jinhua He**[3]

[1]*Department of Pharmacy, Hunan Children's Hospital, Changsha, Hunan 410007, China*
[2]*Department of Neonatology, Hunan Children's Hospital, Changsha, Hunan 410007, China*
[3]*Rehabilitation Center, Hunan Children's Hospital, Changsha, Hunan 410007, China*

Correspondence should be addressed to Jinhua He; hejinhua110@sina.com

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Raoul ornithine-releasing bacteria widely exist in water, plants, and soil, and colonize the digestive tract and upper respiratory tract of the human body. They are aerobic, unpowered, and capsular opportunistic pathogens. The infectivity of this bacterium is still uncertain, but the possibility of nosocomial infection has been mentioned in the literature. Studies have pointed out that the bacterium should be diagnosed in time and sensitive antibiotics should be used early. Once complicated with sepsis, it can cause multiple organ failure with a poor prognosis. In this study, we retrospectively analyzed the clinical data of nine cases of neonatal L. ornithine septicemia, to explore the clinical characteristics of neonatal L. ornithine septicemia and anti-infection therapy.

1. Introduction

In 1989, Sękowska [1] first proposed that Raoule ornithinolytica was an aerobic, amotile, and encapsulated opportunistic pathogen. Raoulella ornitholytica was first classified as *Klebsiella* in the 1980s, but was reclassified as *Klebsiella* in 2001 because 16SrRNA and rpoB gene analysis showed that it was not consistent with *Klebsiella* [2]. In 2009, Morais et al. [3] reported cases of human infection with Raoulia ornitholytica. In recent years, the infection of L. ornithine-releasing bacteria is mostly reported in adults, the infection cases in children are less reported, and the infection cases in neonates are even less reported. [4–7]. In order to explore the clinical features and anti-infective treatment plan of neonatal Raul Ornithinolytica sepsis, 9 cases of neonatal Raul Ornithinolytica sepsis in our hospital were retrospectively analyzed.

2. Objects and Methods

2.1. Research Objects. The subjects of this study were children diagnosed with Raoultia ornithine septicemia in the department of neonatology of our hospital from July 2020 to December 2021.

The diagnostic criteria were positive blood bacterial culture, clinical symptoms and signs of bacterial infection, and abnormal laboratory test results (blood routine, C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6) and other infection indicators) [8].

2.2. Research Methods. In this study, a retrospective analysis was performed. Electronic medical records were consulted to record children's age, gender, maternal and pregnancy status, clinical manifestations, medication history, hospitalization time, hospitalization diagnosis, previous diseases, laboratory tests, auxiliary examinations, treatment, medication status, statistical analysis of the data, and prognosis.

3. Results

3.1. Basic Information. From July 2020 to December 2021, a total of 9 cases of Raoulia ornithinolyticum sepsis were diagnosed in the department of neonatology of our hospital, from 3 neonatal wards, including 2 cases in the NICU ward,

Table 1: Basic information of children with Raoulia ornithine solution sepsis.

Case	Gender	Gestational week (W)	Cause of premature birth	Cesarean section	Birth weight (kg)	History of suffocation	Whether it is a twin or multiple birth	Is it a test tube baby	Age at admission (d)	Maternal pregnancy history
1	Male	30 + 1	Labor initiation	Yes	1.4	Yes	No	No	80	G2P2, pregnancy-induced hypertension
2	Female	27	Onset of labor, massive bleeding from placenta previa, and premature rupture of membranes	Yes	0.9	Yes	No	No	68	G5P2, hypothyroidism, GDM
3	Male	32 + 6	Premature rupture of membranes	No	2.7	No	No	No	3	G2P2
4	Female	28 + 2	Premature rupture of membranes	No	0.9	No	Twins	Yes	84	G1P2
5	Male	35 + 2	Placental abruption	Yes	2.4	No	No	Yes	<1 (2 h)	G5P1
6	Male	36 + 1	Labor initiation	No	3.3	No	No	No	3	G2P2
7	Male	37	-	No	2.4	Unknown	No	No	15	G2P2
8	Male	28 + 6	Maternal cervical insufficiency and premature rupture of membranes	Yes	1.45	No	Triplets	No	31	G5P4
9	Male	33 + 3	Onset of labor and premature rupture of membranes	No	2.1	Yes	No	No	<1 (6 h)	G6P2

3 cases in the surgical ward, and 4 cases in the general ward. There were 7 boys and 2 girls; only 1 was a full-term neonate (37 weeks of gestation), and the remaining 8 were premature infants, the basic situation of children is shown in Table 1.

Respiratory patterns before infection occurred in 9 patients: case 6 was ventilated by using a noninvasive ventilator, the case 4 was given high-flow oxygen, in case 8 was given oxygen by nasal cannula, and the remaining cases did not need oxygen therapy. The use of antibiotics before infection occurred in 9 children: 3 cases did not use antibiotics; the remaining 6 cases all using broad-spectrum antibiotics, including cefoperazone-sulbactam, meropenem, vancomycin, imipenem, cilastatin sodium, and linezolid from birth to the time of the infection and other antibiotics. The other 9 children all required intravenous nutrition; cases 1 and 6 had PICC intubation.

3.2. Blood Routine and Infection Index Monitoring. All the 9 patients had at least one or more abnormal indicators, and all the children had reduced platelets. In case 7, IL-6 was significantly elevated under normal conditions of other indicators. With effective anti-infective treatment, the levels of CRP and PCT in 7 children returned to normal, and the platelet count also gradually returned to normal. However, in case 4 and case 7, the inflammatory indicators did not decrease significantly or were at a continuous high value, and the platelet count gradually decreased or did not return to normal, as shown in Table 2.

3.3. Clinical Features. Among the 9 children with Raoultia ornitholyticum septicemia, 7 had intestinal diseases, including 2 intestinal malformations and 5 neonatal necrotizing enterocolitis (NEC), of which 4 were had a history of intestinal surgery before Raoulia acidic infection. Among the other 9 cases, 2 cases had PICC catheter-related bloodstream infection, 2 cases had abnormal cerebrospinal fluid results and intracranial infection was considered, and 4 cases had different degrees of infection complications. In terms of clinical manifestations, 8 children had fever, of which 7 children showed repeated fever, and the remaining children showed changes in breathing, blood oxygen, and reaction. The length of hospital stay at the time of infection varies from 4 to 50 days, as shown in Table 3 . In addition, after the occurrence of sepsis, 4 patients required invasive tracheal intubation for respiratory support, and 4 patients required oxygen therapy.

3.4. Drug Susceptibility Results. 14 strains were cocultured from 9 neonates with Raoultia ornitholyticum septicemia, 11 strains were carbapenem-resistant strains, of which 6 strains

Table 2: Changes of blood routine and inflammatory indexes in children with Raoultia.

Cases	Days of infection	Monitoring time	WBC ($\times 10^9 \bullet L^{-1}$)	PLT ($\times 10^9 \bullet L^{-1}$)	Hb ($g \bullet L^{-1}$)	N	L	CRP ($g \bullet L^{-1}$)	PCT ($\mu g \bullet L^{-1}$)	IL-6 ($ng \bullet L^{-1}$)
1	The same day	9.19	23.06	8	107	0.737	0.235	13.8	42.11	>5000
	Day 2	9.20	8.22	13	111	0.524	0.433	94.16	53.6	—
	Day 3	9.21	17.14	2	73	0.668	0.253	97.16	15.68	26.66
	Day 4	9.22	7.65	27	95	0.329	0.554	31.89	7.53	32.23
	Day 6	9.24	16.28	80	95	0.59	0.286	18.11	1.49	22.48
	Day 9	9.27	17.66	106	139	0.679	0.276	4.46	0.44	10.53
	Day 11	9.30	15.52	148	102	0.519	0.405	35.59	0.36	13.17
2	The same day	8.23	8.83	11	99	0.61	0.25	249.85	19.8	2266
	Day 2	8.24	5.8	4	72	0.619	1.66	245.61	36.28	3356
	Day 3	8.25	6.22	6	89	0.692	0.236	213.35	—	—
	Day 4	8.26	6.1	2	102	0.736	0.22	117.92	8.17	71.34
	Day 6	8.28	11.56	14	87	0.587	0.228	47.59	3.1	21.29
	Day 9	8.31	18.17	28	125	0.676	0.207	5.89	0.41	5.63
	Day 16	9.7	8.15	150	91	0.51	0.288	10.27	0.1	7.88
3	The same day	9.14	12.46	336	125	0.78		0.7	1.96	36.33
	Day 3	9.16	2.83	112	138	0.353	0.625	0.92	6.87	>5000
	Day 4	9.17	30.57	17	109	0.88	0.061	103.43	>100	>5000
	Day 6	9.19	56	28	80	0.864	0.05	82.34	3.57	9.65
	Day 8	9.21	47.38	11	146	0.677	0.132	15.7	—	—
	Day 12	9.25	15.97	80	113	0.618	0.236	6.46	0.34	3.06
4	The same day	9.2	3.87	200	127	0.516	0.398	6.43	1.75	>5000
	Day 2	9.3	8.62	15	109	0.655	0.21	108.19	35.42	1232
	Day 4	9.5	8.84	4	65	0.735	0.243	170.73	20.67	3081
5	The same day	8.15	15.32	97	113	0.802	0.136	106.78	47.13	3948
	Day 2	8.16	19.09	81	110	0.657	0.198	50.32	12.51	—
	Day 4	8.18	6.72	146	95	0.391	0.327	14.4	—	—
	Day 9	8.23	7.68	544	99	0.243	0.547	1.76	0.14	—
	Day 14	8.30	6.39	390	78	0.23	0.498	0.94	—	—
	Day 20	9.5	7.48	315	97	0.285	0.508	1.7	—	—
6	The same day	8.31	9.05	303	98	0.868	0.064	49.41	2.00	1191
	Day 3	9.2	5	223	85	0.476	0.432	70.26	1.81	164.6
	Day 7	9.6	5.41	8	74	0.694	0.277	116.46	16.45	311.9
	Day 8	9.7	13.92	20	95	0.559	0.328	81.44	6.23	2.52
	Day 10	9.9	11.92	169	103	0.503	0.431	13.3	0.61	<1.5
	Day 14	9.13	6.77	344	97	0.375	0.516	1.8	0.11	—
7	The same day	9.7	8.58	508	92	0.507	0.394	1.89	0.22	3122
	Day 2	9.8	4.09	208	83	0.695	0.262	109.76	8.4	542.2
	Day 3	9.9	3.84	113	87	0.435	0.484	163.66	—	—
	Day 4	9.10	5.69	32	75	0.382	0.476	178.98	8.39	
	Day 5	9.11	4.45	19	119	0.257	0.639	146.18	—	—
	Day 6	9.12	9.29	69	97	0.392	0.463	100.82	34.85	23.16
	Day 7	9.13	14.2	7	82	0.751	0.182	101.62	43.6	140.7
	Day 8	9.14	25.54	72	93	0.685	0.201	91.31	—	—
8	The same day	8.3	46.56	135	98	0.959	0.014	37.58	10.57	>5000
	Day 2	8.4	48.99	22	85	0.825	0.101	164.6	12.14	842.5
	Day 3	8.5	35.19	30	145	0.797	0.121	84.66	4.43	41.49
	Day 6	8.8	10.17	89	124	0.598	0.248	21.22	0.38	25.93
	Day 1	8.14	7.32	237	101	0.421	0.366	2	0.11	1.95
9	The same day	9.16	6.78	209	126	0.809	0.189	52.8	4.53	—
	Day 2	9.17	24.36	38	104	0.667	0.236	15.92	46.96	34.04
	Day 3	9.18	26.74	100	106	0.613	0.283	79.05	25.18	3.42
	Day 5	9.20	15.11	230	99	0.418	0.486	14.97	2	<1.5
	Day 8	9.23	11.22	631	93	0.301	0.585	1.59	0.22	3.54
	Day 13	9.28	11.21	578	77	0.582	0.297	2.7	0.11	3.89

were resistant to levofloxacin, tigecycline, amikacin, and Compound sulfamethoxazole. 5 strains were only sensitive to tigecycline. The remaining 3 strains were sensitive strains, as shown in Table 4.

3.5. Anti-Infective Treatment and Outcome. Cases 1–6 are children with carbapenem-resistant bacteria infection. Among them, cases 1–3 were selected according to drug susceptibility to two sensitive drugs: the infection was

Table 3: Clinical characteristics of 9 neonates with Raoulia.

Cases	Primary disease	Surgery situation	Number of days of surgery at the time of infection	Days in the hospital at the time of infection	Bacterial identification	Clinical manifestations	Whether combined with intracranial infection	Infection complications
1	Ileal scarring strictures after NEC and premature infants	Adhesion bowel release, stricture bowel, and ileocecal resection	8	19	Blood and PICC catheter tip	Fever, shortness of breath, and nasal flaring	No	Liver damage
2	NEC、BPD、premature baby	No	—	7	Blood	Decreased blood oxygen and heart rate	No	DIC
3	Congenital jejunal atresia (diaphragmatic type), enteric nerve dysplasia, and premature infants	Enteroplasty	2	6	Blood	Fever, poor response, frequent apnea, and decreased blood oxygen	No	Kidney damage
4	Premature infants and chronic lung disease	No	—	50	Blood	Fever, poor mental response, visible markings all over the body, and vomiting of white mucus-like fluid	Yes	Septic shock, multiple organ dysfunction: Liver, kidney, myocardial damage, abnormal coagulation function, and ascites
5	Necrotizing enterocolitis in premature infants and neonates	No	—	7	Blood	Fever	Yes	No
6	Congenital malrotation with midgut volvulus and intestinal necrosis and left testicular torsion with necrosis	Necrotic bowel resection	31	32	Blood and PICC lateral blood	Fever and slightly poor mental response	No	No
7	Neonatal necrotizing enterocolitis	No	—	4	Blood	Repeated fever for 9 days	No	No
8	Neonatal necrotizing enterocolitis, premature infants, and BPD	Jejunostomy	18	19	Blood	Fever and occasional transient oxygen desaturation	No	No
9	Aspiration pneumonia and premature infants	No	—	27	Blood	Fever with shallow and irregular breathing	No	No

effectively controlled by levofloxacin combined with amikacin treatment. In cases 5 and 6, the infection was also effectively controlled by removing the PICC catheter, increasing the dose of carbapenem, and prolonging the infusion time. Case 4 died of infection. Cases 7–9 were infected with susceptible strains, and cases 8 and 9 were effectively controlled by selecting sensitive drugs. In case 7, although a sensitive drug was selected for treatment, the effect was not good, and the parents of the child requested to be discharged from the hospital, as shown in Table 5.

Table 4: Statistics of drug susceptibility results of 9 cases of neonatal Raoulia ornithinolytica sepsis.

Cases	Specimen	Positive report time (h)	Amoxicillin-clavulanate potassium	Cefepime	Cefoperazone-sulbactam	Cefoxitin	Ceftazidime	Ceftriaxone	Imipenem	Levofloxacin	Piperacillin-tazobactam sodium	Tigecycline	Amikacin	Cotrimoxazole
1	Blood	9	R	R	R	R	R	R	R	S	R	S	S	S
	Blood	15	R	R	R	R	R	R	R	S	R	S	S	S
	PICC catheter tip	—	R	R	R	R	R	R	R	S	R	S	S	S
	Blood	17	R	R	R	R	R	R	R	S	R	S	S	S
2	Blood	16	R	R	R	R	R	R	R	S	R	S	S	S
3	Blood	16	R	R	R	R	R	R	R	S	R	S	S	S
4	Blood	12	R	R	R	R	R	R	R	R	R	S	R	R
5	Blood	17	R	R	R	R	R	R	R	R	R	S	R	R
	Blood	53	R	R	R	R	R	R	R	R	R	S	R	R
6	Blood	20	R	R	R	R	R	R	R	R	R	S	R	R
	PICC tube side blood	12	R	R	R	R	R	R	R	R	R	S	R	R
7	Blood	13	S	S	S	S	S	S	S	S	S	S	S	S
8	Blood	15	S	S	S	S	S	S	S	S	S	S	S	S
9	Blood	13	S	S	S	S	S	S	S	S	S	S	S	S

Table 5: Anti-infective treatment and outcome of 9 cases of Raoulia ornitholyticum sepsis.

Cases	Use anti-infective drugs and time of use (d)	Other drug treatments	Treatment outcome
1	Meropenem (1d), levofloxacin + amikacin (14 d)	Removal of PICC tube, immunoglobulin, platelets, furosemide, packed red blood cells, frozen plasma, and human albumin	Cure
2	Meropenem (1d), levofloxacin + amikacin (14 d)	Frozen plasma, furosemide, platelets, immunoglobulin, methylphenidate, packed red blood cells, and human serum albumin	Cure
3	Meropenem (2d), levofloxacin + amikacin + (14 d)	Furosemide, human albumin, dopamine, platelets, and packed red blood cells	Cure
4	Meropenem + amikacin (3 d)	Immune globulin, platelets, packed red blood cells, frozen plasma, and furosemide	Death
5	Meropenem (40 mg/kg/time Q8H extended infusion time to 3 h, 21 d)	Immunoglobulin	Cure
6	Imipenem cilastatin sodium (25 mg/kg/time Q6H prolonged infusion time 2 h, 14 d)	Remove the PICC tube	Cure
7	Meropenem (40 mg/kg/time Q8H 8 d)	Human immunoglobulin, furosemide, leukocyte-depleted suspended red blood cells, and platelets	Unknown (request for discharge)
8	Meropenem (14 d)	No	Cure
9	Meropenem + amikacin (14 d)	No	Cure

4. Discussions

Raoultia ornithinolytica is an aerobic, nonmotile, rod-shaped Gram-negative bacterium classified as Enterobacteriaceae of the genus Raoultella. This genus of bacteria also includes cytopathic Raoulia and Raoulia Tulsa. Raoultia is widely present in water, plants, soil and other environments, and mostly colonizes the digestive tract and upper respiratory tract in the human body, and is an opportunistic pathogen [9]. Invasive human infection of Raoulella ornithyloliticus is still rare. In recent years, the reports of Raoulella ornithyloliticus infection are more common in adults, and the reports of children infection, especially neonatal infection, are relatively rare [10]. Recently, Yaprak et al. [11] reported 14 cases of children infected with Raoulella ornithine, including 5 clinical cases, 3 of which were newborns, including 2 premature infants, and the results showed that all of them were bloodstream infections. Of the 9 infants enrolled in this study, 8 were premature infants. It shows that in the neonatal population, premature infants are at high risk of infection by Raoulia ornithine. Perhaps compared with the term infants, in addition to their low birth weight and less mature immune function, preterm infants often have multiple risk factors such as central venous catheterization, tracheal intubation, use of broad-spectrum antibiotics, parenteral nutrition, and nosocomial infection [12],which are all more likely to occur. In addition to preterm birth, among the 9 neonates with Raul Ornitholyticum septicemia analyzed in this paper, 7 neonates had intestinal diseases, and 4 of them had undergone gastrointestinal surgery, suggesting that neonates with intestinal problems or surgery may be more susceptible to infection with Raoulia ornithinolytica. This may be related to the fact that the bacteria are mainly localized in the digestive tract in the human body, and children with intestinal problems, such as NEC, often have impaired digestive gastrointestinal barrier function, which is easy to cause bacterial translocation and lead to infection.

Neonatal sepsis is often subtle and nonspecific in clinical manifestations, and it is not easy to be detected, especially in very low birth weight (VLBW), which is more nonspecific and more difficult to identify early, which is also the anti-infective treatment for neonates [13]. The clinical manifestations of the 9 cases of neonatal Raoulia ornithinolytica septicemia in the author's analysis were mostly only changes in respiration, blood oxygen, reaction, etc., and there was no specificity. This is mainly due to the production of histamine-like substances by L. ornithine, resulting in dyspnea and hypoxemia. However, it is worth noting that, in terms of systemic manifestations, 8 children had fever, suggesting that fever may be one of the clinical features of neonatal Raoulia ornithinolytica infection. In addition to close observation of clinical symptoms in children, early recognition of infection clinically can also be facilitated by assessing risk factors for infection in children and monitoring routine blood tests and infection markers [14, 15]. The combination of IL-6, PCT, and CRP is used to continuously and dynamically monitor high-risk groups of sepsis, which is of great significance for early detection and early treatment. Among them, IL-6 is the first elevated serum marker, and it often occurs when elevations occur before overt clinical symptoms [16, 17]. For example, the IL-6 of the child in case 7 was significantly elevated before clinical symptoms appeared and other infection markers were normal. Therefore, for children at high risk of infection, dynamic monitoring of CRP and PCT combined with IL-6 can help us identify, thereby winning an earlier treatment opportunity for anti-infective treatment. In addition, after initiating anti-infective treatment, dynamic monitoring of these infection markers will help us evaluate the efficacy and adjust the treatment plan in time. Maseda et al. [18] reported that PCT levels can be rapidly reduced after infection control, and

septic patients can be reduced by 50% within 24 hours after effective treatment.

Due to its special physiological characteristics and the toxic and side effects of drugs, neonates have very few drugs to choose from when facing CRE-resistant infection, which is another major difficulty in neonatal anti-infection treatment. In this study, 14 strains of Raoultia ornithinolytica isolated in this paper were highly resistant to the third and fourth generation cephalosporins, enzyme inhibitor compound preparations, and carbapenems. Eleven of them were carbapenem-resistant Enterobacteriaceae (CRE), which were only sensitive to aminoglycosides, quinolones, and tigecycline. In terms of anti-infective treatment, an anti-infective treatment plan should be formulated based on the basic situation of the child, the severity of infection, and drug susceptibility to achieve individualized treatment. For example, cases 1, 2, and 3 in this article showed that the PCT did not decrease significantly after 24–48 hours of meropenem treatment, suggesting that the curative effect may be poor. By changing the treatment plan in time, the infection of the three children was controlled. At the same time, case 5 had a large gestational age and birth weight, did not need oxygen therapy, and only had fever in clinical manifestations without other infection complications. Drug sensitivity results showed that the MIC value of imipenem and cilastatin sodium was 8ug/ml. According to relevant literature reports [19], in the treatment of CRE infection, when carbapenem MIC is 4–16 μg/ml in the treatment of CRE infection, carbapenem antibiotics should be used to increase the frequency or dose and prolong the infusion time. When carbapenems MIC> 16 dou g/ml, carbapenem antibiotics should be avoided. Taking meropenem into consideration, we chose meropenem for anti-infective treatment, increasing the drug dose to 40 mg/kg/time Q8H, optimizing the dosing schedule, and extending the infusion time of meropenem to 3 hours. In the end, the infection of the child was well controlled. In addition, case 6 was a PICC catheter-related infection. Through timely removal of the PICC catheter, increasing the dose of imipenem and cilastatin sodium (100 mg/kg/day, Q6H), and prolonging the drug infusion time to 2 hours, the child also achieved a good anti-infective treatment effect. In case 1, case 2, and case 3, meropenem was selected at the beginning, and then the anti-infective treatment regimen (levofloxacin and amikacin combined therapy) was adjusted promptly in combination with drug sensitivity. After 24–48 hours of treatment, the therapeutic effect was evaluated by strict monitoring of infection indicators. The results showed that all the three children achieved a good therapeutic effect, and no adverse drug reactions were detected. We know that aminoglycosides have ear and kidney toxicity, fluoroquinolones may cause joint and cartilage damage, and tigecycline may cause untoward reactions such as permanent tooth stain, enamel dysplasia, and bone growth inhibition, all of which limit the use of these drugs in the pediatric population [20]. However, when faced with a fatal infection, it should be used with caution after fully weighing the benefits and risks, and the adverse drug reactions should be closely monitored. Regrettably, in case 4, the child eventually developed septic shock and multiple organ dysfunction and died. The child was born very early, with an ultra-low birth weight, and had a variety of underlying diseases such as long-term need for oxygen therapy and extrauterine growth retardation, In addition, the child received multiple antibiotics from birth until infection. For such children, a nosocomial infection is fatal, so hand hygiene, rational use of antibiotics, protective isolation, and other nosocomial infection prevention and control measures are more important.

In conclusion, Raoultella ornithinolytica sepsis in neonates occurred mainly through nosocomial infections and carbapenem-resistant strains were more common. Preterm birth, intestinal disease, and a history of surgery increase the risk of infection; for carbapenem-resistant Raoultella ornithinolytica infection, anti-infection treatment regimens should be formulated based on the basic situation, infection severity, and drug sensitivity of the children, so as to achieve individualized treatment. In addition, dynamic monitoring of infection markers has an important clinical significance for early identification of infection, evaluation of a curative effect, and timely adjustment of anti-infection treatment.

Data Availability

The raw data supporting the conclusion of this article will be available by the authors without undue reservation.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Research Article

Analysis of Cerebrospinal Fluid Routine Biochemical Level, Pathogenic Bacteria Distribution, and Risk Factors in Patients with Secondary Intracranial Infection after Brain Tumor Surgery

Yang Zhang,[1] Ying Zhou,[2] Min Hou,[1] and Sunfu Zhang [1]

[1]*Department of Neurosurgery, The Third People's Hospital of Chengdu, Chengdu, Sichuan 610031, China*
[2]*Department of Cosmetic Minimally Invasive, Sichuan Huamei Zixin Medical Cosmetology Hospital, Chengdu, Sichuan 610000, China*

Correspondence should be addressed to Sunfu Zhang; zhangsunfu@outlook.com

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Purpose. Analysis of routine biochemical levels of cerebrospinal fluid (CSF), distribution of pathogenic bacteria, and risk factors in patients with intracranial infections secondary to brain tumour surgery. *Methods*. A total of 208 patients admitted to our hospital for brain tumour surgery from January 2020 to May 2022 were selected. Fully automated biochemical analyzer was employed for CSF routine and for measuring biochemical parameters such as white blood cell (WBC), micrototal protein (M-TP), glucose (GLU), and chlorine (CI). Double antibody sandwich assay for CSF procalcitonin (PCT), heparin-binding protein (HBP), and matrix metalloproteinase-9 (MMP-9) was performed. Fully automated microbiological analyzer for pathogen identification was utilized. Based on the above results, we determined whether the patients had secondary intracranial infections after surgery and analyzed the risk factors for secondary intracranial infections after brain tumour surgery by univariate and multifactorial logistic regression. *Results*. Among 208 patients with brain tumour surgery, 65 cases (31.25%) had secondary intracranial infection and 143 cases (68.75%) had no secondary intracranial infection. The levels of WBC, M-TP, CI, PCT, HBP, and MMP-9 in the CSF of intracranially infected patients were significantly higher than those of uninfected patients ($P < 0.05$), and GLU was significantly lower than that of uninfected patients ($P < 0.05$), and the levels of PCT, HBP, and MMP-9 in infected patients were significantly lower than those before treatment after 3, 7, and 10 d and tended to decrease over time ($P < 0.05$). A total of 62 pathogenic strains were isolated from 65 intracranial infections, of which 41 (66.13%) were Gram-negative bacteria, mainly resistant to amikacin and ciprofloxacin and sensitive to meropenem and imipenem; 19 (30.65%) were Gram-positive bacteria, mainly highly resistant to penicillin and erythromycin and sensitive to vancomycin. Univariate analysis showed that age, gender, tumour type, history of glucocorticoid application, and prophylactic application of antibiotics were not associated with secondary intracranial infection after brain tumour surgery ($P > 0.05$); tumour site, operation time, postoperative indwelling drainage time, postoperative cerebrospinal fluid leakage, and history of diabetics were all associated with secondary intracranial infection after brain tumour surgery ($P < 0.05$). Multivariate logistic regression analysis showed that infratentorial tumour, operation time ≥4 h, postoperative indwelling drainage time ≥24 h, and postoperative cerebrospinal fluid leakage were independent risk factors for secondary intracranial infection after brain tumour surgery ($P < 0.05$). *Conclusion*. Patients with intracranial infections secondary to brain tumour surgery have abnormal levels of CSF routine and biochemical parameters, and the detection rate of Gram-negative bacteria is higher than that of Gram-positive bacteria in patients. Treatment should be based on the characteristics of pathogenic bacteria and risk factors with targeted interventions to reduce intracranial infections.

1. Introduction

Brain tumours are the most common intracranial tumours in neurosurgery, accounting for approximately 45% of all intracranial tumours, with slightly more men than women [1]. In the early stages of brain tumour development, patients may suffer from dizziness and headache, speech disturbances, visual disturbances, smell disturbances,

hearing loss, unilateral limb numbness, unsteady walking, seizures, or pituitary problems, which are best treated by complete surgical resection [2–4]. However, in the postoperative period, the defensive effect of the blood-brain barrier system and the severe damage to the peripheral tissues of the patient's body make it easy for pathogenic bacteria to invade the cranial tissues and induce secondary intracranial infection, commonly occurring from 3 d to 7 d after surgery (10 d to 12 d after surgery in patients with drainage is the high incidence). It is one of the main causes of prolonged hospital stay, increased disability and mortality, and poor prognosis. Most patients with intracranial infection can be cured by anti-infection treatment, but the patient has an acute onset, accompanied by high fever and meningeal irritation. If the anti-infection treatment is not timely, the patient is still prone to brain injury sequelae and even death [5]. Cerebrospinal fluid (CSF) cultures are the gold standard for the diagnosis of intracranial infections. However, the low culture positivity rate of CSF pathogens, the relatively time-consuming drug sensitivity tests, and the waiting for the results before treatment will definitely delay the disease, coupled with the general increase in drug resistance of pathogenic bacteria, and the empirical use of antibacterial drugs cannot achieve satisfactory results, making the treatment of patients more difficult. CSF routine and biochemical tests are important for the diagnosis, differentiation, and assessment of intracranial diseases. Several studies [6, 7] have shown that white blood cell (WBC) counts in the CSF are elevated in patients with intracranial infections, but with lower sensitivity and specificity, and the measurement of micrototal protein (M-TP), glucose (GLU), and chloride (CI) can further strengthen the diagnosis and differentiation. In addition, in infectious diseases or sepsis, serum levels of infection indicators such as procalcitonin (PCT), heparin-binding protein (HBP), and matrix metalloproteinase-9 (MMP-9) are significantly increased [8,9], but the value of changes in PCT, HBP, and MMP-9 levels in CSF for the diagnosis of intracranial infections remains to be investigated. This study analyzed the CSF routine biochemical levels, pathogenic bacteria distribution, and risk factors in patients with secondary intracranial infections after brain tumour surgery, aiming to provide relevant reference for clinical diagnosis and prevention of secondary intracranial infections after brain tumour surgery.

2. Materials and Methods

2.1. Research Object. A total of 208 patients admitted to our hospital for brain tumour surgery from January 2020 to May 2022 were selected. Our goal is to determine whether the patient had a secondary intracranial infection after surgery by CSF routine and biochemical tests and identification of pathogenic bacteria. Diagnosis of intracranial infection was based on the following: (1) the patient's body temperature continued to rise, >38°C, and there were symptoms or signs such as fatigue, high fever, headache, vomiting, and meningeal irritation; (2) the bacterial culture of intracranial drainage fluid or CSF was positive; and (3) routine and biochemical tests of CSF samples suggested that WBC count in CSF increases; CSF turbidity and M-TP quantitatively increase; or GLU quantitatively decrease, etc., and intracranial infection could be determined if the above one was met [10]. Inclusion criteria were as follows: (1) if they met the diagnostic criteria of the National Institute for Health and Clinical Excellence (NICE) for brain tumours [11]; (2) age >18 years, complete case history, treated with brain tumour resection and meeting the appropriate indications [11], and expected survival time >7 d after surgery; and (3) those without consciousness impairment and voluntarily participated in the trial. Exclusion criteria were as follows: (1) death during or within 3 d after brain tumour surgery; (2) preoperative acute and chronic systemic or local infection; (3) those who had received preoperative medication such as glucocorticoids or antibiotics; (4) combined cranial hematoma, vascular disease, cranial abscess, cranial parasitic disease, soft tissue infection of the head, etc.; and (5) people with cardiac insufficiency and liver and kidney dysfunction.

2.2. Research Methods

2.2.1. Cerebrospinal Fluid Detection. A lumbar puncture was performed to collect 10 ml of CSF from the patients 2 d after surgery (or at the onset of symptoms such as fever and meningeal irritation and so on) and on the 3, 7, and 10 days after drug treatment. AU5800 fully automatic biochemical analyzer (Beckman Coulter Inc) was employed for CSF routine and for measuring biochemical parameters such as WBC, M-TP, GLU, and CI levels. Double antibody sandwich assay was carried out for the determination of PCT, HBP, and MMP-9 levels in CSF, and the kits were purchased from Abcam. Vitek32 fully automated microbiological analyzer (BioMérieux, France) was utilized for pathogen identification. Based on these findings, we determined whether the patient had a secondary intracranial infection after surgery.

2.2.2. Data Collection. The clinical data of patients were collected by querying electronic cases, including age, sex, tumour type, tumour site, operation time, postoperative indwelling drainage time, postoperative cerebrospinal fluid leakage, history of diabetics, history of glucocorticoid application, and prophylactic application of antibacterial drugs. The case data collected were entered and checked centrally using EpiData, which was required to ensure the accuracy of the data in the entry process.

2.2.3. Drug Treatment. Treat with broad-spectrum antibacterial drugs or select sensitive antibacterial drugs based on the patient's drug sensitivity test results. Antibacterial drugs that could cross the blood-brain barrier such as amikacin, meropenem, and vancomycin should be chosen.

2.3. Statistical Analysis. SPSS 22.0 was employed for statistical analysis. The measurement data were expressed as $\overline{x \pm s}$, and independent samples t-test was performed for both groups. Statistical data were described in terms of cases and percentages (%), with the χ^2 test. Univariate analyses

that were statistically significant were included in multivariate analyses, and risk factors for secondary intracranial infection after brain tumour surgery were analyzed by multivariate logistic regression. $P > 0.05$ was considered statistically significant.

3. Result

3.1. Postoperative Infections in 208 Patients Operated for Brain Tumours. Among 208 patients with brain tumour surgery, 65 cases (31.25%) had secondary intracranial infection and 143 cases (68.75%) had no secondary intracranial infection (Table 1, Figure 1).

3.2. Analysis of CSF Routine and Biochemical Parameters in 208 Patients Operated for Brain Tumors. The levels of WBC, M-TP, and CI in the CSF of intracranially infected patients were significantly higher than those of uninfected patients ($P < 0.05$), and GLU was significantly lower than that of uninfected patients ($P < 0.05$). (Figure 2).

3.3. Analysis of PCT, HBP, and MMP-9 Levels in CSF of 208 Patients Operated for Brain Tumours. The levels of PCT, HBP, and MMP-9 in the CSF of intracranially infected patients were significantly higher than those of uninfected patients ($P < 0.05$), and the levels of PCT, HBP, and MMP-9 in infected patients were significantly lower than those before treatment after 3, 7, and 10 d and tended to decrease over time ($P < 0.05$). (Figures 3 and 4).

3.4. Analysis of the Pathogenic Bacteria Distribution and Drug Resistance Rate in 65 Cases of Intracranial Infections. A total of 62 pathogenic strains were isolated from 65 intracranial infections, of which 41 (66.13%) were Gram-negative bacteria, mainly resistant to amikacin and ciprofloxacin and sensitive to meropenem and imipenem; 19 (30.65%) were Gram-positive bacteria, mainly highly resistant to penicillin and erythromycin and sensitive to vancomycin (Tables 2–4).

3.5. Single Factor Analysis of Intracranial Infection Secondary to Brain Tumour Surgery. Univariate analysis showed that age, gender, tumour type, history of glucocorticoid application, and prophylactic application of antibiotics were not associated with secondary intracranial infection after brain tumour surgery ($P > 0.05$); tumour site, operation time, postoperative indwelling drainage time, postoperative cerebrospinal fluid leakage, and history of diabetics were all associated with secondary intracranial infection after brain tumour surgery ($P < 0.05$). (Table 5).

3.6. Multifactorial Logistic Regression Analysis of Intracranial Infections Secondary to Brain Tumour Surgery. Multivariate logistic regression analysis showed that infratentorial tumour, operation time ≥4 h, postoperative indwelling drainage time ≥24 h, and postoperative cerebrospinal fluid leakage were independent risk factors for secondary intracranial infection after brain tumour surgery ($P < 0.05$). (Table 6).

4. Conclusion

During craniotomy, patients may present with clinical symptoms similar to those of intracranial infections due to irritation by the implant or other factors, making the differential diagnosis of intracranial infections difficult. CSF's laboratory-related tests are of great interest because of their ease of operation and rapidity of detection. The results of CSF routine and biochemical parameters in this study showed that the levels of WBC, M-TP, and CI in the CSF of those with intracranial infection secondary to brain tumour surgery were significantly higher than those of without infection, and the GLU was significantly lower than those of without infection. This suggests that CSF routine and biochemical tests can go some way to diagnosing intracranial infections. Nevertheless, as intracranial infections have many causes, the main common ones being bacterial, viral, and tuberculosis infections [12, 13], this study further analyzed the markers of infection in the CSF of patients after brain tumour surgery. The results found that the levels of PCT, HBP, and MMP-9 in the CSF of those with intracranial infection were significantly higher than those of without infection. It is suggested that PCT, HBP, and MMP-9 tests are potentially valuable in the early diagnosis of intracranial infection after brain tumour surgery. PCT is a common biological indicator for the diagnosis of bacterial infections and sepsis and is now recognized to be significantly elevated in bacterial infections combined with a systemic inflammatory response, and its elevation correlates with the severity of the patient's infection, whereas in viral infections or aseptic inflammation, PCT is normal or mildly elevated [14]. Studies [15, 16] found that the PCT levels of serum and cerebrospinal fluid in patients with intracranial infection on the first day after craniotomy were significantly higher than those in noninfected patients, and their sensitivity and specificity in the diagnosis of intracranial infection were more than 80%. HBP is an acute reactive protein with the function of regulating macrophages and mediating inflammatory response. In the early stage of infection, endotoxin of pathogenic bacteria stimulates neutrophils to release a large amount of HBP, which leads to acute inflammatory response, resulting in damage to blood-brain barrier and increased permeability. It has been pointed out [17] that when the level of cerebrospinal fluid HBP is >11.84 μg/L, the sensitivity of its differential diagnosis between acute bacterial meningitis and viral meningitis can reach more than 90%. MMP-9 is a novel marker of infection that relies on the assistance of metal ions such as Ca^{2+} and Zn^{2+} to exert extracellular matrix degradation [18]. Animal studies [19] have shown that when the content of MMP-9 in the blood increases, the vascular basement membrane and blood-brain barrier are damaged, and inflammatory cells enter the cerebral vessels, resulting in angiogenic brain edema, which is prone to intracranial infection. In this study, PCT, HBP, and MMP-9 levels were significantly lower than before treatment after 3, 7 and 10 d in those with intracranial

Table 1: Postoperative infections in 208 patients operated on for brain tumours.

Infection status	*n*	Percentage
Infected	65	31.25
Uninfected	143	68.75

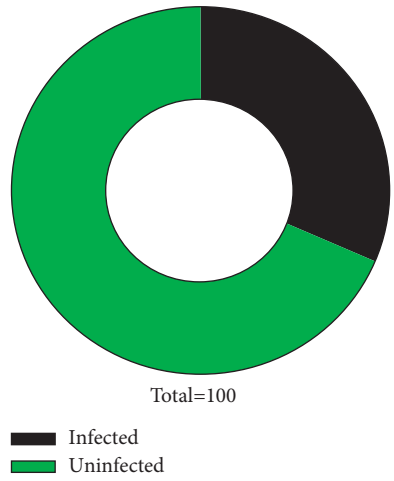

Figure 1: Pie chart of postoperative infections in 208 patients operated for brain tumours.

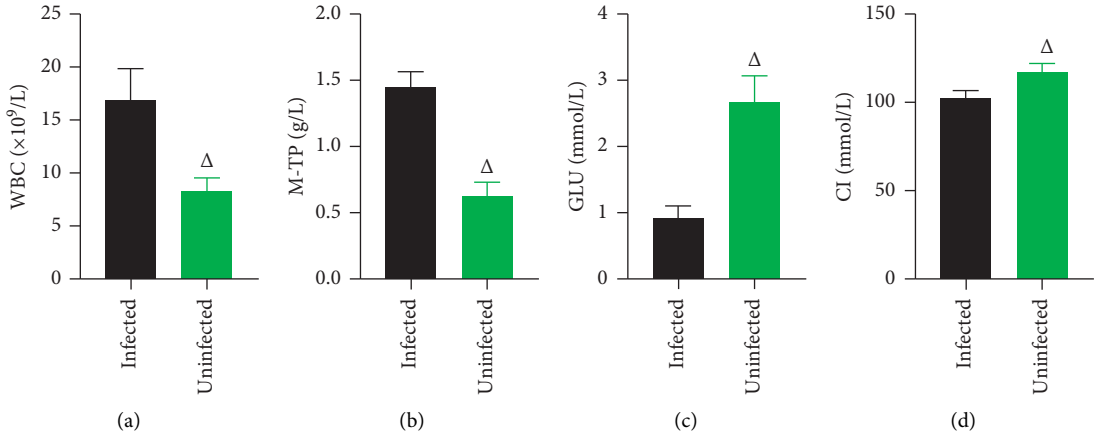

Figure 2: Analysis of CSF routine and biochemical parameters in 208 patients operated for brain tumours. *Note*. Comparison with the same indicator in infected persons, $^{\Delta}P < 0.05$.

infection secondary to brain tumour surgery and tended to decrease over time. It indicates that PCT, HBP, and MMP-9 can be used for early assessment of the extent of intracranial infections and to guide rational clinical management.

Brain tumours occur in a confined environment formed by the tissues of the meninges, skull, and scalp, and when patients need to undergo craniotomy, the disruption of the anatomical structure caused by the surgery and the placement of postoperative drains can open up the brain tissue to the outside world; thus, causing germs to invade the skull and increasing the probability of infection. CSF pathogenic cultures are the gold standard for the diagnosis of intracranial infections, and their epidemiological surveillance is important in guiding the empirical clinical use of drugs. In this study, 62 strains of pathogenic bacteria were isolated from 65 cases of intracranial infections, of which Gram-negative bacteria accounted for 66.13%, with Acinetobacter baumannii and *Klebsiella pneumoniae* being the most distributed, and these two bacteria were mainly highly resistant to amikacin and ciprofloxacin and sensitive to meropenem and imipenem, so we presume that intracranial infections caused by Gram-negative bacteria should be treated with beta-lactam antibiotics; Gram-positive bacteria accounted for 30.65%, with coagulase-negative staphylococci and *Staphylococcus aureus* being the most distributed, and these two bacteria were mainly highly resistant to penicillin and erythromycin and sensitive to vancomycin, suggesting that vancomycin could be the antibacterial drug of choice for intracranial infection caused by Gram-positive bacteria.

Intracranial infection after craniocerebral surgery often coexists with encephalocele, intracerebral hypertension,

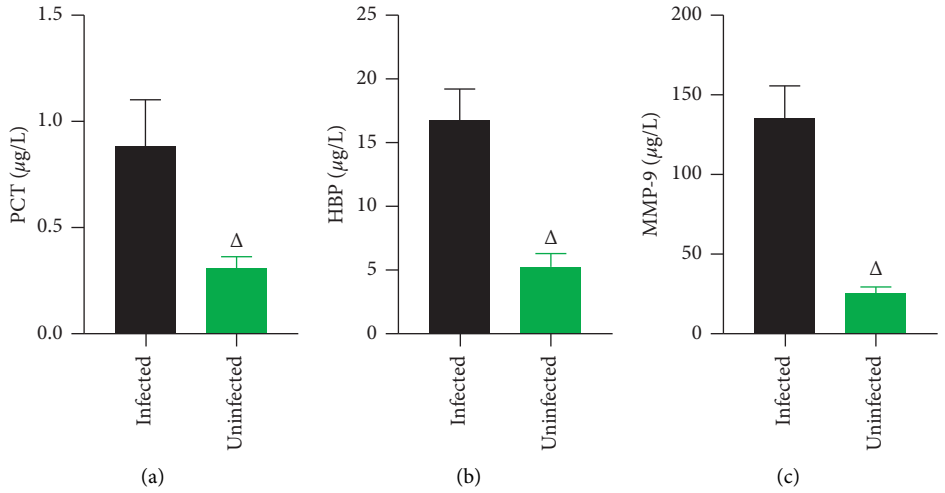

Figure 3: Analysis of PCT, HBP, and MMP-9 levels in CSF of infected and uninfected patients (μg/L). *Note*. Comparison with the same indicator in infected persons, $^{\Delta}P < 0.05$.

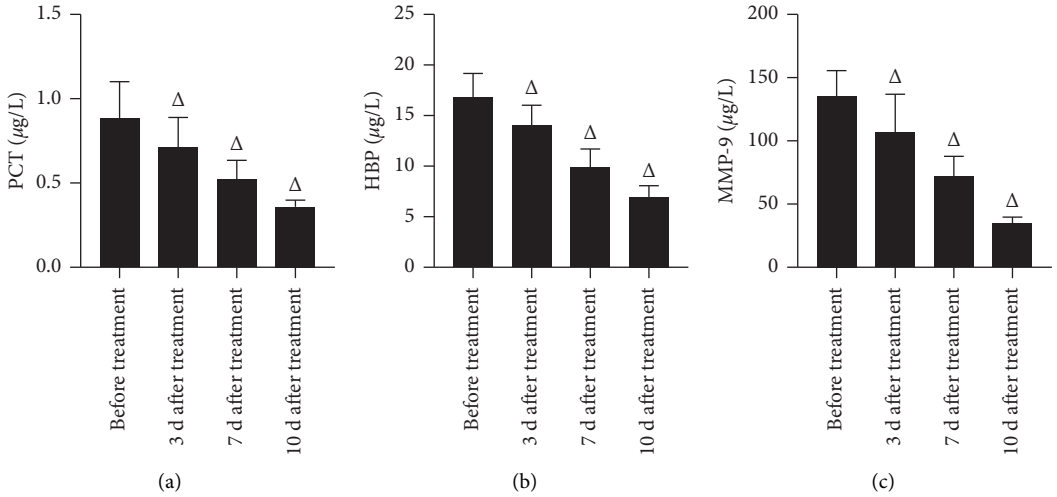

Figure 4: Analysis of PCT, HBP, and MMP-9 levels before and after treatment in 65 patients with intracranial infections (μg/L). *Note*. Comparison with the same indicator before treatment, $^{\Delta}P < 0.05$.

brain edema, and hydrocephalus, and they interact with each other to aggravate the condition; thus, directly affecting the prognosis. At present, it is believed that there are some differences in the related factors of secondary intracranial infection after brain tumour surgery at home and abroad. In this study, multivariate logistic regression was used to adjust for confounding factors. It was found that the independent risk factors of intracranial infection after brain tumour surgery include the following: first, infratentorial tumour: according to the report [20], the incidence of intracranial infection in infratentorial craniotomy is 6 times higher than that in supratentorial craniotomy, which may be due to the complex anatomical structure of the infratentorial posterior cranial fossa, difficult exposure of the surgical site, and long operation time of microscope and other equipment, which can increase the risk of intracranial infection; also, the surgical approach of the posterior cranial fossa is adjacent to the mastoid air chamber, and the sudden opening of the mastoid air chamber during craniotomy will also increase the risk factor of intracranial infection. Secondly, operation time ≥4 h: craniocerebral surgery requires strict asepsis, and indoor air is an important source of pollution in the occurrence of intracranial infection; the more 10000 to 20000 bacteria fall into the surgical field per hour during surgery, the longer the operation time, the higher the probability of pollution exposure, and the higher the probability of postoperative infection [21]. Thirdly, postoperative indwelling drainage time ≥24 h: brain tumour surgery often requires the placement of intracranial or subcutaneous drains to facilitate the smooth drainage of cerebrospinal fluid or blood, but improper management of the drainage device or overpositioning of the drainage tube can result in poor drainage or even reflux of drainage fluid into the skull.

Brain tumour surgery often requires intracranial or subcutaneous indwelling drainage tubes in order to successfully drain cerebrospinal fluid or hematocele, but if the drainage

Table 2: Analysis of the pathogenic bacteria distribution in 65 cases of intracranial infections.

Pathogenic bacteria	Number	Percentage (%)
Gram-negative bacteria	41	66.13
Acinetobacter baumannii	13	20.97
Klebsiella pneumoniae	13	20.97
Pseudomonas aeruginosa	9	14.51
Escherichia coli	6	9.68
Gram-positive bacteria	19	30.65
Coagulase-negative staphylococci	7	11.29
Staphylococcus aureus	6	9.68
Staphylococcus epidermidis	3	4.84
Enterococcus	3	4.84
Fungus	2	3.22
Candida albicans	2	3.22
Total	62	100.00

Table 3: Resistance rates of major Gram-negative bacteria to antibacterial drugs.

Antibacterial drug	Acinetobacter baumannii ($n = 13$)		*Klebsiella pneumoniae* ($n = 13$)	
	Number	Resistance rate (%)	Number	Resistance rate (%)
Amikacin	11	84.62	11	84.62
Ciprofloxacin	13	100.00	8	61.54
Gentamicin	10	76.92	7	53.85
Ceftazidime	10	76.92	8	61.54
Cefuroxime	9	69.23	8	61.54
Piperacillin	6	46.15	6	46.15
Meropenem	0	0.00	0	0.00
Imipenem	0	0.00	0	0.00

Table 4: Resistance rates of major Gram-positive bacteria to antibacterial drugs.

Antibacterial drug	Coagulase-negative staphylococci ($n = 7$)		*Staphylococcus aureus* ($n = 6$)	
	Number	Resistance rate (%)	Number	Resistance rate (%)
Penicillin	7	100.00	6	100.00
Erythromycin	7	100.00	6	100.00
Oxacillin	5	71.43	5	83.33
Levofloxacin	5	71.43	3	50.00
Vancomycin	0	0.00	0	0.00
Rifampicin	1	14.29	1	16.67

Table 5: Univariate analysis of intracranial infection secondary to brain tumour surgery.

Risk factor	Infected ($n = 65$)		Uninfected ($n = 143$)		χ^2	P
	n	Percentage	n	Percentage		
Age (years)					2.239	0.327
<35	10	15.38	35	24.47		
3535~<60	24	36.92	45	31.47		
≥60	31	47.70	63	44.06		
Gender					0.009	0.925
Male	35	53.85	78	54.55		
Female	30	46.15	65	45.45		
Tumour type					6.182	0.103
Meningioma	25	38.46	40	27.97		
Glioma	23	35.39	66	46.15		
Pituitary adenoma	6	9.23	23	16.09		
Acoustic nerve tumour	11	16.92	14	9.79		

Table 5: Continued.

Risk factor	Infected ($n = 65$)		Uninfected ($n = 143$)		χ^2	P
	n	Percentage	n	Percentage		
Tumour site					15.820	<0.001
Supratentorial	32	49.23	110	76.92		
Infratentorial	33	50.77	33	23.08		
Operation time (h)					21.083	<0.001
<4	15	23.08	82	57.34		
≥4	50	76.92	61	42.66		
Postoperative indwelling drainage time					20.302	<0.001
Not put or <24 (h)	25	38.46	102	71.33		
≥24	40	61.54	41	28.67		
Postoperative cerebrospinal fluid leakage					17.033	<0.001
Yes	52	80.00	71	49.65		
No	13	20.00	72	50.35		
History of diabetes					7.608	0.006
Yes	19	29.23	19	13.29		
No	46	70.77	124	86.71		
History of glucocorticoid application					0.002	0.966
Yes	17	26.15	37	25.87		
No	48	73.85	106	74.13		
Prophylactic application of antibiotics					0.573	0.449
Yes	25	38.46	63	44.06		
No	40	61.54	80	55.94		

Table 6: Multifactorial logistic regression analysis of intracranial infections secondary to brain tumour surgery.

Risk factor	β	SE	Wald	OR	95% CI	P
Infratentorial tumour	1.946	0.665	8.514	7.001	1.901~25.775	0.004
Operation time ≥4 h	1.015	0.328	9.790	2.759	1.451~5.248	0.002
Postoperative indwelling drainage time ≥24 h	0.725	0.303	5.768	2.065	1.140~3.739	0.018
Postoperative cerebrospinal fluid leakage	0.844	0.248	11.420	2.306	1.430~3.781	0.001

device is not managed properly and the position of the drainage tube is too high, it can lead to poor drainage and even the drainage fluid flowing back to the brain; in addition, the risk of pollution exposure is correspondingly increased due to the long time of tube placement. Fourthly, postoperative cerebrospinal fluid leakage: cerebrospinal fluid leakage can be divided into rhinorrhea and otorrhea, and pathogenic bacteria can enter the brain along the channel of cerebrospinal fluid leakage, resulting in intracranial infection. It can be seen from the above that for patients with brain tumour surgery, adequate preparation and detailed operation plan should be made before operation, the operation time should be shortened as far as possible, aseptic operation should be strictly implemented, the wound should be closely sutured after operation, cerebrospinal fluid leakage should be prevented, drainage tubes should be placed to avoid reflux and blockage caused by improper placement, and drainage time should also be controlled. For patients with brain tumour surgery with high-risk factors, prophylactic drugs should be used and monitoring should be strengthened during the perioperative period. Once there are suspected symptoms of intracranial infection such as high fever and meningeal irritation, diagnosis and treatment should be carried out as soon as possible without any delay.

In summary, patients with intracranial infections secondary to brain tumour surgery have abnormal levels of CSF routine and biochemical parameters, and the detection rate of Gram-negative bacteria is higher than that of Gram-positive bacteria in patients. Treatment should be based on the characteristics of pathogenic bacteria and risk factors with targeted interventions to reduce intracranial infections. This study also has shortcomings. There are many factors that contribute to cerebrospinal fluid infection after craniotomy, and the clinical symptoms of each type of infection lack specificity. Studying the routine and biochemistry of the cerebrospinal fluid in different types of infections may further strengthen the diagnosis and differentiation. However, given the inadequate sample size and technical support in this study, further classification analysis is pending for future studies with larger samples.

Data Availability

The data used in the current study are available from the corresponding author.

Conflicts of Interest

The authors declare that there are no relevant conflicts of interest to disclose.

Authors' Contributions

Yang Zhang and Ying Zhou are the co-first authors.

Acknowledgments

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Retraction

Retracted: A Retrospective Study of Diaphragmatic Breathing Training Combined with Discharge Care Bundles in Patients with Chronic Obstructive Pulmonary Disease

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] S. Yu, C. Lu, and L. Qin, "A Retrospective Study of Diaphragmatic Breathing Training Combined with Discharge Care Bundles in Patients with Chronic Obstructive Pulmonary Disease," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 9649986, 8 pages, 2022.

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Research Article

A Retrospective Study of Diaphragmatic Breathing Training Combined with Discharge Care Bundles in Patients with Chronic Obstructive Pulmonary Disease

Shuhui Yu, Chen Lu, and Lingling Qin

Respiratory Department, Huzhou Central Hospital & Affiliated Central Hospital, HuZhou University, Huzhou, China

Correspondence should be addressed to Lingling Qin; m13511233263@163.com

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Objective. Both physical exercise and discharge care bundles can improve patient outcomes and reduce hospitalization rates among subjects with chronic obstructive pulmonary disease (COPD). The retrospective analysis aims to determine the advantages of care bundles combined with diaphragmatic breathing training (DBT) in COPD patients after discharge. *Methods*. Of the 110 COPD patients, 55 patients received DBT alone (DBT group) and 55 participants received the combined intervention (care bundle + DBT group). Three months after discharge, we assessed the outcomes of patients using Bristol COPD Knowledge Questionnaire (BCKQ), Hospital Anxiety and Depression Scale (HADS), COPD Assessment Test (CAT), and St. George's Respiratory Questionnaire (SGRQ). Meanwhile, COPD-related hospital readmissions were also recorded. *Results*. The BCKQ score for assessing the disease knowledge level was increased in patients at 3 months after the combined interventions as compared to the baseline values, which was higher in the care bundle + DBT group than the DBT group at 3 months. Moreover, improvements in negative emotion and clinical symptoms from baseline to 3-month follow-up were seen in both the two groups. Besides, the care bundle + DBT group showed the mitigation of depression and anxiety and the alleviation of clinical symptoms in comparison with the DBT group at 3 months. Participants who received combined interventions had lower SGRQ scores than those who received DBT alone. The time to first COPD-related readmission was shorter for patients in the care bundle + DBT group compared with the DBT group. *Conclusions*. DBT combined with discharge care bundles for COPD patients resulted in improvements in disease-specific knowledge, negative emotions, and clinical symptoms with better HRQOL and lower readmission rate.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic progressive respiratory disease that leads to irreversible airway obstruction, with a high global prevalence of about 20.9%, and it is responsible for the leading cause of death worldwide [1]. In 2016, COPD was the fifth leading cause of death in China with the prevalence ranging from 2% to 21% [2]. Patients with COPD often show a series of symptoms such as coughing, dyspnea, wheezing, and chest tightness [3]. Furthermore, compared with the general population, COPD patients are frequently attacked by cardiovascular and metabolic diseases [4], lung cancer [5], anxiety, and depression [6], which significantly diminish the quality of life and increase health resource utilization [7, 8]. Furthermore, approximately one-third of COPD patients were reported to be readmitted within 90 days of discharge, resulting in 13.9% of death [9]. The good thing is that the management of COPD has improved, including early detection and treatment and primary care practice.

Currently, as a kind of low-intensity aerobic exercise, diaphragmatic breathing training (DBT) with special breathing techniques is a commonly used intervention in pulmonary rehabilitation [10]. DBT contributes to alleviate dyspnea, improve pulmonary function and enhances health-related quality of life in patients with COPD by increasing the strength and endurance of respiratory muscles along with diaphragmatic excursion, reducing accessory muscle

use, and guiding the correct breathing patterns [10–12]. As reported in some studies, DBT has been extremely beneficial for increasing tidal volume, reducing respiratory rate, and improving breathing patterns [13, 14]. Moreover, DBT intervention as a home-based pulmonary rehabilitation was reported to be feasible in COPD patients, with high retention and adherence [15, 16].

Care bundles, consisting of a series of structured evidence-based interventions, aimed to improve patient recovery and outcomes, and have been applied to various diseases that include bloodstream infections [17], postpartum hemorrhage [18], and ventilator-associated pneumonia in pediatrics [19]. As for COPD patients, care bundles were reported to be used as an effective approach for improving the quality of life and reducing mortality after discharge [20, 21]. However, evidence to explore the efficacy of DBT combined with care bundles in COPD patients remains to be elucidated.

The retrospective study enrolled 110 patients diagnosed with COPD and assigned them into two groups, receiving DBT alone and DBT combined with care bundles, respectively. The aim of our study is to assess the superiority of the combination treatment in terms of disease-related knowledge mastery, clinical symptoms, and readmission rates in COPD patients after discharge.

2. Methods

2.1. Study Population. Participants ($n = 110$) with a primary diagnosis of moderate to severe COPD by a pulmonologist or spirometry were recruited in this retrospective study according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [22] (Table 1), who were able to read, write, and speak. Moreover, all patients had stable respiratory conditions without changes in medication or symptoms for at least 4 weeks, and they were given regular treatment with inhaled bronchodilators and steroids. The exclusion criteria were as follows:: (1) diagnosis of cancer; (2) presently attending a pulmonary rehabilitation course or other similar COPD education course; (3) diagnosis of developed serious cardiopulmonary, neuromuscular disease, or dementia; (4) previous engagement in any exercise training program in the prior 2 years; and (5) drug abuse or alcohol abuse. Of these 110 COPD patients, 55 patients received DBT alone (DBT group) and 55 participants received the combined intervention (care bundle + DBT group). All patients completed the baseline and 3-month follow-up assessments. The flow diagram of participants in this retrospective study is illustrated in Figure 1.

2.2. DBT Program. At discharge, all patients in the care bundle + DBT group and the DBT group were instructed on how to complete a DBT program according to previous studies [12, 23]. The DBT program consisted of three 45-minute weekly sessions for 3 months. The patients performed a total of 150 breathing exercises in each session in the five positions (supine, right lateral decubitus, left lateral decubitus, sitting, and standing) with 3 series of 10 repetitions in each position. These exercises were taught to patients in detailed face-to-face sessions held on three successive days as to how to carry out the DBR intervention at home. The patients would receive a telephone call to remind them of doing the breathing exercises.

2.3. COPD Discharge Care Bundles. Except for the DBT exercises, the patients in the care bundle + DBT group also received the discharge care bundles for 3 months of follow-up based on the previous studies [24, 25], including adequate assessment of the patient's understanding on the use of medications and effective inhaler technique, educational programme on disease management, referral for pulmonary rehabilitation, arrange outpatient follow-up in the respiratory clinic, referral to a smoking-cessation programme, and 3- month telephone calls from respiratory nurses.

2.4. Assessment of the Knowledge Level in COPD Patients. The disease-specific knowledge level of patients with COPD was assessed using the Bristol COPD Knowledge Questionnaire (BCKQ) with a total score ranging from 0 to 65 (higher scores indicate greater knowledge of COPD) [26]. The BCKQ was composed of 13 domains, and each domain with five statements giving a total of 65 questions for which there is a response option of "true," "false," and "do not know". Correct and wrong responses are scored as "1" and "0", respectively.

2.5. Assessment of the Negative Emotion and Clinical Symptoms in COPD Patients. The Hospital Anxiety and Depression Scale (HADS) was used to determine the negative emotion (anxiety and depression) in patients with total scores ranging from 0 to 21. The clinical symptoms in patients were determined by the COPD Assessment Test (CAT) [27]. It comprises 8 questions, each presented as a semantic 6-point (0–5) differential scale, providing a total score out of 40.

2.6. Assessment of Health-Related Quality of Life (HRQOL) in COPD Patients. The St. George's Respiratory Questionnaire (SGRQ) was used to evaluate COPD-specific HRQOL [28], which has 50 topics with four scores, including total, symptoms, activity, and impact. Each score ranged from 0 to 100. The higher SGRQ score indicated the worse possible HRQOL.

2.7. Readmission Rate. Readmission data included inpatient, emergency department, and outpatient (classified as a short stay or 24-hour observation and not admitted as inpatients); hospital admissions [29] were obtained through electronic health records even if the patient did not complete the study calls. The time to first COPD-related readmission was recorded to determine the impact of the intervention on patient outcomes.

2.8. Statistical Analysis. Sample size was calculated based on the SGRQ scores in COPD patients after the intervention (effect size = 0.492; α error = 0.05, power = 0.8). To account

Table 1: Global initiative for chronic obstructive lung disease (GOLD) of severe to moderate COPD.

Stage	Characteristics
Moderate	FEV1/FVC < 70% 50% ≤ FEV1 < 80% With or without chronic symptoms (cough and sputum production)
Severe	FEV1/FVC < 70% 30% ≤ FEV1 < 50% With or without chronic symptoms (cough and sputum production)

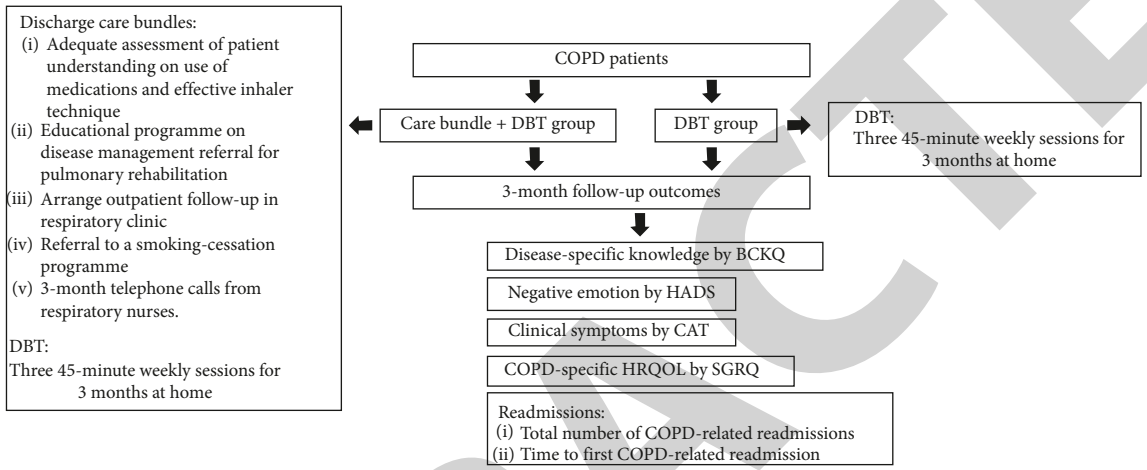

Figure 1: The flow diagram of participants in this retrospective study.

for possible 5% losses to follow-up, 55 patients with COPD in each group had to be recruited. A $P < 0.05$ was considered to indicate a statistical significance in all analyses, which were performed in GraphPad Prism. In order to investigate the distribution of data, we employed the Shapiro–Wilk test, and all data were expressed as mean ± SD for variables with parametric distributions in our study. The comparison of measurement data and counting data (n) was done using the student's t test for unpaired or paired samples and the χ^2 test, respectively.

3. Result

3.1. Baseline and Clinical Characteristics of COPD Patients. The basic information of the patients in the care bundle + DBT group ($n = 55$) and DBT group ($n = 55$) are listed in Table 2. There were no statistically significant differences between both the groups regarding the age ($P = 0.274$), sex ($P = 0.525$), BMI ($P = 0.725$), COPD duration ($P = 0.475$), smoking status ($P = 0.658$), COPD severity ($P = 0.558$), marital status ($P = 0.463$), employment status ($P = 1.000$), educational level ($P = 0.109$), FEV1 (%) ($P = 0.261$), FEV1/FVC (%) ($P = 0.694$), PaO_2 ($P = 0.138$), $PaCO_2$ ($P = 0.667$), and 6MWD ($P = 0.177$).

3.2. Comparison of the Disease Knowledge Level between the Two Groups. Figure 2(a) shows no obvious difference in the overall BCKQ scores at baseline between the care bundle + DBT group and the DBT group (22.8 ± 13.24 vs. 24.78 ± 11.91, $t = 0.825$, $P = 0.411$), which was increased significantly at 3 months after the combined interventions (34.65 ± 13.86 vs. 22.8 ± 13.24, $P < 0.05$). However, for the disease-specific knowledge level, no improvement was found in the DBT group from baseline to 3-month follow-up (25.71 ± 11.79 vs. 24.78 ± 11.91, $P > 0.05$). As compared with the DBT group, the patients in the care bundle + DBT group had a higher total score of BCKQ at 3 months after the interventions (34.65 ± 13.86 vs. 25.71 ± 11.79, $P < 0.05$).

3.3. Comparison of the Negative Emotion between the Two Groups. As demonstrated by Figures 2(b) and 2(c), the improvements in negative emotions from baseline to 3-month follow-up were seen in both the care bundle + DBT group and DBT group with reduced HADS score (both $P < 0.05$). Besides, the care bundle + DBT group showed statistically significant alleviation of depression and anxiety in comparison with the DBT group at 3 months (both $P < 0.05$). At baseline, participants in both the study groups revealed no significant differences regarding the HADS score (both $P > 0.05$).

3.4. Comparison of the Clinical Symptoms and HRQOL between the Two Groups. Although the difference in clinical symptoms as assessed by CAT scores between the two groups was not statistically significant at baseline (DBT group: 16.64 ± 5.76; care bundle + DBT group: 15.67 ± 8.06, $P > 0.05$), the patients after the intervention had lower CAT

Table 2: The basic information of COPD patients in the care bundle + DBT ($n = 55$) and the DBT group ($n = 55$).

Parameter	DBT group	Care bundle + DBT group	P
Age (years)			
>60	49	45	
≤60	6	10	0.274
Sex			
Male	41	38	
Female	14	17	0.525
BMI (kg/cm^2)	21.09 ± 1.74	20.96 ± 1.87	0.725
COPD duration (years)	3.13 ± 1.29	2.95 ± 1.37	0.475
Smoking status			
Current	30	28	
Former	11	15	
Never	14	12	0.658
COPD severity			
Moderate	35	32	
Severe	20	23	0.558
Marital status			
Single	5	3	
Married	50	52	0.463
Employment status			
Employed	3	3	
Retired	52	52	1.000
Educational level			
≤9 years	32	40	
>9 years	23	15	0.109
FEV1 (%)	54.85 ± 13.59	52.00 ± 12.91	0.261
FEV1/FVC (%)	56.27 ± 6.95	55.76 ± 6.59	0.694
PaO_2	63.25 ± 7.20	61.07 ± 8.08	0.138
$PaCO_2$	37.44 ± 5.36	37.89 ± 5.68	0.667
6MWD	381.73 ± 118.95	414.58 ± 134.17	0.177

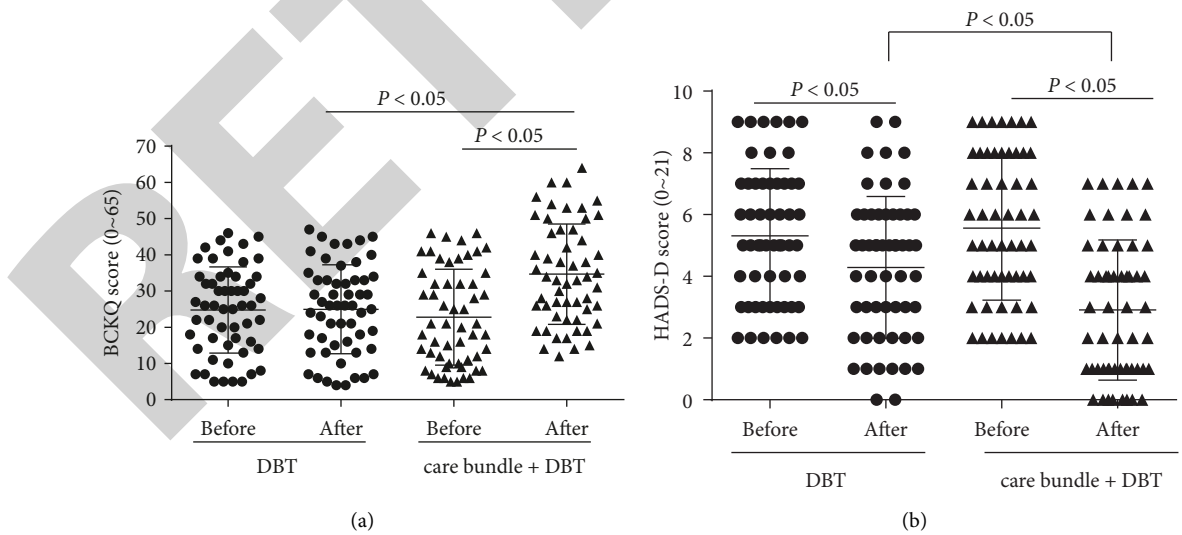

Figure 2: Continued.

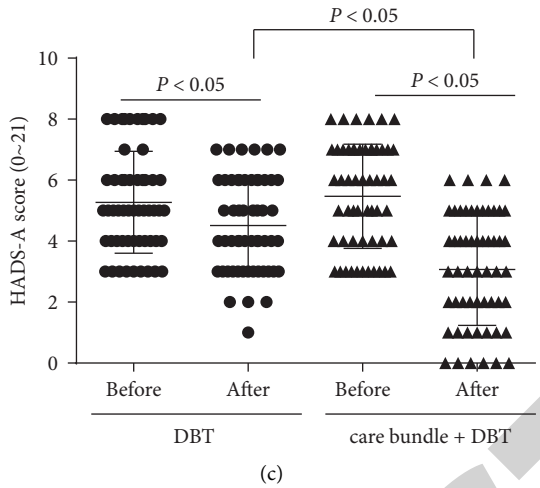

Figure 2: Comparison of the disease knowledge level and negative emotions between the two groups. (a) The disease-specific knowledge level of patients with COPD was assessed using the Bristol COPD Knowledge Questionnaire (BCKQ); (b)-(c): Hospital Anxiety and Depression Scale (HADS) was used to determine the negative emotion (anxiety and depression) in COPD patients.

scores than the baseline values in both the DBT group and care bundle + DBT group. Moreover, the care bundle + DBT group (10.95 ± 6.31) experienced an obvious reduction compared with the DBT group (13.45 ± 5.69) at 3 months ($P < 0.05$, Table 3). Furthermore, the care bundle + DBT group had a slightly higher proportion of people who experienced clinically alleviated clinical symptoms than the DBT group without a statistical difference ($P > 0.05$). In addition, differences in SGRQ scores between the care bundle + DBT group (54.22 ± 16.62) and DBT group (54.40 ± 16.64) were small and statistically not significant at baseline ($P > 0.05$), but participants in the care bundle + DBT group (3652 ± 17.61) had better HRQOL (lower SGRQ scores) than those in the DBT group (45.00 ± 16.88) at 3 months ($P < 0.05$, Table 3).

3.5. Comparison of the Readmission Rates between the Two Groups. We found that 15 (27.27%) of 55 patients in the DBT group had at least one readmission during the course of the study compared with 6 (10.91%) of 55 persons in the care bundle + DBT group. There was an increased total number of COPD-related readmissions in the DBT group than in the care bundle + DBT group (30 cases vs. 12 cases). Kaplan–Meier analysis of the time to first COPD-related hospital readmission is presented in Figure 3. Overall, the time to first COPD-related readmission was longer for patients in the care bundle + DBT group compared with the DBT group ($\chi^2 = 4.810$, $P = 0.028$), with more events occurring in the DBT group after the program completion.

4. Discussion

COPD is the third leading cause of death worldwide, which seriously affects human health and causes a heavy social and economic burden [30]. Breathing exercises and care bundles are widely used in the treatment of COPD, aiming to improve the physical and psychological status of COPD patients [20, 31]. As part of the pulmonary rehabilitation method (comprehensive intervention program), breathing exercises are a simple but highly targeted training that can be completed at home independently by patients with COPD, resulting in strengthening the respiratory muscle and ultimately improving long-term management of dyspnea [32, 33]. DBT is a common physiotherapy technique used to relieve dyspnea, improve pulmonary function, and enhance the psychological condition of COPD patients [34, 35]. Significant variations in readmission outcomes and provision of COPD care have been noted. Furthermore, the care bundle was associated with significant improvements in pulmonary rehabilitation, smoking cessation, and relevant knowledge of inhalers [21]. In our retrospective study, we included a total of 110 participants with a primary diagnosis of moderate to severe COPD. Among them, 55 patients were treated with DBT alone and the remaining 55 patients received DBT combined with the discharge care bundle.

In recent years, professionals have emphasized the importance of patient self-management and increased patients' want to better understand their condition. Therefore, it is particularly important to carry out medical education for patients and their families. Due to the variations in the form and content of medical education, there are differences in the results of education for COPD patients [26, 36, 37]. The BCKQ is a kind of questionnaire used to assess the knowledge of individual patients. "Incorrect" or "do not know" options indicate that patients have insufficient knowledge where specific education is needed [38]. In our study, after a 3-month intervention, we found that the overall BCKQ score of the care bundle + DBT group was significantly increased compared to the baseline data. White et al. implied that the average BCKQ scores of COPD patients was 54.7% before education but the score was increased to 73%, which was maintained for six months in most patients, following an eight-week education programme [26].

Table 3: Comparison of the clinical symptoms by CAT scores and HRQOL by SGRQ scores between the two groups.

Groups	*CAT scores*			*SGRQ scores*		
	Before	After	*P*	Before	After	*P*
DBT group	16.64 ± 5.76	13.45 ± 5.69	<0.001	54.40 ± 16.64	45.00 ± 16.88	<0.001
Care bundle + DBT group	15.67 ± 8.06	10.95 ± 6.31	0.003	54.22 ± 16.62	36.52 ± 17.61	<0.001
P	0.866	0.027		0.954	0.024	

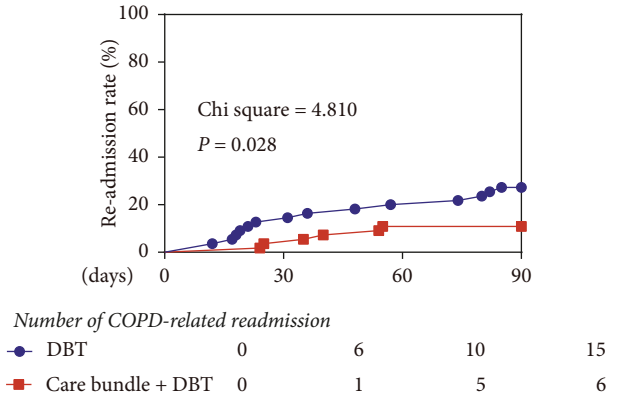

Figure 3: Kaplan–Meier analysis of the time to first COPD-related hospital readmission between the two groups.

COPD patients are more likely to suffer from psychological diseases including depression and anxiety, which might induce poor treatment compliance [6]. Hence, we evaluated the psychological condition of the two groups through the HADS score. The HADS has been developed as a simple measurement of clinical symptoms of depression, anxiety, and fear in patients with mental diseases [39]. HADS has been widely used in lung-related diseases including lung cancer [40], thromboembolism [41], and pneumonia [42]. Compared with the baseline, the care bundle + DBT group and DBT group both the groups revealed reduced HADS scores, indicating alleviation in negative emotion after interventions. In addition, a significantly lower HADS score was found in the care bundle + DBT group than that of the DBT group at 3 months.

The present study also assessed clinical symptoms via CAT scores and COPD-specific HRQOL by the SGRQ score. The findings demonstrated that both the two groups had reduced CAT scores after the intervention, and this trend was more obvious in the care bundle + DBT group. People with specific diseases are related to an increased risk of death, and these diseases may lead to dysfunction and symptoms, affecting personal activities of daily living. HRQOL terms are often used specifically to assess the health status of individuals with diseases that impair daily functions or cause symptoms [43]. Our study observed that the patients with care bundle + DBT intervention had lower SGRQ scores compared to the DBT group, suggesting care bundle + DBT intervention improved HRQOL.

It has been proposed that the care bundle is an effective method to prevent COPD readmission after hospitalization, reducing the 30-day all-cause readmission rate from 22.7% to 14.7% [28]. As reported by Laverty et al. discharge care bundle has an advantage in the reduction in the readmission rate of COPD [9]. Fewer patients in the care bundle + DBT group were readmitted to the hospital compared to the DBT group. Furthermore, Kaplan–Meier analysis indicated that the patients in the care bundle + DBT group showed a longer time of first COPD-related readmission than that in the DBT group. Of note, some limitations were presented in our study, for instance, 3-month follow-up may not be enough to evaluate the long-term efficacy of the combined intervention. Besides, we need a large number of subjects to verify our findings. Furthermore, fatigue is one of the most disabling symptoms of COPD [44], and COPD was reported to result in poor cardiopulmonary endurance [45], indicating fatigue level and cardiopulmonary should be taken into consideration in future analysis. The explanations of abbreviations in this study have been listed in Supplementary Table 1.

To sum up everything, DBT combined with the discharge care bundle appeared to be associated with improvement in disease-specific knowledge levels and a reduction in readmission rate. Combined intervention is superior to the DBT intervention alone in terms of assessment of depression and anxiety, clinical symptoms, and HRQOL.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

The explanations of abbreviations in this study have been listed in Supplementary Table 1. (*Supplementary Materials*)

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Retraction

Retracted: A Study on the Effects of a Cartoon Text Version of Health Education Manual with Sandplay on the Psychological Status and Cognitive Function of Children with Attention Deficit Hyperactivity Disorder

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] L. He and L. Huang, "A Study on the Effects of a Cartoon Text Version of Health Education Manual with Sandplay on the Psychological Status and Cognitive Function of Children with Attention Deficit Hyperactivity Disorder," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 1816391, 7 pages, 2022.

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Research Article

A Study on the Effects of a Cartoon Text Version of Health Education Manual with Sandplay on the Psychological Status and Cognitive Function of Children with Attention Deficit Hyperactivity Disorder

Lei He and Lifeng Huang

Guangzhou Women and Children's Medical Center Pediatric Clinic, Guangzhou 510000, Guangdong, China

Correspondence should be addressed to Lei He; yuandle2022@163.com

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Purpose. The study aimed to examine the effects of a cartoon text version of a health education manual with sandplay on the psychological status and cognitive function of children with attention deficit hyperactivity disorder (ADHD). *Methods*. Eighty cases of children with ADHD admitted from February 2019 to September 2021 were selected for the study. They were numbered according to the order of consultation, and after obtaining family consent, they were divided into the control group ($n = 40$) and the observation group ($n = 40$) using the random number table method. The control group received only medication and verbal health education, while the observation group received a cartoon text version of the health education manual together with sandplay on top of the above, and both groups were treated for 30 weeks. The attention test results and the Swanson, Nolan, and Pelham-IV rating scales (SNAP-IV) were used to assess the effectiveness of the treatment for both groups of children. The awareness rate of health education knowledge of children and their families in both groups was counted. The Conners Parent Symptom Questionnaire (PSQ) and the Combined Raven's test (CRT) were used to assess the psychological status and cognitive functioning of the children in both groups. *Results*. After treatment, the response time, the number of errors, and the number of missed alarms in the attention test results were lower in the observation group than in the control group ($P < 0.05$). After treatment, the inattention, antagonism and defiance, and impulsiveness and hyperactivity scores on SNAP-IV were lower in the observation group than in the control group ($P < 0.05$). After treatment, the knowledge of disease and treatment, medical and nursing cooperation, safety and protection, and dietary precautions were higher in the observation group than in the control group ($P < 0.05$). After treatment, the learning problems, conduct problems, psychosomatic problems, anxiety, impulsivity-hyperactivity, and hyperactivity index scores on the PSQ were lower in the observation group than in the control group ($P < 0.05$). After treatment, the A, B, C, D, and E theme scores in the CRT were higher in the observation group than in the control group, and the IQ score was also higher in the observation group than in the control group ($P < 0.05$). *Conclusion*. The cartoon text version of the health education manual with sandplay can significantly improve the attention deficit, hyperactive behaviour, psychological status, and cognitive function of children with ADHD on the basis of pharmacological treatment, which has a good clinical application.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders in children. The main manifestations are that attention that is not commensurate with age is easy to be distracted, the attention span is reduced, excessive activities, emotional impulses, and willfulness. Children are often accompanied by different degrees of psychological behaviour abnormalities, cognitive dysfunction, and learning difficulties, and their intelligence is normal or close to normal [1, 2]. At present, most children and their families do not have a good understanding of

ADHD. They still believe that the clinical symptoms of the children are poor ideological and moral character and do not accept discipline. Parents and teachers often give rude education. Students, relatives, and friends are more likely to alienate and discriminate against them. Children cannot correctly face their diseases, which will continue to affect their mental health, behaviour, and cognitive function. It seriously affects the quality of life and normal development of children.

At present, there are many methods to treat ADHD. In addition to drug treatment, there are multiple targeted treatment methods [3]. Sandplay is a form of therapy that is fun and educational and has become a widely accepted form of therapy as the concept of humanistic therapy continues to develop [4, 5]. In addition, the young age and poor self-management skills of children with ADHD, as well as the mobility of their family chaperones, often due to time constraints, make it difficult for many children with ADHD to receive verbal health education and behaviour management guidance. In recent years, the department has been actively using the cartoon text version of the health education manual to treat 40 cases of children with ADHD together with sandplay, which has not only enabled all children and their accompanying family members to learn the relevant health education and care knowledge and reduce the safety risks but also effectively improved the clinical treatment results of the children, as reported below.

2. Materials and Methods

2.1. General Materials. Eighty cases of children with ADHD admitted from February 2019 to September 2021 were selected for the study. Inclusion criteria were as follows: ① those who met the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [6] criteria for the diagnosis and staging of ADHD in the United States; ② those with an intelligence quotient (IQ) score of 85 to 110 on the Wechsler Intelligence Scale for Children (WISC-CR) [7]; ③ ages 6 to 12 years; ④ those who accepted the treatment with good compliance and completed the assessment. Exclusion criteria were as follows: ① exclusion of children with mental retardation, epilepsy, organic encephalopathy, autism, affective disorders, schizophrenia, tic disorders, digestive disorders, and malnutrition; ② children with a history of psychotropic substance use; ③ those who had received other medication before the study. All children were numbered according to the order of consultation, and after obtaining family consent, they were divided into the control group ($n = 40$) and the observation group ($n = 40$) by using the random number table method. The comparison of general information between the two groups is shown in Table 1, and none of them were significantly different and comparable ($P > 0.05$).

2.2. Methods

(1) The control group received only medication and verbal health education. The drug of choice was methylphenidate hydrochloride extended-release tablets (Janssen-Cilag Limited, State Drug Administration J20120028), administered orally at a starting dose of 18 mg/d once a day in the morning for 30 weeks, and during that time, the child's clinical response and drug tolerance were strictly monitored and the dose was adjusted as necessary. Oral education of health education knowledge: according to the requirements of routine nursing, the children and their families were provided with health education through oral explanation, public class lectures, and action demonstrations.

(2) The observation group received a cartoon text version of the health education manual together with sandplay on top of the above. Cartoon text version of the health education manual: the main contents of health education (e.g., greetings on admission, names, and contact details of the attending physician and responsible nurse, information on the child's illness and treatment, knowledge on the cooperation between health care and nursing, safety and protection, and dietary precautions) were made into the cartoon text version of the health education manual, and the cartoon text version of situation maps in different situations with cartoon characters (e.g., GG Bond, Pleasant Goat, Bear senior, and Bear junior) loved by children was drawn. Sandplay: the therapists were counselors with practical experience in sandplay psychotherapy. The sandplay room was configured according to international standards, with toy shelves on both sides containing household items, transport, military machinery, and plant and animal toys, creating a very safe, free, and relaxing environment for children to draw on sandplay. Once the child entered the sandplay room, the therapist instructed him/her on the basic operation of the sand play and guided him/her to focus on the game, asking him/her to signal when he/she had finished playing, while the nursing staff took notes, and the parents observed and did not disturb the child's play. The length of the game was controlled at ≤60 min/time. After the game, the nursing staff asked the child what he or she had shaped and induced him or her to describe his or her feelings during sandplay therapy so that the nursing staff could understand his or her personality and signs and purposefully set different sandplay themes each week to stimulate the child's imagination and creativity, 1 time/week for 30 weeks of treatment.

2.3. Assessment Indicators

(1) Attention test results: the integrated visual and auditory continuous performance test (IVA-CPT) [8] was administered to all children after treatment for 12 minutes to measure visual, auditory, and sustained attention. The response time, the number of errors, and the number of missed alarms were automatically recorded by the program.

Table 1: Comparison of general information between the two groups.

Items	Control group ($n = 40$)	Observation group ($n = 40$)	t/χ^2	P
Age (years old)	9.30 ± 1.73	9.23 ± 1.27	0.206	0.837
Disease duration (months)	14.38 ± 4.16	14.60 ± 3.75	0.248	0.805
Male (n, %)	24 (60.00)	26 (65.00)	0.213	0.644
Type (n, %)			1.461	0.482
Attention deficit type	24 (60.00)	23 (57.50)		
Hyperactive-impulsive type	2 (5.00)	5 (12.50)		
Combination type	14 (35.00)	12 (30.00)		

(2) ADHD rating scale 4th edition (Swanson, Nolan, and Pelham-IV rating scales, SNAP-IV) scores: the SNAP-IV rating scales [9] had 26 items including 3 areas of inattention, antagonism and defiance, and impulsiveness and hyperactivity. Each entry was rated from 0 to 3 according to the frequency of occurrence, with higher scores indicating more severe ADHD in individuals.

(3) Awareness rate of health knowledge: after treatment, the awareness of the children and their families of the knowledge of disease and treatment, medical and nursing cooperation, safety and protection, and dietary precautions were counted in both groups.

(4) Conners Parent Symptom Questionnaire (PSQ) scores: PSQ [10] had 48 entries including six factors learning problems, conduct problems, psychosomatic problems, anxiety, impulsivity-hyperactivity, and hyperactivity index. Each entry was scored from 0 to 3, with higher scores indicating more serious problems in this area in children. The scale had been extensively tested for clinical validity and was adequate for general assessment. The PSQ was used in this study to assess the behavioural problems and psychological status of children with ADHD.

(5) Combined Raven's test (CRT): the main tests were divided into five groups of themes: A (perceptual discrimination, graphical comparison, and graphical imagination), B (similarity, comparison, and graphical combination), C (comparison, inference, and graphical combination), D (series relations, graphical sets, and sums), and E (abstract thinking skills). Each group consisted of 12 questions and the test lasted 30 to 40 minutes, with 1 mark for a correct answer and 0 marks for an incorrect answer. The scores were added to get the original score. The original total score of the child was converted into the percentage grade according to the percentage grade norm table, and then, the percentage grade was converted into the corresponding IQ value according to the IQ norm table. CRT was used in this study to evaluate the cognitive function of children with ADHD.

2.4. Statistical Methods. The data analysis software was SPSS 22.0, and the plotting software was GraphPad Prism 8.0. Statistical information was described in (%) and adopted the χ^2 test, and measurement information was expressed in ($x \pm s$) and adopted the t-test. A two-sided test of $P < 0.05$ was considered a statistically significant difference.

3. Results

3.1. Comparison of Attention Test Results between the Two Groups. After treatment, the response time, the number of errors, and the number of missed alarms in the attention test results were lower in the observation group than in the control group ($P < 0.05$) (Figure 1).

3.2. Comparison of SNAP-IV Scores between the Two Groups. After treatment, the inattention, antagonism and defiance, and impulsiveness and hyperactivity scores on SNAP-IV were lower in the observation group than in the control group ($P < 0.05$) (Figure 2).

3.3. Comparison of the Awareness Rate of Health Education Knowledge between the Two Groups. After treatment, the knowledge of disease and treatment, medical and nursing cooperation, safety and protection, and dietary precautions were higher in the observation group than in the control group ($P < 0.05$) (Figure 3).

3.4. Comparison of PSQ Scores between the Two Groups. After treatment, the learning problems, conduct problems, psychosomatic problems, anxiety, impulsivity-hyperactivity, and hyperactivity index scores on the PSQ were lower in the observation group than in the control group ($P < 0.05$) (Figure 4).

3.5. Comparison of CRT Scores and IQ Values between the Two Groups. After treatment, the A, B, C, D, and E theme scores in the CRT were higher in the observation group than in the control group, and the IQ score was also higher in the observation group than in the control group ($P < 0.05$) (Figures 5 and 6).

4. Discussion

ADHD, also known as hyperactivity disorder, is the result of a combination of genetic, biological, psychological, social, and environmental factors that contribute to the disease. The disease is characterized mainly by hyperactivity during school age, more pronounced attention deficit during primary school, and impulsivity, impatience, restlessness, and attention deficit in adulthood, which can lead to poor

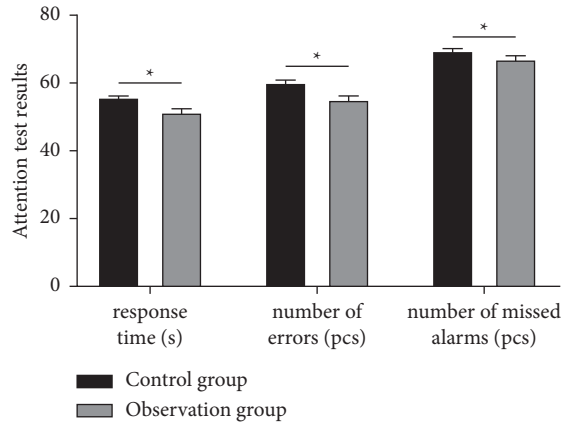

Figure 1: Comparison of attention test results between the two groups. *Note*. The symbol *indicates a statistically significant difference between the two groups.

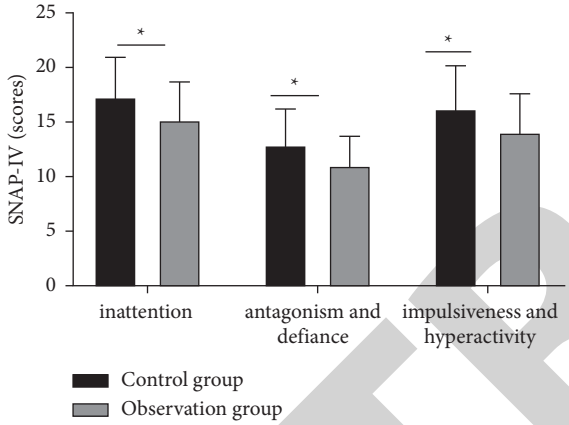

Figure 2: Comparison of SNAP-IV scores between the two groups. *Note*. The symbol *indicates a statistically significant difference between the two groups.

academic performance, poor peer relationships, and social exclusion, and then conduct disorder and antisocial personality disorder and seriously affect children's physical and mental health, as well as work and learning in adulthood [11].

The nonpharmacological treatment of ADHD with few side effects and the little economic burden has now attracted much attention from the parents of low-age children and scholars at home and abroad. In 2001, the American Academy of Pediatrics [12] recommended behavioural interventions for preschoolers (4 to 5 years old); for primary schools children (6 to 11 years old) using FDA-approved medications for ADHD and/or behavioural interventions by parents and/or teachers, with a combination of both resulting in better outcomes. Our latest guidelines for the prevention and treatment of ADHD also place special emphasis on the use of behavioural interventions for children up to the age of 12 years [13]. The results of this study showed that after treatment, the response time, the number of errors, and the number of missed alarms in the attention test results were lower in the observation group than in the control group, and the scores of inattention, antagonism and defiance, and impulsiveness and hyperactivity on SNAP-IV were lower in the observation group than in the control group. This suggests that medication combined with a psychological-behavioural intervention of the cartoon text-based health education manual and sandplay can improve the child's ADHD symptoms better than medication alone.

Health education aims to improve patients' compliance with treatment, reduce the psychological burden, and enhance treatment outcomes [14]. However, in our clinical practice, most of the guardians of children are shared by grandparents and parents, with grandparents' cognitive and information-receiving abilities being relatively poor and the parents spending relatively little time with them, thus making health education less effective. In recent years, our department has printed content requiring health education and behavioural guidance in simple, heartwarming language on a cartoon background booklet that children like. This attracts the child's attention and can promote active access to health education knowledge by the child and his or her chaperones, enabling health education guidance to be put into practice and increasing the rate of knowledge of health education.

Sandplay is a bridge for adults to connect children's inner world before children's expressive language functions are fully mature [15]. In sandplay, a quiet treatment environment and a self-pleasant play course allowed all children to feel their dominant strength and thus gain a sense of controllability, which improved gradually as a " sense of controllability " was recovered. Sandplay provides a way for children to vent bad feelings and express aggressive behaviour, allowing them to channel their excess energy into appropriate behaviour and reduce hyperactivity, impulsivity, and aggressive behaviour. During the production of sandplay, those that are attractive, palpable, and mobile offer the ability to stimulate children's brain nerves with tactile and muscular motion senses to enhance attention. In addition, sandplay can also develop children's imagination and creativity, as well as help with logical thinking and language skills.

The PSQ is an assessment tool used to screen children for behavioural problems (especially ADHD) [16]. This study applies it to the assessment of behavioural problems and the psychological status of children with ADHD. The CRT is a test instrument with special features not found in general text-based intelligence tests. It can be used in situations where verbal communication is difficult and is suitable for a variety of cross-cultural comparative studies, or for testing the cognitive functioning of certain special populations, and is suitable for ages 5 to 75 years [17]. This study uses CRT for the assessment of cognitive function in children with ADHD. The results showed that after treatment, the observation group had better scores for each factor item in the PSQ, CRT, and IQ values than the control group. This suggests that the cartoon text version of the health education booklet combined with sandplay therapy, in addition to medication, can significantly improve the psychological status and cognitive function of children with ADHD, as well as improve their intelligence.

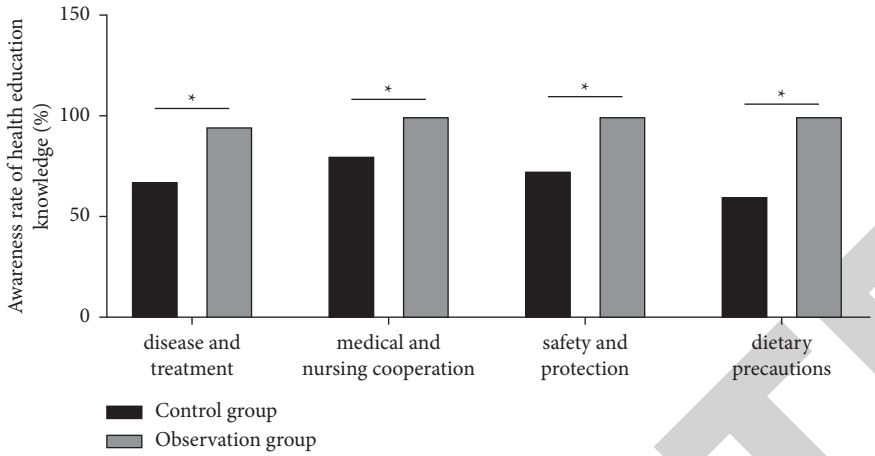

Figure 3: Comparison of the awareness rate of health education knowledge between the two groups. *Note*. The symbol * indicates a statistically significant difference between the two groups.

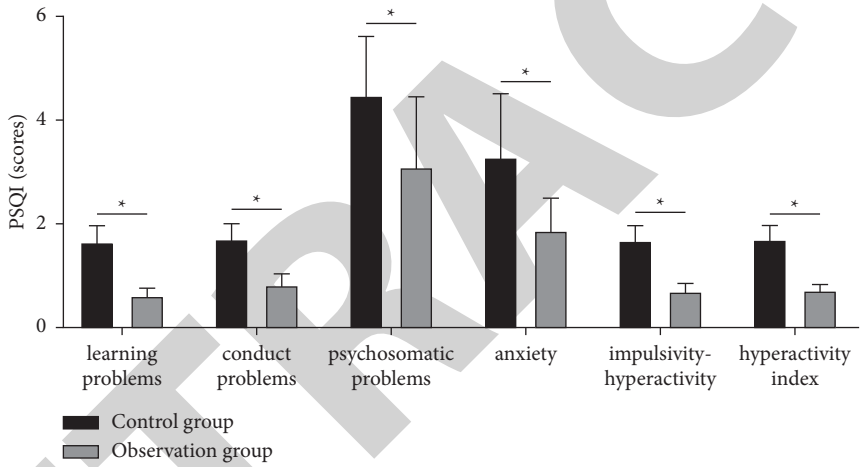

Figure 4: Comparison of PSQ scores between the two groups. *Note*. The symbol * indicates a statistically significant difference between the two groups.

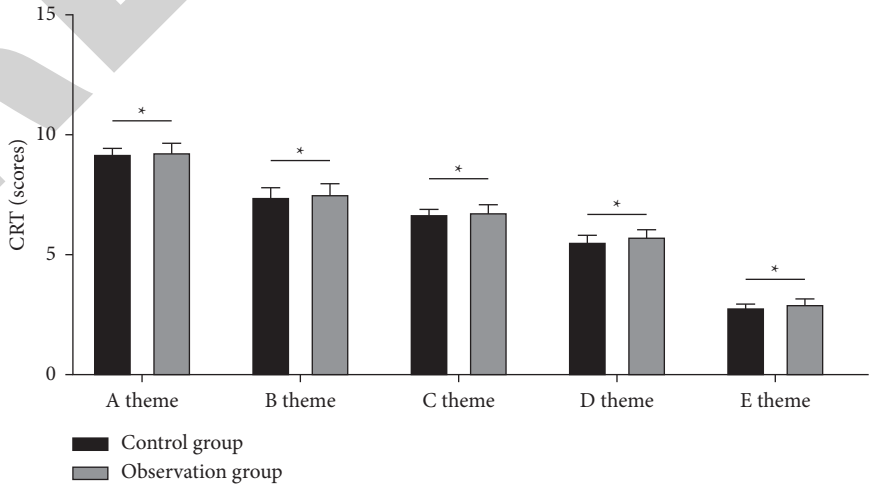

Figure 5: Comparison of CRT scores between the two groups. *Note*. The symbol * indicates a statistically significant difference between the two groups.

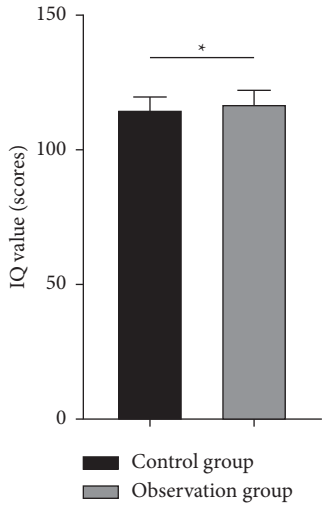

Figure 6: Comparison of IQ values between the two groups. *Note*. The symbol *indicates a statistically significant difference between the two groups.

Sandplay therapy has the following advantages: ① the games are fun and rich, in line with the psychological characteristics of the age group of the child, who rarely perceives them as therapy and participates in them as a game, ensuring that the therapy is quiet, comfortable, relaxing and enjoyable, and therefore highly acceptable and cooperative [18]. ② The therapist's company can fully induce the child to create works that vividly reflect the child's inner world. Through the construction of a safe, warm, supportive, custodial, empathic, and caring space, the child removes the psychological barrier and fully shows his or her inner self, and the negative personality and character behaviour are fully eased [19]. ③ Objective information reference: in conventional therapy, the child has a psychological barrier, and it is difficult for the practitioner to read the child's inner world from just a few words while using the work as an objective information reference; through the work, the therapist can clearly observe the child's inner world. Then, according to the cognitive-behavioural theory of psychology, the therapist provides targeted guidance to help the child find strength in self-growth and promote deep personality integration, which helps the child's emotional and mental stability and behavioural and cognitive improvement after treatment [20].

5. Conclusion

The cartoon text version of the health education manual with sandplay can significantly improve the attention deficit, hyperactive behaviour, psychological status, and cognitive function of children with ADHD on the basis of pharmacological treatment, which has good clinical application.

Data Availability

The data supporting this study are available to the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Article

Application Effect of Silver-Containing Dressings in the Repair of Chronic Refractory Wounds

Rui Wang, Yuan Guo, Bao Li, Jingjing Zheng, Zhishui Tang, and Maoguo Shu

The First Affiliated Hospital of XI'AN Jiaotong University Plastic and Cosmetic Maxillofacial Surgery, Xi'an, Shanxi 710061, China

Correspondence should be addressed to Maoguo Shu; shumaoguo19760509@outlook.com

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Chronic refractory wounds have complicated pathogenesis, repeatedly prolonged course of disease, high difficulty in cure, and may even endanger life due to the spread of wound infection. Silver ion dressing is a new type of dressing applied clinically in recent years. It can prevent infection and promote wound healing by releasing a low level of active silver ions into wound fluid or secretion. Some scholars have found that silver ion dressings can promote the healing of refractory wounds. In this study, 80 cases of chronic refractory wounds treated in our department from June 2019 to January 2022 were selected as the research subjects and the effect of silver ion dressing coverage on the repair of chronic refractory wounds after debridement was explored.

1. Introduction

Clinically, wounds are usually divided into acute wounds and chronic wounds according to the time of healing. Acute wounds refer to wounds that can heal spontaneously within 2 weeks. However, due to some adverse factors such as infection, foreign body, and ischemia that affect the wound healing and partially or completely stop the wound healing, the wound that still cannot heal after more than two weeks is clinically called a chronic refractory wound [1, 2]. Chronic refractory wounds (wounds) are common in pressure ulcers, diabetic foot ulcers, venous ulcers, residual burn wounds, traumatic ulcers, vascular extravasation of strongly irritating drugs, and malignant radiation ulcers [3, 4]. These chronically infected wounds have a high probability of clinical infection, which reduces the quality of life of patients and affects the life and health of patients. Moreover, chronic refractory wounds are difficult to manage and often require multiple methods of coordinated intervention, posing great challenges for clinical health care workers [5, 6]. The challenge of how to reduce wound exudation, reduce pain during wound dressing change, and promote wound healing is an urgent problem to be solved by medical staff.

Silver-containing dressings is a new type of dressing used clinically in recent years, which is mainly composed of sodium carboxymethyl fibers and silver. It prevents infection by releasing a low level of active silver ions into wound fluid or secretions and has the effects of absorbing wound exudate and potent sterilization, improving the wound microenvironment while controlling infection, facilitating wound healing recovery, and promoting wound granulation formation [7, 8]. However, there are still few reports on its clinical application effects and mechanism in China. Based on this, the aim of this study was to investigate the effect of silver-containing dressings coverage after debridement on the repair of chronic refractory wounds from the aspects of wound infection and wound scars, in order to provide a reference for the treatment of chronic refractory wounds.

2. Materials and Methods

2.1. General Information. Eighty patients with chronic refractory wounds admitted from June 2019 to January 2022 were selected as the study subjects. The patients were randomly divided into a control group ($n = 40$) and an observation group ($n = 40$). The wound area of patients in the

two groups was between 10 cm × 15 cm and 30 cm × 50 cm. All patients had slow granulation tissue growth, were not fresh, and had an ischemic pale appearance.

2.2. Standards

2.2.1. Inclusion Criteria. The inclusion criteria were as follows: ① prolonged healing of ulcer wound for more than 2 weeks; ② no blood system disease; and ③ gave informed consent and was reviewed and approved by the Ethics Committee of the hospital.

2.2.2. Exclusion Criteria. The exclusion criteria were as follows: ① anaerobic infection or wet gangrene; ② those who had used glucocorticoids and immunosuppressive agents and chemotherapeutic drugs; ③ wound caused by tumors; ④ confirmed allergy to silver preparations or dressings; and ⑤ poor compliance due to cognitive impairment, mental illness, etc.

2.3. Study Methods. All patients were given basic medical treatment such as diet control, nutritional improvement, smoking and alcohol deprivation, and application of antibiotics according to the bacterial examination of the wound.

The patients in the control group were treated with conventional dressing change methods: the wound surface was washed and disinfected, the necrotic tissue was removed, the drug was applied after hemostasis, the dressing change was regularly cleaned, an iodoform gauze or a gauze was placed to cover the wound surface according to the patient's wound surface; then, a sterile gauze or cotton pad was used to cover it. The dressing change time was determined according to the amount of exudate and secretion of the patient. The dressing change was started every day or every other day. When the wound surface was fresh or there was little secretion, the dressing change could be performed at an interval of 2-3 d.

The patients in the observation group were treated with silver-containing dressings for dressing change: first, the inactivated tissues in the wound surface and lacunae and the tissues prone to necrosis were completely removed, all lacunae were opened, and the wound skin was cleaned. An appropriately sized silver dressing (Biatain Alginate Ag, United Kingdom) was cut, the wound was sealed with a thin silver dressing pad on the wound, and the dressing needed to be replaced due to subsidence of the dressing. The wound was protected and compression of the wound was prevented from continuing, and the dressing was changed according to the wound condition for 1 day–3 days.

2.4. Observation Index. The observation indexes were as follows:

(1) The degree of pain was compared between the two groups: the numerical rating scale (VAS) was used. The patients were counted as 0–10 points according to the degree of pain [9]. The patients scored the overall feelings of the two methods according to the dressing change period and assessed before treatment, 7 d, 14 d, and 1 month after treatment.

(2) The dressing change and wound healing of the two groups were observed: the times of dressing change, granulation growth, wound formation, and healing time during treatment were statistically analyzed. Wound healing criteria: the wound area is less than 5% of the initial total area [10]. A transparent square paper of 0.25 cm × 0.25 cm was applied for measuring the wound area. Percentage of wound healing % = healing area/original wound area × 100%.

(3) Wound scars in the two groups were observed: before treatment and after 1 month of treatment, the Vancouver Scar Scale (VSS) [11] was used to assess the thickness of the scar (0 indicates the same height as the surrounding normal skin, 1 indicates ≤2 mm higher than normal skin, 2 indicates 2 to 5 mm higher than normal skin, and 3 indicates >5 mm higher than normal skin), color (0 indicates that the scar color is similar to the skin of normal parts of the adjacent body, 1 indicates a slight pink color, 2 indicates a mixed color, and 3 indicates a darker color), softness (0 indicates normal, 1 indicates soft, 2 indicates flexible and bendable, 3 indicates hard, that is, inelastic and lumpy during hand pressure, 4 indicates that the tissue is cord-like, and 5 indicates contracture deformity), and vascularity (0 indicates that the scar color is similar to the normal parts of the body, 1 indicates that the pink local area is slightly higher, 2 indicates that the red local area is increased, and 3 indicates that the purple or dark red area is abundant) in four aspects, and the score indicates that the scar hyperplasia is more severe.

(4) The wound infection of the two groups was observed: the wound was cultured for bacteria, and the results of bacterial culture were analyzed. The positive rate of bacterial culture before and after treatment was compared.

2.5. Statistical Methods. SPSS 22.0 software was applied for processing, and the measurement data of experimental data were analyzed using the mean ± standard deviation ($\overline{x} \pm s$), and enumeration data are expressed as (%) (metrological data). Pairwise comparisons were analyzed by t-test. Enumeration data were analyzed by the χ^2 test. The test level is $\alpha = 0.05$; $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of General Data between the Two Groups. There were no significant differences in gender, age, and wound area between the two groups ($P > 0.05$, Table 1).

3.2. Comparison of Pain Intensity between the Two Groups. There was no significant difference in the VAS score between the two groups before treatment ($P > 0.05$). The VAS score of

Table 1: Comparison of general data between the two groups.

Group	N	*Sex* Male/Female	Age (years)	*Trauma site* Thoracoabdominal	Extremities	Other
Control group	40	26/14	38.43 ±5.24	12	24	4
Observation group	40	27/13	39.05 ± 5.05	14	23	3
t/χ^2 value		0.056	0.539		0.318	
P value		0.813	0.592		0.853	

Group	N	Wound area (cm^2)	*Etiology* Diabetic ulcer	Epilepsy	Radiation ulcer	Hot/Burn
Control group	40	29.45 ± 5.26	10	8	7	15
Observation group	40	30.92 ± 5.74	11	7	6	16
t/χ^2 value		1.194		0.223		
P value		0.236		0.974		

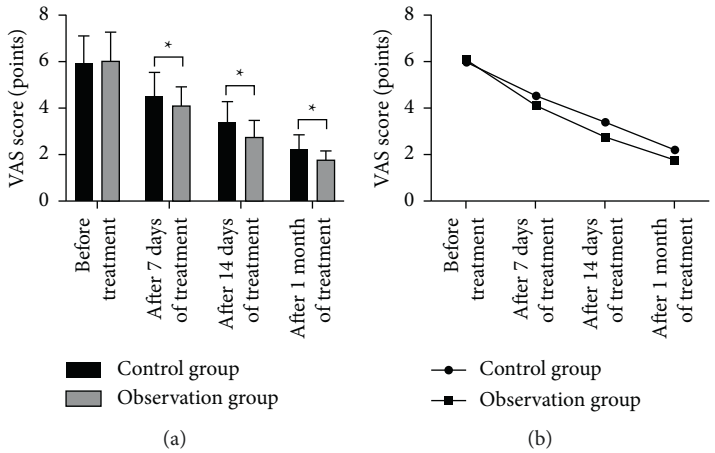

Figure 1: Comparison of pain intensity between the two groups. (a) Comparison of VAS scores between the two groups; (b) change trend of VAS score in two groups. $^*P < 0.05$, compared with before treatment.

the observation group decreased significantly after 7 days, 14 days, and 1 month of treatment, and the score was lower than that of the control group (Figure 1(a), 1(b)), and the differences were statistically significant ($P < 0.05$).

3.3. Comparison of Dressing Change and Wound Recovery between the Two Groups. The times of dressing change in the observation group were significantly less than that in the control group (Figure 2(a)). The granulation tissue growth time (Figure 2(b)), wound epithelialization time (Figure 2(c)), and wound healing time (Figure 2(d)) in the observation group were significantly higher than that in the control group, and the differences had a statistical significance ($P < 0.05$).

3.4. Comparison of Wound Scar between the Two Groups. There was no significant difference in wound scar before treatment between the two groups ($P > 0.05$). After treatment, the scores of wound scar thickness (Figure 3(a)), color (Figure 3(b)), softness (Figure 3(c)), and vascularity (Figure 3(d)) in the observation group were significantly reduced and the scores were significantly lower than those in the control group, and the differences had a statistical significance ($P < 0.05$).

3.5. Comparison of Wound Infection between the Two Groups. There was no significant difference in wound infection between the two groups before treatment ($P > 0.05$). After treatment, the positive rate of wound bacterial culture in the observation group was significantly lower than that in the control group (Figure 4), and the difference had a statistical significance ($P < 0.05$).

3.6. Analysis of a Typical Patient. The patient in the observation group, male, 28 year-old, was injured due to poor wound healing with an infection after right renal transplant resection (Figure 5(a)). After debridement, silver dressing was given to cover the day of treatment (Figure 5(b)). The granulation tissue grew well after 7 days of treatment, and there was no infection in the incision (Figure 5(c)). The dressing was continued for 46 days to heal (Figure 5(d)).

4. Discussion

Chronic refractory wounds have become one of the difficulties in the global health care field. With the in-depth understanding of the mechanism of chronic refractory wounds and the process of wound healing, a variety of theoretical systems have been proposed for chronic refractory

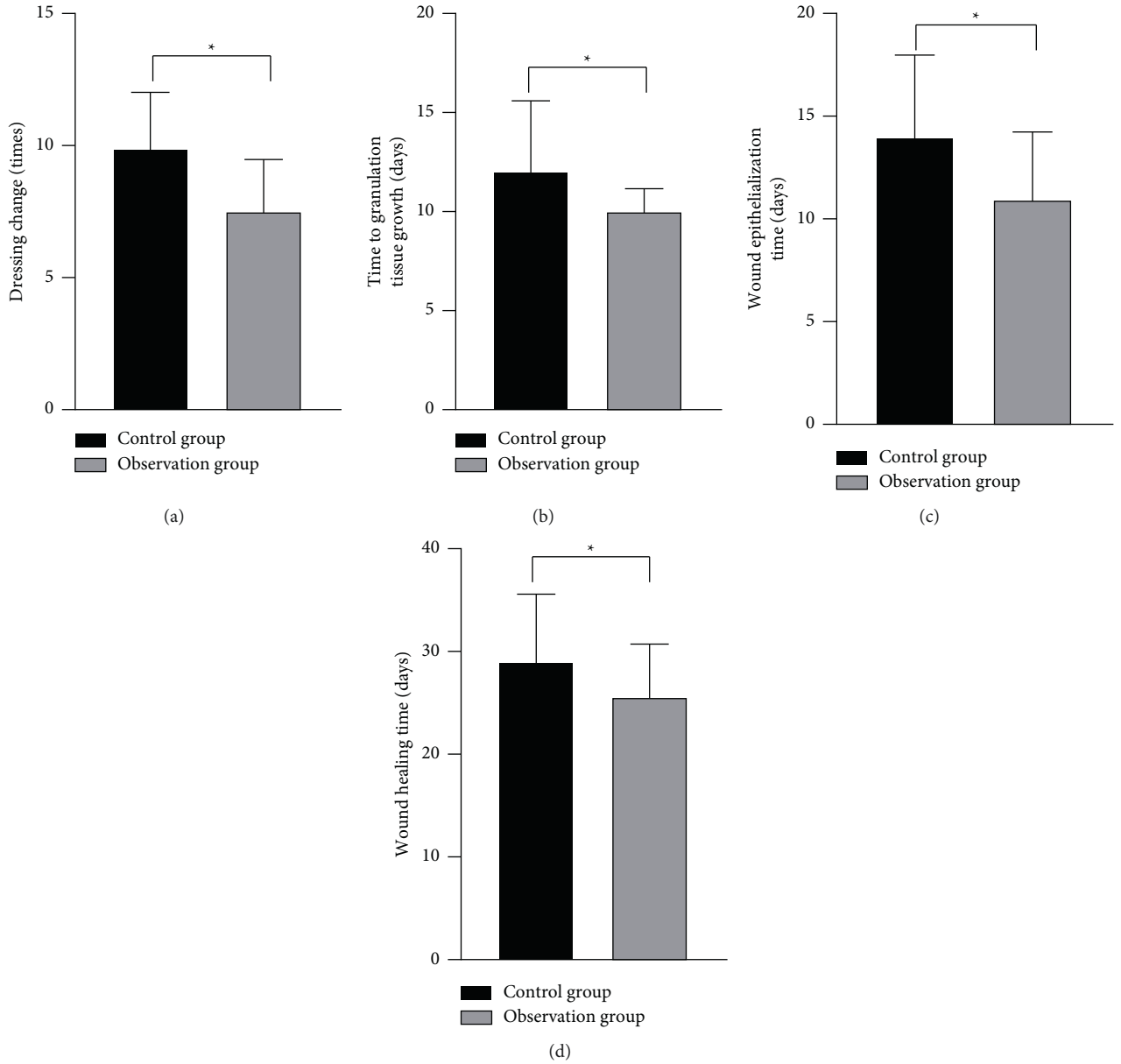

Figure 2: Comparison of dressing change and wound recovery between the two groups. (a) Dressing change; (b) the granulation tissue growth time; (c) wound epithelialization time; and (d) wound healing time. $^*P < 0.05$, compared with before treatment.

wounds in clinic. The WBP theory focuses on the following four aspects of the wound that affect healing, namely, TIME: T (tissue nonviable) necrotic tissue, I (infection or inflammation) infection or inflammation, M (moisture imbalance) wet balance, and E (edge of wound) wound margin [12]. The TIME system was originally proposed by Schultz et al. [13], who focused on removing the bacterial, necrotic and cellular load affecting the wound surface, trying to maintain the wet balance of the wound surface, using various biological factors to actively create a relatively appropriate wound microenvironment, and accelerating wound healing or creating conditions for surgery. Supported by these scientific theories, the effect of silver ion dressing covering caused a hot debate.

Silver-containing dressings are composed of a 100% continuous nondeformable polyester fiber mesh hydrocolloid (sodium carboxymethylcellulose) and an antibacterial agent (silver ion complex). The mesh that is not easy to be deformed avoids the wound, can tolerate multiple mechanical stress effects, can be completely removed during dressing change, does not worry about dressing residues, and this dressing does not adhere to the wound and can significantly reduce pain [14, 15]. The dressing has a mesh which is not easy to deform, does not adhere to the wound, and can obviously relieve pain; and it can withstand mechanical stress for many times, which can be completely taken out during dressing change without leaving dressing [16–18]. In this study, after continuous treatment, the VAS score was significantly decreased, and the score in the observation group was lower than that in the control group. It is suggested that silver-containing dressings can not only continuously release highly active antibacterial

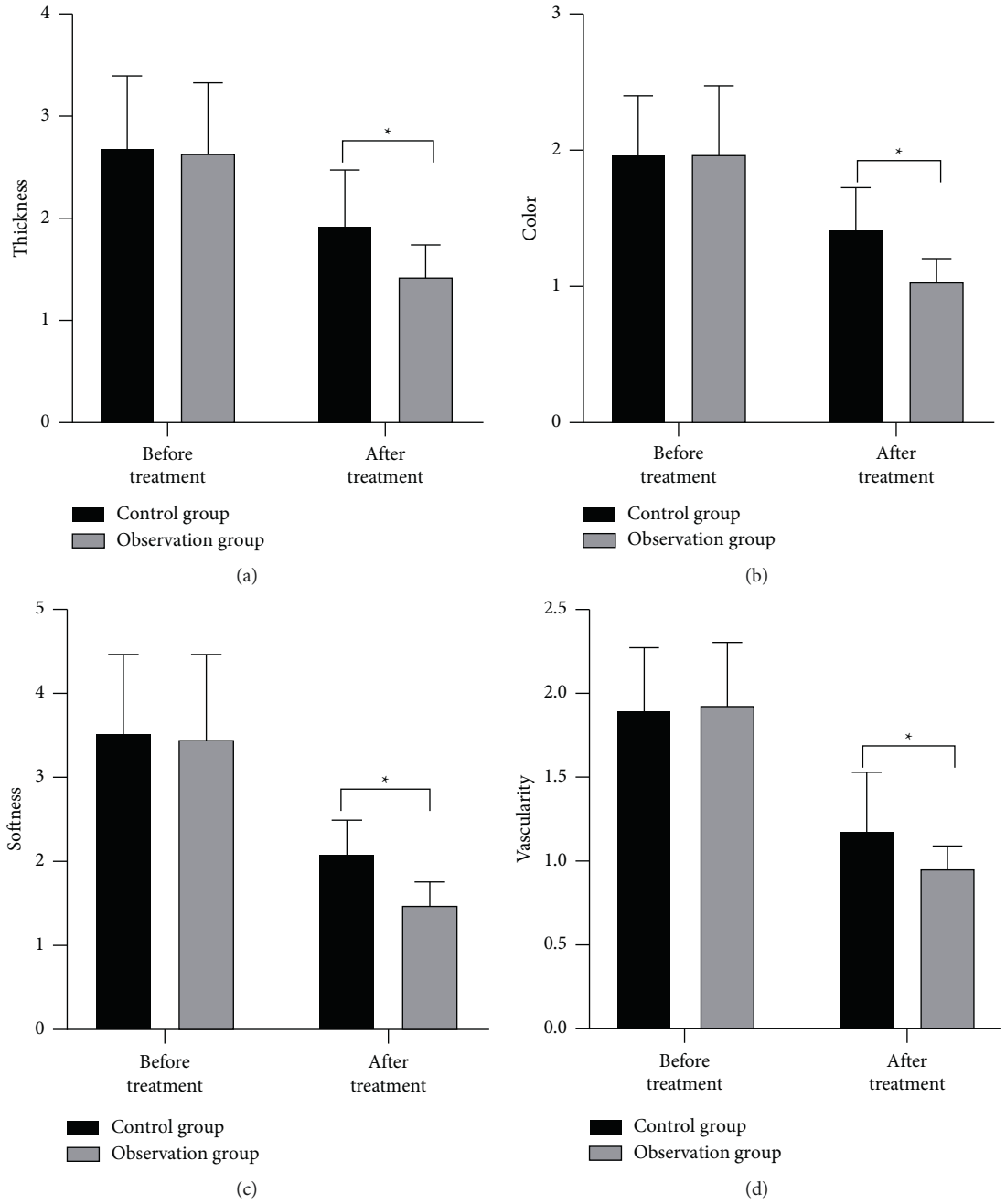

Figure 3: Comparison of wound scar between the two groups. (a) Thickness; (b) color; (c) softness; and (d) vascularity. $^*P < 0.05$, compared with before treatment.

silver ion but also has multiple effects such as absorbing exudate, promoting healing, no adhesion to wound surface, and preventing repeated injury caused by the next dressing change, indirectly reducing the pain level of dressing change for patients.

In this study, the times of dressing change in the observation group were significantly less than that in the control group, and the wound recovery of the patients in the observation group was significantly better than that in the control group. These results indicated that silver-containing dressings provided a moist healing environment for the wound surface and could promote granulation hyperplasia and epithelial tissue crawling. At the same time, our study found that the wound scar healing in the observation group was better than that in the control group. These results suggest that silver-containing dressings are beneficial to wound repair and accelerate the process of wound healing compared with common dressing. The reason is that silver-containing dressings are a clinical wound treatment material developed under the background of moist healing theory and wound negative pressure therapy theory, which can accelerate the healing of refractory wound and control the chronic infection of wound [19]. Once in contact with wound exudate, the hydrocolloid particle (CMC sodium carboxymethylcellulose)

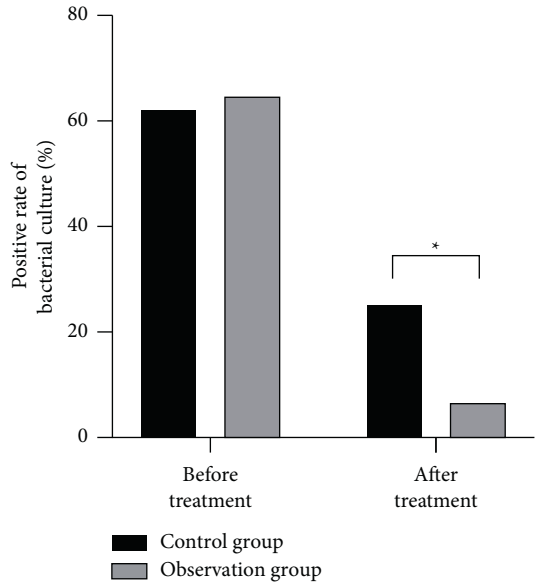

Figure 4: Comparison of wound infection between the two groups. $^{*}P < 0.05$, compared with before treatment.

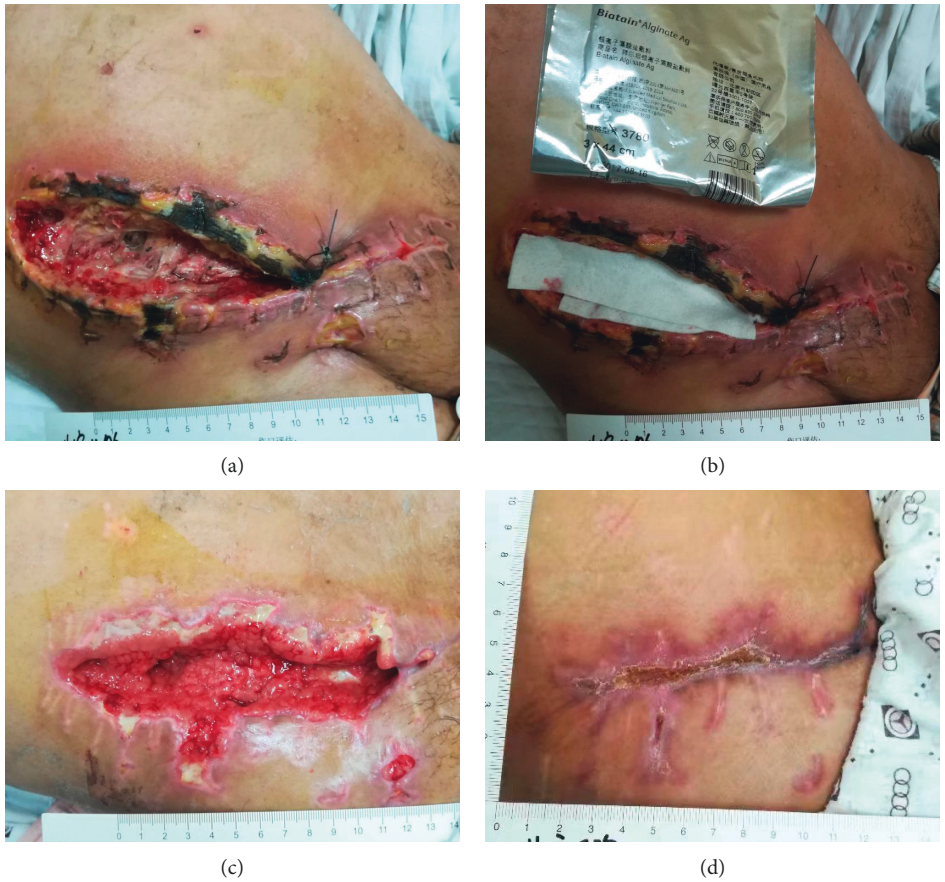

Figure 5: Process of silver-containing dressings in the treatment of chronic refractory wound. (a) Before treatment; (b) on the day of treatment; (c) after 7 days of treatment; and (d) 46days to heal.

in the dressing swells after absorbing the exudate, forms a soft, cohesive hydrogel that allows it to absorb the wound exudate while locking it in place within the gel, avoiding the risk of exudate leakage as well as macerating the wound skin. Intrasite gel also creates a moist environment conducive to wound healing [20–22].

The results of this study showed that after treatment, the positive rate of wound bacterial culture in the observation group was significantly lower than that in the control group. Silver-containing dressings effectively eliminated susceptible bacteria, avoided the occurrence of clinical complications, and further ensured the cure rate of the disease. The reason why, silver sulfadiazine in silver dressings has a broad antibacterial spectrum and is active against both positive and negative bacteria, including molds and yeasts, especially *Staphylococcus aureus* and *Pseudomonas aeruginosa* (*Pseudomonas aeruginosa*) [23–25]. At the same time, the effective action time of the dressing is long, and after the silver ion-containing dressing loses its activity in the bacteria, the silver ion is freed from the bacteria and the bactericidal activity is repeated, with a longer antibacterial effect [26, 27]. Viruses and pathogenic bacteria will not produce drug resistance and drug resistance to them, so germs are not easy to produce variant varieties.

In summary, silver-containing dressings have a significant effect on the repair of chronic refractory wounds, which is conducive to reduce pain and scar hyperplasia, effectively promote the generation of granulation tissue and epithelial tissue and wound healing process, inhibit the growth of bacteria on the wound, and provide a reference for clinical treatment of chronic refractory wounds. The shortcoming of this study lies in the small included sample size and selective bias of the results. In the future, the sample size should be expanded to be confirmed by a more in-depth study.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author on request.

Conflicts of Interest

The authors declare that they have no conflicts of interest, financially or otherwise.

Acknowledgments

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Volume 2023, Article ID 9780976, 1 page
https://doi.org/10.1155/2023/9780976

Retraction

Retracted: Inhibition of miR-29b-1-5p Attenuates Inflammatory Response and Pulmonary Fibrosis in LPS-Induced Acute Lung Injury by Regulating RTN4 Expression

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] J. Wang, M. Chen, W. Xu et al., "Inhibition of miR-29b-1-5p Attenuates Inflammatory Response and Pulmonary Fibrosis in LPS-Induced Acute Lung Injury by Regulating RTN4 Expression," *Evidence- Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7523591, 11 pages, 2022.

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Research Article

Inhibition of miR-29b-1-5p Attenuates Inflammatory Response and Pulmonary Fibrosis in LPS-Induced Acute Lung Injury by Regulating RTN4 Expression

Jieqiong Wang, Ming Chen, Weihua Xu, Lu Shou, Xiaosheng Jin, Xianrong Xu, and Feihua Huang

Respiratory Department, TongDe Hospital of Zhejiang Province, No. 234, Gucui Road, Xihu, Hangzhou, Zhejiang 310000, China

Correspondence should be addressed to Feihua Huang; huanghfh310238@163.com

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Objective. Acute lung injury (ALI) is a severe respiratory disorder causing alveolar-capillary barrier, leading to a high rate of morbidity and death in critically ill individuals. microRNAs (miRNAs)-mediated mechanism in the pathogenesis of ALI has attracted much interest. Herein, we attempt to characterize a candidate miRNA and its downstream target that is linked to the pathogenesis of ALI. *Methods*. LPS-conditioned MH-S cells were treated with miR-29a-1-5p mimic, inhibitor, and RNT4 expression vector, and the ALI animal model was injected with agomir and antagomir of miR-29b-1-5p and RNT4 expression vector, in which the pro-inflammatory cytokine production, cell viability and apoptosis, myeloperoxidase (MPO) activity, wet/dry (W/D) ratio, and expression of TGF-β1, α-smooth muscle actin (α-SMA), E-cadherin, and vimentin were examined. miR-29a-1-5p inhibition of RTN4 translation was confirmed by luciferase activity assays. *Results*. An elevated miR-29a-1-5p expression was demonstrated in LPS-conditioned MH-S cells. miR-29a-1-5p inhibitor transfection attenuated the production of pro-inflammatory cytokines and MH-S cell viability but enhanced the apoptosis. miR-29a-1-5p inhibition of RTN4 translation was demonstrated in the setting of LPS-induced ALI. LPS-induced murine models demonstrated upregulated miR-29a-1-5p. Intravenous injection of miR-29b-1-5p agomir attenuated mouse lung injury and pulmonary fibrosis. RTN4 overexpression resisting to miR-29a-1-5p overexpression was demonstrated in LPS-induced murine models. *Conclusion*. The findings obtained from the study that disturbing the action of miR-29a-1-5p may be a novel therapeutic strategy for preventing ALI.

1. Introduction

As a lethal complication resulting from distant organ dysfunction or acute injury such as shock and sepsis, acute lung injury (ALI) is described as the major cause of Intensive Care Unit (ICU) death across the world [1]. Moreover, it has been reported that inflammatory response is the major pathological change of ALI, leading to accumulated inflammatory cells, interstitial edema, and disrupted epithelial integrity [2]. Lipopolysaccharide (LPS) is known as a leading element of the outer membrane in Gram-negative bacteria, which serves as a key factor for the occurrence of ALI [3, 4]. Owing to limited treatment options and complex pathogenesis, ALI is considered a significant contributor to global morbidity and mortality concerning acute respiratory failure [5, 6]. Although there are great advancements in developing candidate therapy strategies for ALI, its mortality rate remains from 22% to 40% [7]. Therefore, it is important to further investigate new prevention strategies and therapeutic methods against ALI.

microRNAs (miRNAs) represent a group of small noncoding RNA and have the ability to modulate gene expression via targeting mRNA for early degradation or inhibition of its translation. In light of miRNA control of inflammatory-immune responses and cell-cell interactions from previous evidence [8], miRNAs are reported to be involved in the pathological processes of various lung diseases, including ALI [9]. Dysregulation of miR-29 family

occurs in several human cancers, such as breast cancer [10], osteosarcoma [11], and bladder urothelial cancer [12]. Recently, upregulated miR-29b-1-5p was observed in hearts following I/R injury and in cardiomyocytes following hydrogen peroxide treatment [13]. The bioinformatics prediction shows RTN4 (encoding Nogo protein) is a putative target gene of miR-29b-1-5p. RTN4, also known as neurite outgrowth inhibitor, consists of three different splice variants (termed RTN4-A, RTN4-B, and RTN4-C) through different splicing [14]. RTN4-A could inhibit the migration and invasion ability of human malignant glioma cells [15]. A murine study has reported that the RTN4-B overexpression ameliorates lung injury, alveolar protein exudation, and neutrophil infiltration in LPS-induced ALI mice, suggesting protective effects of RTN4-B against ALI [16]. In this study, we propose a prevailing hypothesis that high miR-29b-1-5p expression contributes to the development of ALI by negatively regulating the RTN4. To prove this hypothesis, we examined the viability and apoptosis of LPS-induced murine alveolar macrophages MH-S, as well as the release of proinflammatory cytokines, lung injury, and pulmonary fibrosis LPS-induced murine models.

2. Materials and Methods

2.1. In Vitro ALI Models. The murine alveolar macrophages (MH-S) were purchased from Beijing Union Cell Institute (Beijing, China) and then maintained in the medium containing sodium bicarbonate (1.59/L), fetal bovine serum (FBS, 15%), and glutamine (2 mL). To condition the ALI cell model, MH-S cells were harvested in 100 μg/mL LPS for 18 h. Subsequently, LPS-conditioned MH-S cells were treated with miR-29a-1-5p mimic, inhibitor, and RNT4 expression vector (GenePharma, Shanghai, China) using Lipofectamine 3000 reagents (Invitrogen, USA) as guided by the standard protocol provided by the manufacturer.

2.2. In Vivo ALI Models. A total of 74 C57BL/6J male mice, aged 7 weeks, were used to establish ALI murine models by intratracheal drip of 7.5 mg/kg LPS into the lungs of mice as described previously [7]. A longitudinal incision with about 0.5 cm in length was made in the neck for trachea exposure, and a mixture of LPS solution and 300 μl of sterile saline solution was injected into exposed trachea. Finally, we obtained 65 ALI murine models. At 6 h after modeling, 54 mice were injected with agomir and antagomir of miR-29b-1-5p, and RNT4 expression vector (GenePharma, Shanghai, China) *via* caudal vein. Among the remaining 11 LPS-induced ALI mice, 9 were served as control and 2 were spared. After 48 hours, experimental mice underwent tracheal intubation and bronchoalveolar lavage using 1.2 mL phosphate-buffered saline (PBS) three times to collect bronchoalveolar lavage fluid (BALF). At last, mice were euthanized by cervical dislocation. Animal experiments were carried out with the approval of the Institutional Animal Care and Use Committee of TongDe Hospital of Zhejiang Province.

2.3. Luciferase Assays. The wild-type RTN4 mRNA 3′UTR containing the binding sites of miR-29b-1-5p and the mutated one were cloned into the pGL3-reporter vectors (Sangon, Shanghai, China), respectively. Well-designed reporter vectors pGL3-RTN4-Wt and pGL3-RTN4-Mut with miR-29b-1-5p mimic were delivered into HEK293T cells (Beinuo, Shanghai, China). The dual-luciferase reporter assay system kit (K801-200, BioVision, USA) was utilized to determine the luminescence of firefly luciferase.

2.4. Enzyme-Linked Immunosorbent Assay (ELISA). The ELISA kit was used to measure levels of IL-1β, IL-8, TNF-α, and IL-6 in the supernatant of mouse alveolar macrophages MH-S and of LPS-treated mouse alveolar lavage fluid.

2.5. Myeloperoxidase Activity Assays. Myeloperoxidase (MPO) is the functional and activating marker of neutrophils, and its level and activity change represent the function and active state of neutrophil polymorphonuclear leukocytes (PMN). The lung tissues were collected to measure MPO activity according to the manufacturer's instructions of the MPO Activity Assay Kit (K747-100, BioVision (Milpitas, CA, USA).

2.6. Cell Viability Assays. MH-S cells were harvested, and their viability at 0, 24, 48, and 72 h was evaluated by another incubation with 10 μl CCK-8 solution for 2 h. The optical value, also absorbance, was read at 450 nm, with growth curves plotted.

2.7. Annexin V-FITC/PI-Labeled Flow Cytometry. Annexin V-FITC/PI double staining was performed to examine cell apoptosis. The MH-S cell suspension (100 μl, 4×10^5 cells) was incubated with 10 μL Annexin V-FITC and 5 μL PI without light exposure at room temperature for 15 min. The flow cytometer (6HT, Wuhan Cellwar Biotechnology Co., Ltd., Wuhan, China) was employed to measure the apoptosis.

2.8. Wet Weight/Dry Weight (W/D) Ratio. The left lung of mice without bronchoalveolar lavage was taken out following thoracotomy. After sucking the blood on the lung surface by filter paper, the lung was weighed to show the wet weight. With regard to measurement of the dry weight, the lung was maintained in an oven at 80°C for 48 h. The degree of pulmonary edema was evaluated by the dry/wet ratio (W/D).

2.9. RNA Isolation and Quantitative Real-Time PCR (qRT-PCR). Total RNA was extracted using RNeasy Mini Kit (Qiagen, Valencia, CA, USA). For quantitation of miR-29b-1-5, total RNA was reverse-transcribed into cDNA using the miRNA first-strand cDNA synthesis (Tailing reaction) kit (B532451-0020, Shanghai Sangon Biotechnology Co. Ltd., China). For the quantitation of mRNA, total RNA was reverse-transcribed into cDNA using the kit (Takara, Japan). The qRT-PCR was conducted using the SYBR® Premix Ex

TaqTM II kit (Takara) on the ABI7500 instrument (ABI, USA). The other primer sequences (Table 1) were synthetized by Shanghai Sangon Biotechnology Co., Ltd. The Ct value was recorded, and the relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method, with GAPDH or U6 used to normalization.

2.10. Western Blot Analysis. The total protein was extracted and then loaded into the wells added with 10% SDS-PAGE. After membrane wet transfer, immunoreaction was performed using anti-RTN4A/B antibody (ab47085), anti-Akt antibody (ab81283), anti-p-Akt antibody (ab38449), anti-ERK1/2 antibody (ab17942), anti-p-ERK1/2 antibody (ab223500), anti-TGF-β1 antibody (ab92486), anti-α-SMA antibody (ab5694), anti-E-cadherin antibody (ab1416), antivimentin antibody (ab92547), and anti-β-actin antibody (ab8226). All antibodies were purchased from Abcam Inc. (Cambridge, UK). Immunoreactive blots were visualized and quantified using a gel documentation system (Bio-Rad Quantity One Software v4.6.2, USA).

2.11. Statistical Analysis. Statistical comparisons including unpaired *t*-test, one-way analysis of variance, and repeated measurement analysis of variance and figure creation were carried out by GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA), with $P < 0.05$ showing statistical significance. All data were summarized by mean ± standard deviation.

3. Results

3.1. Inhibition of miR-29b-1-5p Ameliorated LPS-Induced MH-S Injury in vitro. An enhanced miR-29b-1-5p expression was observed in MH-S cells after LPS induction (Figure 1(a)). We next manipulated miR-29b-1-5p in LPS-conditioned MH-S cells with miR-29b-1-5p inhibitor (Figure 1(b)) to confirm the functional role of miR-29b-1-5p in the development of ALI. ELISA was performed to measure the production of pro-inflammatory cytokines (IL-1β, IL-8, TNF-α, and IL-6) in the supernatant derived from LPS-conditioned MH-S cells (Figure 1(c)), and the results showed that the levels of pro-inflammatory cytokines were increased in the supernatant derived from LPS-conditioned MH-S cells. Inhibited miR-29b-1-5p by its specific inhibitor reduced the release of pro-inflammatory cytokines in the supernatant derived from LPS-conditioned MH-S cells. As shown by data obtained from cell viability and apoptosis assays, inhibited miR-29b-1-5p by its specific inhibitor protected MH-S cells against LPS-induced injury as evidenced by enhanced viability and inhibited apoptosis (Figures 1(d) and 1(e)). Overall, we concluded that the inhibition of miR-29b-1-5p protected MH-S cells against LPS-induced injury and inflammatory response in vitro.

3.2. miR-29b-1-5p Regulated LPS-Induced MH-S Injury In Vitro through the Akt/ERK Signaling Pathway via RTN4. We next decipher the underlying mechanism by which miR-29b-1-5p modulates the development of ALI. We performed

Table 1: Primer sequences for qRT-PCR.

Target	Primer
miR-29b-1-5p	5′-GCTGGTTTCATATGGTGGTTTA-3′
RTN4	Forward: 5′-CTCCTCTGGTCTCGTCCTC-3′ Reverse: 5′-GTCCTCGTCCTCCTCTTCC-3′
TGF-β1	Forward: 5′-AAACGGAAGCGCATCGAA-3′ Reverse: 5′-GGGACTGGCGAGCCTTAGTT-3′
α-SMA	Forward: 5′-CAGGGAGTAATGGTTGGAATG-3′ Reverse: 5′-ATCGGATACTTCAGCGTCAG-3′
E-Cadherin	Forward: 5′-CCCACCACGTACAAGGGTC-3′ Reverse: 5′-CTGGGGTATTGGG GGCATC-3′
Vimentin	Forward: 5′-GACAATGCGTCTCTGGCACGTCTT-3′ Reverse: 5′-TCCTCCGCCTCCTGCAGGTTCTT-3′
GAPDH	Forward: 5′-TTAGCACCCCTGGCCAAGG-3′ Reverse: 5′-CTTACTCCTTGGAGGCCATG-3′

a miRNA-mRNA prediction across the miRWalk and RNA22 databases (Figure 2(a)). We speculate that RTN4 may be implicated in the regulation mechanism of miR-29b-1-5p in ALI. Initially, dual-luciferase reporter gene assay revealed that the luciferase activity of RTN4-Wt was declined after adding exogenous miR-29b-1-5p, while we found an enhanced luciferase activity of RTN4-Wt after miR-29b-1-5p inhibitor transfection (Figure 2(b)). The inhibition of RTN4-B could suppress the activation of Akt in proliferative diabetic retinopathy [17], while the activation of the Akt signaling pathway attenuates LPS-induced inflammatory in lungs [18]. Thus, we attempt to examine the expression pattern of RTN4 and the regulation of miR-29b-1-5p on the RTN4 and the Akt/ERK signaling pathway in the context of ALI. The findings (Figure 2(c)) displayed that the mRNA level of RTN4 and the protein expression of RTN4A/B, the p-Akt and p-ERK1/2 extent, was declined in LPS-conditioned MH-S cells following LPS induction. We observed that partial loss of miR-29b-1-5p function by its specific inhibitor enhanced the mRNA level of RTN4 mRNA and the protein expression of RTN4A/B, the p-Akt and p-ERK1/2 extent, in LPS-conditioned MH-S cells. The result was also confirmed by the gain-of-function study using miR-29b-1-5p mimic. Accordingly, we delivered RTN4 expression vector into MH-S cells to achieve RTN4-overexpressed MH-S cells. Expression vector containing the RTN4 gene mimicked the effect of miR-29b-1-5p inhibitor on the Akt/ERK signaling pathway and enhanced the mRNA level of RTN4 mRNA and the protein expression of RTN4A/B, the p-Akt and p-ERK1/2 extent, in LPS-conditioned MH-S cells. Besides, we determined lower expression of RTN4 in LPS-conditioned MH-S cells treated with miR-29b-1-5p mimic and RTN4 expression vector in combination than in LPS-conditioned MH-S cells treated with RTN4 expression vector alone, suggesting miR-29b-1-5p negatively regulated the RTN4. To demonstrate that RTN4 is indeed responsible for the regulation of miR-29b-1-5p on LPS-induced MH-S injury, we performed the ELISA method (Figure 2(d)), CCK-8 assay (Figure 2(e)), and Annexin V-FITC/PI-labeled flow cytometric analysis (Figure 2(f)) in LPS-conditioned MH-S

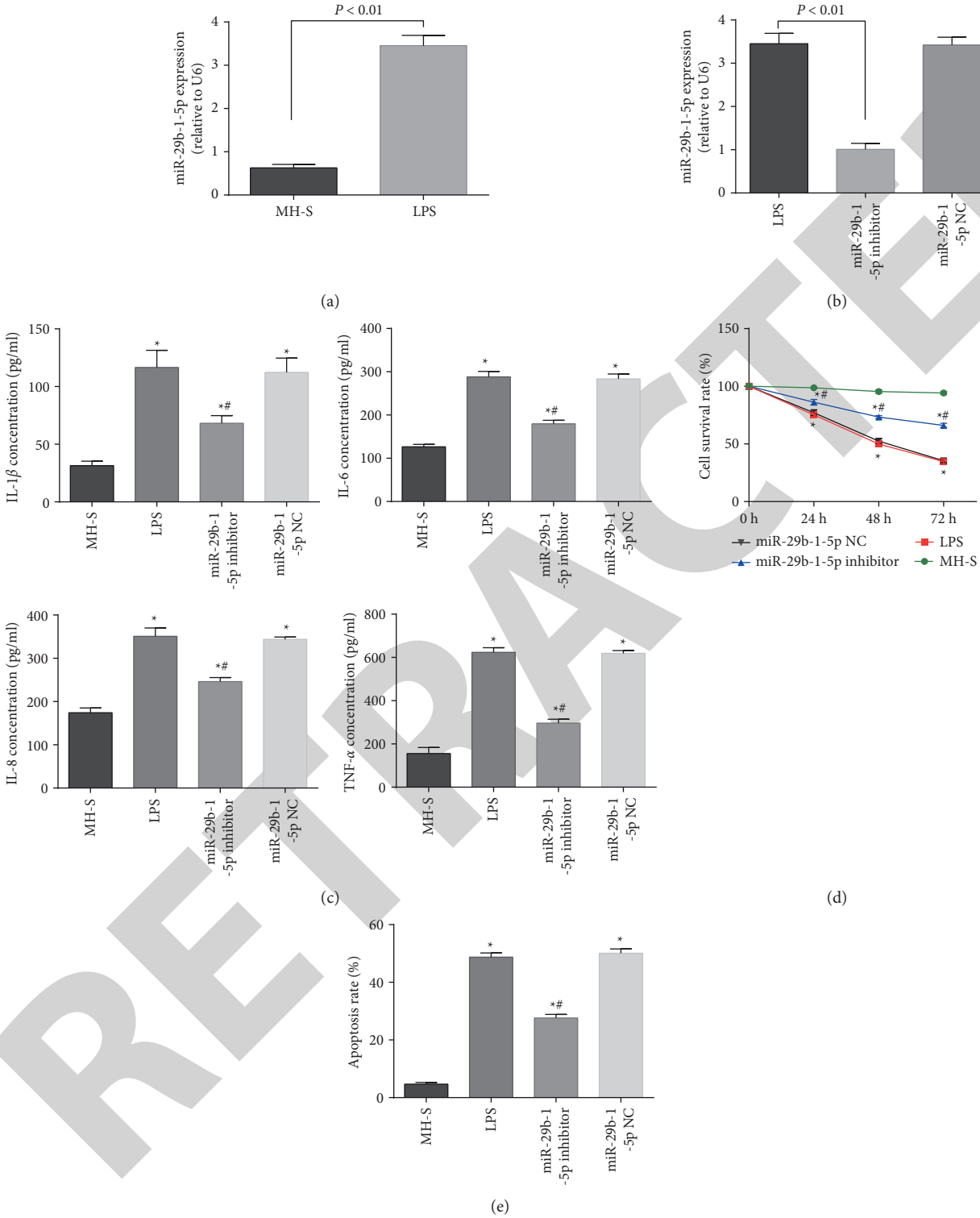

Figure 1: Inhibition of miR-29b-1-5p protected MH-S cells against LPS-induced injury and inflammatory response *in vitro*. (a) The expression of miR-29b-1-5p in untreated MH-S cells and LPS-conditioned MH-S cells was determined using qRT-PCR. (b) The inhibition of miR-29b-1-5p in LPS-conditioned MH-S cells following the transfection of miR-29b-1-5p inhibitor was confirmed using qRT-PCR. (c) The levels of IL-1β, IL-8, TNF-α, and IL-6 in the supernatant derived from LPS-conditioned MH-S cells were measured using the ELISA method. (d) The viability of LPS-conditioned MH-S cells following the transfection of miR-29b-1-5p inhibitor was evaluated using the CCK-8 assay. (e) The apoptosis rate of LPS-conditioned MH-S cells following the transfection of miR-29b-1-5p inhibitor. *, $p < 0.05$ vs. MH-S cells and $^{\#}p < 0.05$ vs. LPS-conditioned MH-S cells.

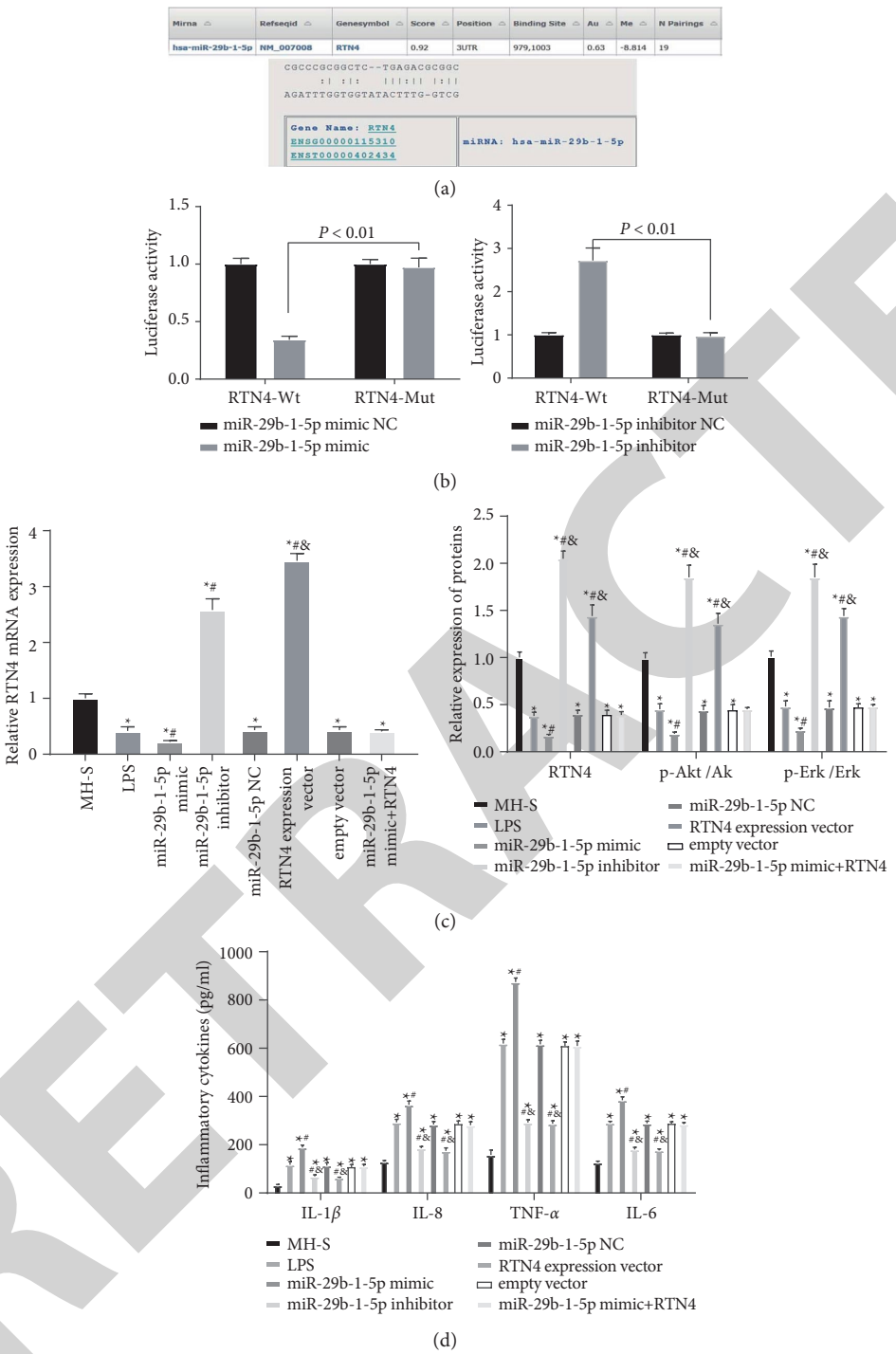

Figure 2: Continued.

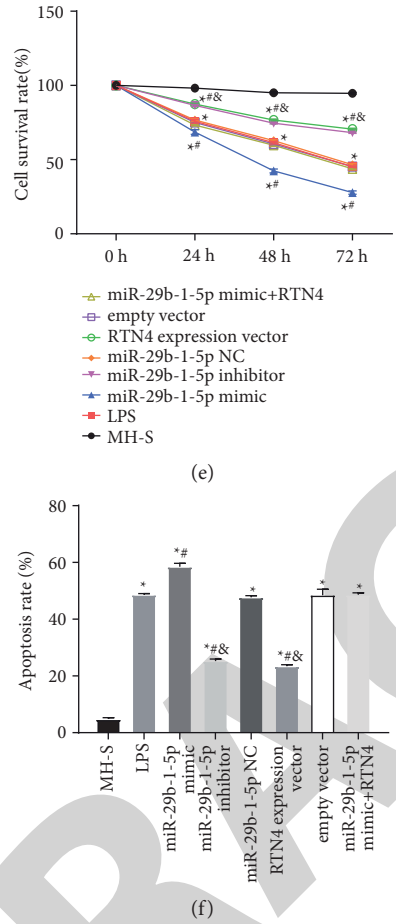

Figure 2: miR-29b-1-5p negatively regulates the RTN4 and Akt/ERK signaling pathway, thus promoting LPS-induced injury and inflammatory response *in vitro*. (a) Analysis of the miRWalk and RNA22 databases. (b) Luciferase activity assays of the RTN4-Wt and RTN4-Mut in the presence of miR-29b-1-5p mimic or inhibitor. (c), The mRNA level of RTN4 was determined by using qRT-PCR and the protein expression of RTN4A/B, the p-Akt and p-ERK1/2 extent by using Western blot analysis. (d) The levels of IL-1β, IL-8, TNF-α, and IL-6 in the supernatant derived from LPS-conditioned MH-S cells were measured using the ELISA method. (e) The viability of LPS-conditioned MH-S cells was evaluated using CCK-8 assay at indicated time points. (f) The apoptosis rate of LPS-conditioned MH-S cells. *, $p < 0.05$ vs. MH-S cells, $^{\#}p < 0.05$ vs. LPS-conditioned MH-S cells, and $p < 0.05$ vs. MH-S cells treated with miR-29b-1-5p mimic.

cells treated with RTN4 expression vector and/or miR-29b-1-5p mimic. Likewise, we found RTN4 expression vector exerted similar effects on the pro-inflammatory cytokine production, cell viability, and apoptosis in LPS-conditioned MH-S cells, as miR-29b-1-5p inhibitor. RTN4 overexpression attenuated the pro-inflammatory cytokine production in the supernatant derived from LPS-conditioned MH-S cells, enhanced MH-S cell viability, and inhibited the apoptosis, suggesting that RTN4 could protect MH-S cells against injury and inflammatory response caused by LPS *in vitro*. Furthermore, the RTN4 gene resisting to miR-29b-1-5p attack on MH-S cells and inflammatory response was also detected. The aforementioned results together demonstrate RTN4 plays anti-apoptotic and anti-inflammatory roles in LPS-induced ALI and is implicated in the regulation of miR-29b-1-5p in LPS-induced ALI.

3.3. Upregulated miR-29b-1-5p in ALI Animal Model. Our next effort is to confirm the contributory role of miR-29b-1-5p and inhibitory role of RTN4 in ALI *in vivo*. The lungs of normal mice presented intact alveolar structure, with the absence of lymphocyte infiltration. However, we observed evidenced pathological changes in the lungs of LPS-conditioned mice, as shown by thickening alveolar wall, collapsed alveolar, and red blood cell and inflammatory cell infiltration. After LPS induction, the W/D ratio and MPO activity were increased in mice (Figures 3(a) and 3(b)). The ELISA method determined elevated levels of pro-inflammatory cytokines (IL-1β, IL-8, TNF-α, and IL-6) elevated in the BALF of LPS-conditioned mice (Figure 3(c)). As we expected, an increased miR-29b-1-5p expression with a declined RTN4 expression was found in the mouse lung tissue after LPS treatment (Figure 3(d)).

3.4. miR-29b-1-5p-Mediated Inflammatory Response and Lung Injury in ALI Animal Model through the Akt/ERK Signaling Pathway via RTN4. In this part, the LPS-induced ALI mouse model was injected with agomir and antagomir of miR-29b-1-5p and RTN4 expression vector *via* tail vein to perturb the expression of miR-29b-1-5p and RTN4

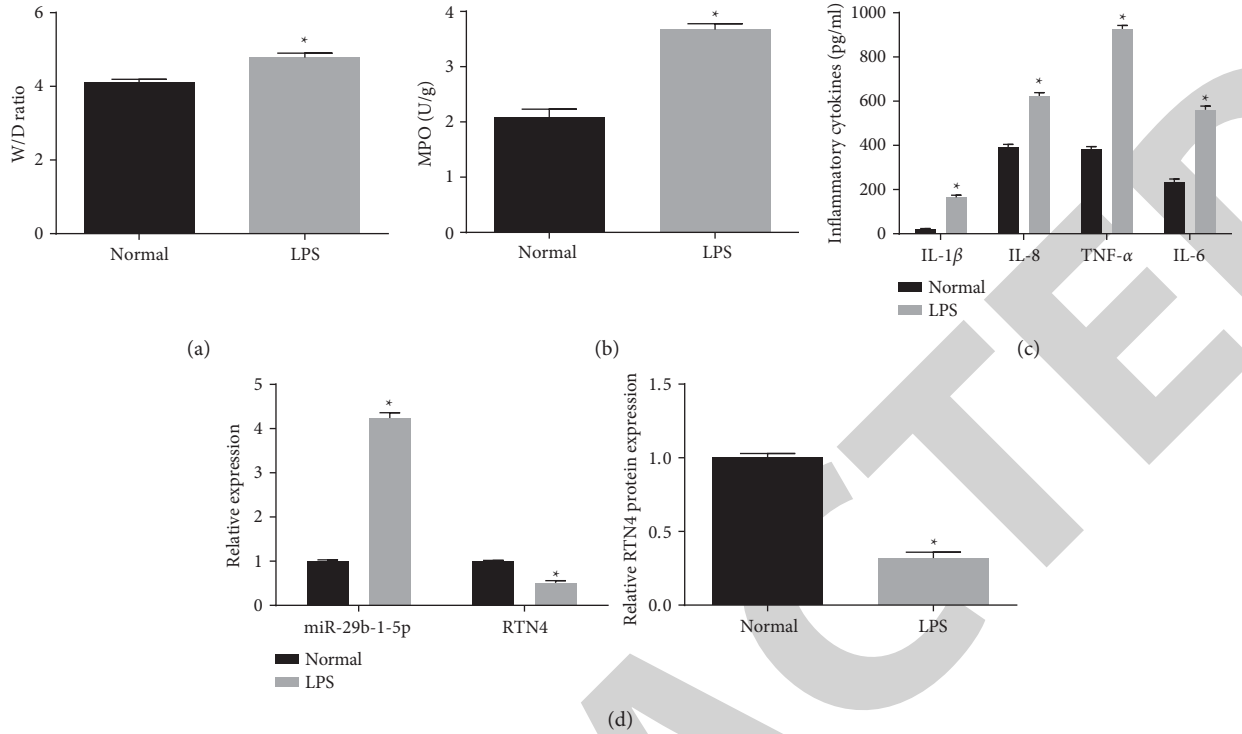

Figure 3: miR-29b-1-5p is overexpressed in LPS-induced ALI *in vivo*. (a), The W/D ratio of normal mouse lung and LPS-induced ALI mouse lung. (b) The MPO activity of lung tissues in normal mice and LPS-induced ALI mice. (c) The levels of pro-inflammatory cytokines (IL-1β, IL-8, TNF-α, and IL-6) in the BALF of normal mice and LPS-induced ALI mice. (d) Detection of miR-29b-1-5p and RTN4 expressions in mouse lung tissues was determined using the qRT-PCR and Western blot analyses. *, $p < 0.05$*vs.* normal mice.

(Figure 4(a)). As we expected, the expression of RTN4 in lung tissues of LPS-induced ALI mice was declined and increased in response to injection with agomir and antagomir of miR-29b-1-5p. Accordingly, caudal vein injection of miR-29b-1-5p antagomir or RTN4 expression vector contributed to decreased W/D ratio, weakened MPO activity, and declined levels of pro-inflammatory cytokines in the BALF in LPS-conditioned mice (Figures 4(b)–4(d)). We found an increased ratio of p-Akt/total Akt and p-ERK1/2/total ERK1/2 in LPS-conditioned mice injected with miR-29b-1-5p antagomir or RTN4 expression vector (Figure 4(e)), while we observed a declined ratio of p-Akt/total Akt and p-ERK1/2/total ERK1/2 in LPS-conditioned mice injected with miR-29b-1-5p agomir. Meanwhile, when LPS-conditioned mice were injected with miR-29b-1-5p antagomir and RTN4 expression vector in combination, we observed the overexpression of RTN4 rescued LPS-conditioned mice against miR-29b-1-5p attack, as evidenced by decreased W/D ratio and MPO activity, activation of the Akt/ERK signaling pathway, and reduced release of pro-inflammatory cytokines. The aforementioned results together prove the hypothesis that miR-29b-1-5p mediates inflammatory response and lung injury in LPS-induced ALI *in vivo* through the Akt/ERK signaling pathway *via* the RTN4.

miR-29b-1-5p mediated pulmonary interstitial fibrosis in ALI animal model by targeting RTN4.

Subsequently, we determined the expression of TGF-β1, E-cadherin, α-SMA, and vimentin by using qRT-PCR and Western blot analyses to further confirm the occurrence of EMT (Figures 5(a) and 5(b)). The results revealed that TGF-β1, α-SMA, and vimentin mRNA and protein expressions declined but the E-cadherin was increased in LPS-conditioned mice injected with miR-29b-1-5p antagomir or RTN4 expression vector, while the results were opposite in those injected with agomir. Likewise, the overexpression of RTN4 by its expression vector mimicked the effect of miR-29b-1-5p inhibition on the expression of TGF-β1, E-cadherin, α-SMA, and vimentin in the ALI animal model.

4. Discussion

Despite tremendous efforts in clinical trials, ALI still brings tremendous fatality and morbidity rates [19]. Recently, the functional roles of miRNAs focusing on ALI pathogenesis have been well characterized [9]. Herein, we attempt to elucidate the effect of miR-29b-1-5p on inflammatory response and pulmonary fibrosis in LPS-conditioned ALI. The study reveals that the inhibition of miR-29b could relieve inflammatory response and pulmonary fibrosis in LPS-conditioned ALI by modulating RTN4 and the Akt/ERK pathway.

In this report, our results demonstrated an elevated miR-29b-1-5p in LPS-conditioned MH-S cells and in LPS-conditioned ALI mice. As reported previously by Zhang et al., inhibited miR-29b could reduce the numbers of apoptotic cells and inflammatory reaction in H9c2 cells following LPS

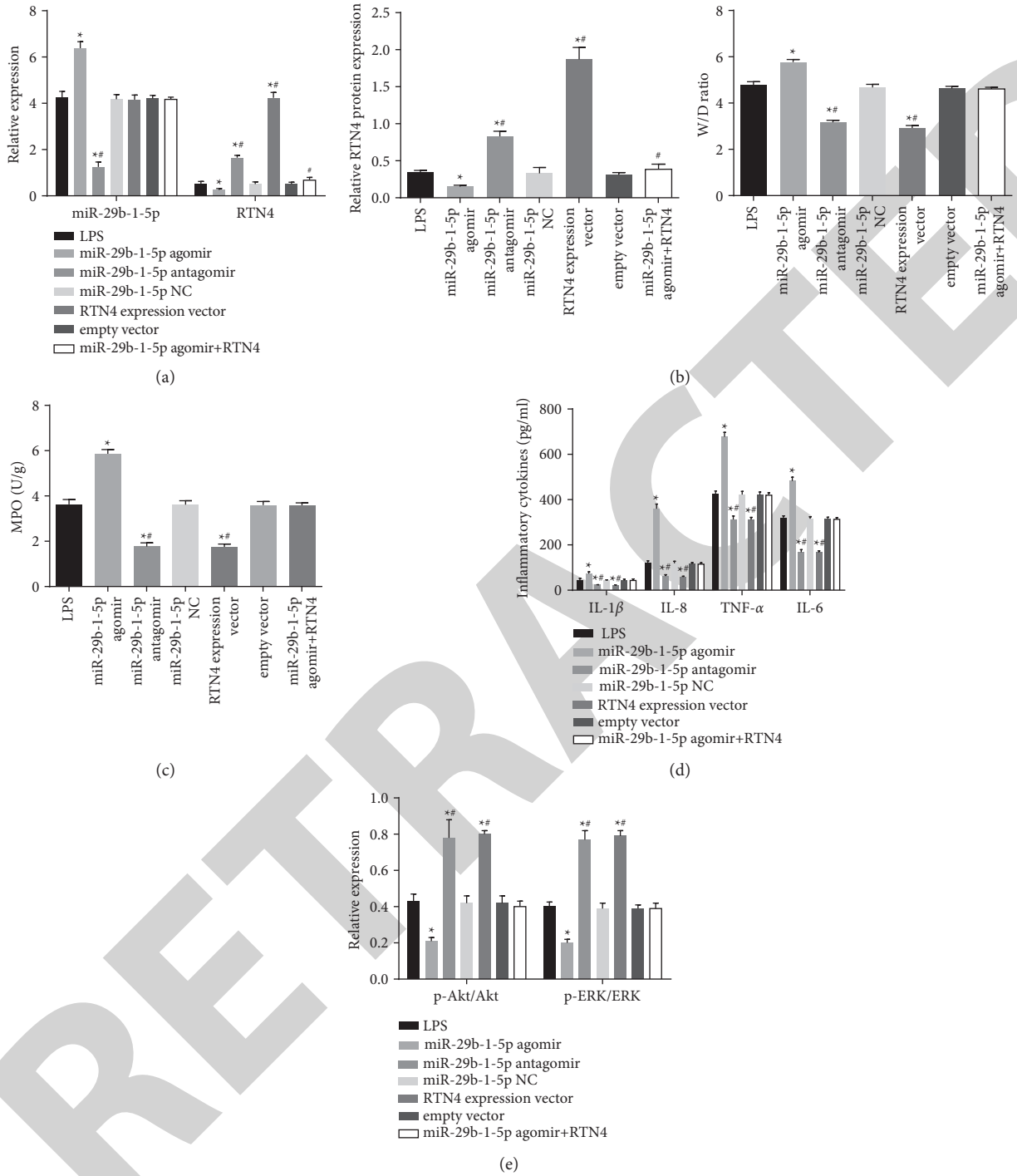

Figure 4: miR-29b-1-5p mediates inflammatory response and lung injury in LPS-induced ALI *in vivo* through the Akt/ERK signaling pathway *via* the RTN4. (a) qRT-PCR and Western blot analyses of miR-29b-1-5p and RTN4 expressions in mouse lung tissues of LPS-conditioned mice. (b) W/D ratio of LPS-induced mouse lungs. (c) MPO activity of LPS-induced mouse lungs. (d) The levels of IL-1β, IL-8, TNF-α, and IL-6 in the BALF of normal mice and LPS-induced ALI mice. (e) The ratio of p-Akt/total Akt and p-ERK1/2/total ERK1/2 in lung tissues of LPS-conditioned mice. *, $p < 0.05$*vs.* LPS-induced ALI mice and $^{\#}p < 0.05$*vs.* miR-29b-1-5p agomir.

treatment [20], suggesting the upregulation of miR-29b when exposure to LPS. Likewise, we determined miR-29b-1-5p in LPS-induced murine alveolar macrophages MH-S and LPS-induced murine models. LPS is still a common stimulator used to induce ALI *in vivo* and *in vitro*. Therefore, we may conclude the overexpression of miR-29b-1-5p following ALI. In addition to Zhang et al., Long et al. reported upregulated miR-29b-1-5p in hearts following I/R injury and in hydrogen peroxide-treated cardiomyocytes [13], suggesting that miR-29b-1-5p appears to upregulate following

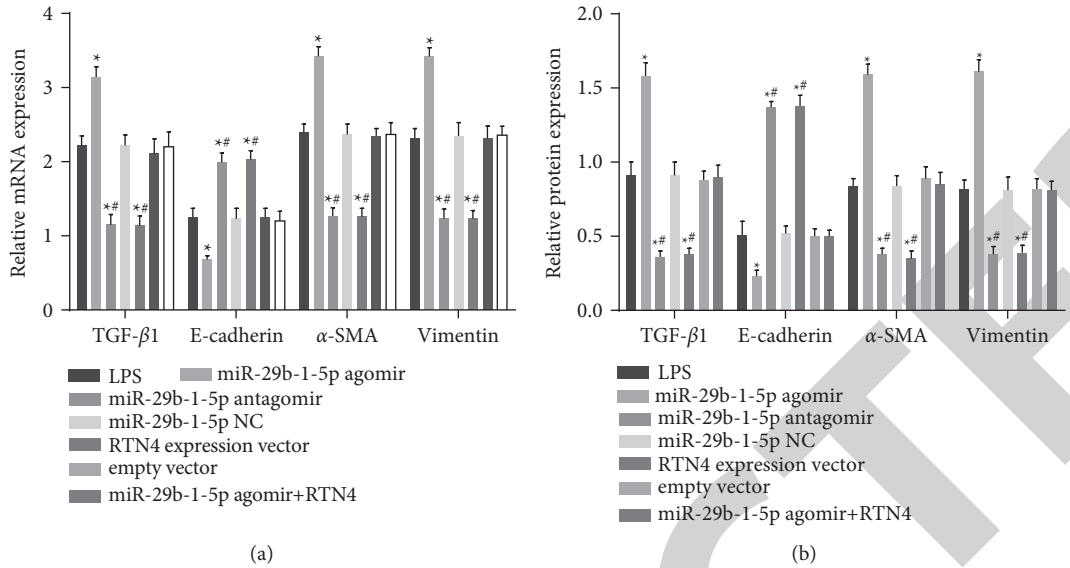

Figure 5: miR-29b-1-5p mediated pulmonary interstitial fibrosis in the ALI animal model by targeting RTN4. LPS-induced ALI mice were injected with miR-29b-1-5p agomir, miR-29b-1-5p antagomir, miR-29b-1-5p NC, RTN4 expression vector, and empty vector alone or in combination as required *via* caudal vein to manipulate the expression of miR-29b-1-5p and RTN4 *in vivo*. (a) The mRNA levels of TGF-β1, E-cadherin, α-SMA, and vimentin in LPS-induced ALI mouse lung tissues were determined using qRT-PCR. (b) The protein expressions of TGF-β1, E-cadherin, α-SMA, and vimentin in LPS-induced ALI mouse lung tissues were determined using Western blot analysis. *, $p < 0.05$ vs. LPS-induced ALI mice and $^{\#}p < 0.05$ vs. miR-29b-1-5p agomir.

tissue injury. A large set of functional miRNAs have been well characterized, which can regulate gene expression at various levels, including transcription and post-transcriptional processing. Furthermore, we determined an upregulation of RTN4 expression in response to miR-29b-1-5p inhibition. In addition to that, we found RTN4 overexpression resisting to miR-29a-1-5p overexpression in LPS-induced murine alveolar macrophages MH-S and LPS-induced murine models both, suggesting miR-29a-1-5p-mediated ALI partially by targeting RTN4. Till now, the demonstration that miR-29a-1-5p-mediated ALI partially by targeting RTN4 has not been reported in ALI. The family of RTN4 encompasses three different isoforms, among which RTN4-B is highly expressed in the lung tissue. A murine study demonstrated RTN4-B overexpression ameliorates lung injury, alveolar protein exudation, and neutrophil infiltration in lipopolysaccharide (LPS)-induced ALI mice, suggesting protective effects of RTN4-B against ALI [16]. Likewise, the loss of RTN4-B was identified as an unfavorable feature in the context of intrahepatic cholangiocarcinoma [21]. Therefore, miR-29b-1-5p-mediated RTN4 inhibition may explain the development of ALI.

Additionally, the data in the present study support the notion that miR-29b-1-5p regulates RTN4 expression and its overexpression contributes to the release of pro-inflammatory cytokines, IL-1β, IL-8, TNF-α, and IL-6. In addition to inflammation, miR-29b-1-5p upregulation following LPS stimulation was associated with cell apoptosis in ALI. Exposure to LPS often leads to the accumulation of inflammatory cells in alveolus as well as inflammatory cytokine secretion [22]. miR-29b-1-5p upregulation was found to increase endothelial permeability and apoptosis, and increase the expression of NF-κB and cell adhesion molecule-1 in atherosclerosis [23]. A disruption of the alveolar epithelial barrier and an enhanced capillary endothelial permeability commonly accompany with ALI [24]. Furthermore, LPS stimulation was followed by an elevated expression of vascular cell adhesion molecule-1 [25]. Therefore, it is reasonable that miR-29b-1-5p upregulation following LPS stimulation triggers the inflammation and apoptosis in LPS-induced ALI. Interestingly, we found RTN4 overexpression negated the inducible role of miR-29b-1-5p in inflammation during ALI. The products of RTN4 gene may be multifunctional, modulating the apoptosis, inflammation, tumor development, and neuronal regeneration. In a previous murine study, mice with Th2-driven lung inflammation exhibited a loss of Nogo expression in the airway epithelium and smooth muscle when compared to nonallergic mice [26]. RTN4-B required for tissue repair was also observed from previous evidence [27]. Additionally, our study demonstrated miR-29b-1-5p mediated pulmonary interstitial fibrosis in ALI via RTN4. In this study, TGF-β1, E-cadherin, α-SMA, and vimentin were determined to reflect the degree of fibrosis in mouse lungs following LPS stimulation. As evidenced by our experimental ALI mouse models, the expression of TGF-β1, α-SMA, and vimentin was declined but the E-cadherin was increased in LPS-conditioned mice with miR-29b-1-5p inhibition or with RTN4 expression. Similar to our study, RTN4B is nonparenchymal cells in the liver and its expression was downregulated with the progression of liver fibrosis [21].

In conclusion, the findings obtained in this study provide evidence that the inhibition of miR-29b-1-5p could

decelerate the inflammation, apoptosis, and pulmonary interstitial fibrosis in LPS-induced ALI. Likewise, we demonstrated the contributory role of miR-29b-1-5p overexpression in ALI was achieved by functioning as a negative regulator of RTN4. In addition to that, the PI3K/AKT pathway was found to be suppressed in the presence of miR-29b-1-5p or to be activated in the presence of RTN4 in LPS-induced ALI, while a further demonstration that this signaling pathway engages in the regulation of miR-29b and RTN4 in ALI is required. Although the present study shows preliminary nature, clinical translation can be improved by the drug delivery system targeting miR-29b-1-5p or restoring RTN4 for ALI.

Data Availability

The data supporting this study are included within the article.

Conflicts of Interest

The authors declare there are no conflicts of interest.

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Research Article

Molecular Mechanisms of *Gynostemma pentaphyllum* in Prevention and Treatment of Non-Small-Cell Lung Cancer

Renji Liang,[1] Jinzheng Wu,[2] Ronghua Lin,[3] Liling Ran,[4] Bo Shu,[5] and Hao Deng[1]

[1]*Department of Cardiothoracic Surgery, The First Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang 421001, China*
[2]*Department of Anesthesiology, The Second Xiangya Hospital, Central South University, Changsha 410011, China*
[3]*Department of General Surgery, Huichang County People's Hospital, Huichang 342600, Jiangxi, China*
[4]*Hunan Aerospace Tianlu Advanced Material Testing Co., Ltd., Changsha 410000, China*
[5]*Department of General Surgery, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, China*

Correspondence should be addressed to Hao Deng; denghao@usc.edu.cn

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Objective. Lung cancer represents the leading cause of cancer death on a global scale. *Gynostemma pentaphyllum* (*G. pentaphyllum*), a traditional medicinal material with a high medicinal and health value, has recently been reported for its anticancer activity. However, the pharmacological mechanism of *G. pentaphyllum* in non-small-cell lung cancer (NSCLC) remains to be elucidated. *Methods*. The active ingredients of *G. pentaphyllum* were obtained from the TCMSP database and known therapeutic targets of NSCLC from the GeneCards and OMIM databases. Disease-drug common targets are subjected to protein-protein interaction (PPI), GO enrichment analysis, and KEGG pathway enrichment analysis. A molecular docking strategy was performed to verify the interaction between molecules. *Results*. We found a total of 24 compounds of *G. pentaphyllum* fulfilling OB ≥ 30% concomitant with DL ≥ 0.18 and corresponding 81 target genes in the TCMSP database, with 5062 NSCLC-related genes collected in the GeneCards and OMIM databases. The network consisting of the disease-target compound was obtained, including 8 active ingredients and 69 common targets. The PPI network with 65 nodes and 645 edges was visualized. After functional enrichment analysis, it was revealed that the therapeutic effects of *G. pentaphyllum* on NSCLC were achieved through response to ketone, gland development, and cellular response to xenobiotic stimulus. After molecular docking analysis, it was revealed that the two active ingredients of *G. pentaphyllum,* quercetin and rhamnazin, bound well and stably to their targets (MYC, ESR1, and HIF1A). *Conclusion*. Our study, based on network pharmacology, identifies active ingredients, targets, and pathways model mechanism of *G. pentaphyllum* when it is used to treat NSCLC.

1. Introduction

In spite of remarkable progress in understanding of pathogenesis, application of predictive biomarkers, immunologic control, and therapeutic strategies for lung cancer in the past two decades, lung cancer still contributes to a heavy global burden of cancer mortality and morbidity, with an estimated 2 million new diagnoses and 1.76 million deaths each year [1]. Although the male-to-female ratio differs across regions, higher incidence and death rates of lung cancer (roughly 2 times) have been estimated in men than in women on the whole [2]. Lung cancer is a heterogeneous disease that consists of various histological and molecular types with clinical relevance, and the vast majority of patients (accounting for roughly 85%) are afflicted by non-small-cell lung cancer (NSCLC). Surgical care for early-stage NSCLC has been developed with new procedures, techniques, and care pathways [3]. When patients are diagnosed with NSCLC, locally advanced but surgically resectable, the optimal treatment includes at least radiochemotherapy. With regard to those with unresectable or inoperable locally advanced disease, radiochemotherapy followed by immunotherapy consolidation has evolved as a new standard of care [4]. Over the past two decades, a proportion of NSCLC

patients have experienced long-term clinical benefits from molecular targeted therapies and immunotherapies, but acquired resistance to current treatments during treatment or after treatment is still a clinical challenge [5, 6].

Emerging studies with experimental models have proved therapeutic effects of herbal medicines on several common human cancers including NSCLC [7, 8]. *Gynostemma pentaphyllum* (*G. pentaphyllum*) is a creeping perennial herb that is sourced from the family Cucurbitaceae, which is widely used as a herbal medicine and distributed in Asian regions, especially in China [9]. *G. pentaphyllum* was first recorded as Traditional Chinese Medicine (TMC) in *Jiuhuang Bencao,* written by Zhu Su, who was a Chinese botanist in AD 1406 [10]. The anticancer activity [11], antiobesity effect [12], antioxidant and anti-inflammatory effects [13], and antifibrotic effect [14] of the main active ingredients of *G. pentaphyllum* have been widely reported.

TMC has several characteristics, such as multicomponent and multitarget synergistic effects, while it is difficult to systematically and comprehensively detect the exact mechanism of TMC through traditional methods. Network pharmacology is a novel approach that was proposed by Hopkins in 2008 to study the molecular mechanisms of drug action, for example, natural herbs and TCM, by establishing computer-aided networks on the basis of "multigene," "multitarget," and "multichannel" linking with multiple compounds [15]. In addition, molecular docking verification is performed to estimate the binding energy between TCM components and disease targets and to explain how ligands act on complex molecular networks. In this work, we aim to elucidate the therapeutic mechanism of *G. pentaphyllum* for NSCLC based on network pharmacology followed by molecular docking analysis.

2. Methods

2.1. Active Ingredients and Putative Target Genes of G. pentaphyllum. To obtain the active ingredients of *G. pentaphyllum*, we performed a computer-based retrieval in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://lsp.nwu.edu.cn/tcmsp.php), which is a popular pharmacology database where there are almost 500 formulae of TCM concomitant with 30,069 compounds. Two pharmacokinetic parameters related to ADME (absorption, distribution, metabolism, and excretion), oral bioavailability (OB), and drug-likeness (DL), were evaluated to retain the active ingredients of *G. pentaphyllum* for further investigation. In this study, the active ingredients of *G. pentaphyllum* must fulfill $OB \geq 30\%$ and $DL \geq 0.18$. The protein targets of the active ingredients were also predicted in the TCMSP database, with the gene names obtained from the UniProt Knowledgebase (UniProtKB), which collects functional information on proteins covering accurate, consistent, and rich annotation.

2.2. Common Target Genes of NSCLC and G. pentaphyllum. The known therapeutic targets of NSCLC were dug up in the GeneCards combined database with the Online Mendelian Inheritance in Man database (OMIM, https://omim.org/). The proteins (only "*Homo sapiens*") associated with NSCLC were chosen. Using the Venn functional intersection in the *R* software, overlapping targets of *G. pentaphyllum* and NSCLC were obtained.

2.3. Protein-Protein Interaction (PPI) Network Construction. The common targets of *G. pentaphyllum* and NSCLC were entered into the STRING database (https://www.string-db.org/) to estimate their PPIs. The species should be "*Homo sapiens*" and the confidence score should be no less than 0.4. The PPI network was visualized by importing the TSV-based file to Cytoscape software (3.8.1). According to the degree value obtained using the cytoHubba plug-in of Cytoscape, the key genes were extracted.

2.4. Functional Enrichment Analysis. The disease-drug overlapping targets of *G. pentaphyllum* and NSCLC were subject to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses using the "clusterProfiler" package in R/Bioconductor. We mapped them into the DAVID Bioinformatics Resources 6.7 (https://david-d.ncifcrf.gov/), with the species set as "*Homo sapiens*" and P value < 0.05 set as a cutoff value. Results of GO analysis were visualized using the OmicShare platform (https://www.omicshare.com/), focusing on three levels: biological process (BP) analysis, cellular component (CC) analysis, and molecular function (MF) analysis.

2.5. Molecular Docking Verification. The protein ligand complexes of targets with high-ranking degree values in the PPI network were obtained using the RCSB database (https://www.rcsb.org/). The molecular docking verification was performed on the Systems Dock Website (https://systemsdock.unit.oist.jp/iddp/home/index) to evaluate the binding strength and activity between those protein ligand complexes and the active ingredients of *G. pentaphyllum*, with core chemical compounds sorted out.

3. Results

3.1. The Active Ingredients of G. pentaphyllum. When searching the active ingredients of *G. pentaphyllum* and set $OB \geq 30\%$ concomitant with $DL \geq 0.18$ in the TCMSP database, we found a total of 24 compounds of *G. pentaphyllum* (Table 1), including 3′-methyleriodictyol, rhamnazin, sitosterol, ruvoside_qt, spinasterol, campesterol, isofucosterol, ginsenoside f2, CLR, quercetin, (24S)-Ethylcholesta-5,22,25-trans-3beta-ol, 4α,14α-dimethyl-5α-ergosta-7,9(11),24(28)-trien-3β-ol, cucurbita-5,24-dienol, cyclobuxine, and 10 from gypenoside.

3.2. Identification of Disease-Drug Common Targets. After removal of duplicate values and conversion of protein names into gene symbols, we obtained 81 target genes of the active ingredients of *G. pentaphyllum* in the TCMSP database. Subsequently, we searched for known therapeutic targets of

Table 1: The active ingredients of *G. pentaphyllum* with OB ≥ 30% concomitant with DL ≥ 0.18 in the TCMSP database.

Molecule ID	Molecule name	OB (%)	DL
MOL000338	3′-methyleriodictyol	51.61	0.27
MOL000351	Rhamnazin	47.14	0.34
MOL000359	Sitosterol	36.91	0.75
MOL004350	Ruvoside_qt	36.12	0.76
MOL004355	Spinasterol	42.98	0.76
MOL005438	Campesterol	37.58	0.71
MOL005440	Isofucosterol	43.78	0.76
MOL007475	Ginsenoside f2	36.43	0.25
MOL000953	CLR	37.87	0.68
MOL000098	Quercetin	46.43	0.28
MOL009855	(24S)-ethylcholesta-5,22,25-trans-3beta-ol	46.91	0.76
MOL009867	4α,14α-dimethyl-5α-ergosta-7,9(11),24(28)-trien-3β-ol	46.29	0.76
MOL009877	Cucurbita-5,24-dienol	44.02	0.74
MOL009878	Cyclobuxine	84.48	0.70
MOL009888	Gypenoside XXXVI_qt	37.85	0.78
MOL009928	Gypenoside LXXIV	34.21	0.24
MOL009929	Gypenoside LXXIX	37.75	0.25
MOL009938	Gypenoside XII	36.43	0.25
MOL009943	Gypenoside XL	30.89	0.21
MOL009969	Gypenoside XXXV_qt	37.73	0.78
MOL009971	Gypenoside XXVII_qt	30.21	0.74
MOL009973	Gypenoside XXVIII_qt	32.08	0.74
MOL009976	Gypenoside XXXII	34.24	0.25
MOL009986	Gypentonoside A_qt	36.13	0.80

NSCLC in authoritative open databases and obtained 4861 and 201 targets in the GeneCards and OMIM databases, respectively. After the removal of duplicate values, 4970 therapeutic targets of NSCLC were obtained. Venn intersection analysis by *R* software showed there were 69 overlapping target genes of NSCLC and *G. pentaphyllum* (Figure 1). We then used Cytoscape software to visualize the disease-target-compound network, which consisted of 8 active ingredients and 69 common targets (Figure 2). The 8 bioactive compounds included *3′-methyleriodictyol* (1 node), *rhamnazin* (9 nodes), *sitosterol* (2 nodes), *spinasterol* (16 nodes), *campesterol* (1 node), *isofucosterol* (16 nodes), *CLR* (2 nodes), and *quercetin* (107 nodes).

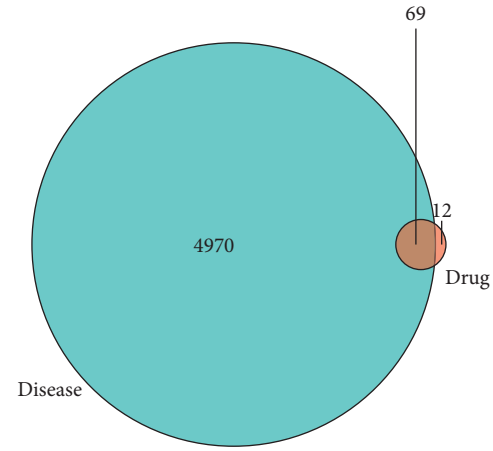


Figure 1: Venn intersection analysis by R software showed there were 69 overlapping target genes of NSCLC and *G. pentaphyllum*.

3.3. PPI Network Construction. We imported 69 common targets between NSCLC and the active ingredients of *G. pentaphyllum* into the STRING database. As shown by Figure 3(a), there were 65 nodes with 645 edges of the PPI network where higher degree values reflecting closer correlation (Figure 3(b)), and PRSS1, EIF6, RUNX1T1, and NPEPPS were removed due to weak interaction.

3.4. Enrichment Analysis for Disease-Drug Common Targets. Next, we conducted GO annotation and KEGG pathway analyses of 69 disease-drug common targets. After GO analysis, we found 1211 GO terms were significantly enriched by these disease-drug common targets (Figure 4(a), $p < 0.05$). At the level of BP, the active ingredients of *G. pentaphyllum* were associated with 1106 terms. At the level of CC, the active ingredients of *G. pentaphyllum* were associated with 11 terms. At the level of MF, the active ingredients of *G. pentaphyllum* were associated with 94 terms. After KEGG pathway analysis, we found 11 KEGG pathways were significantly enriched by these disease-drug common targets (Figure 4(b), $p < 0.05$).

3.5. Molecular Docking Verification. For the sake of estimating the interaction between ligand and receptor and to assess the binding mode and affinity according to their-comprehensive characteristics, a molecular docking strategy was performed by the AutoDockTools. Three candidate targets, MYC, ESR1, and HIF1A, were selected for molecular docking analysis according to higher degree values in the

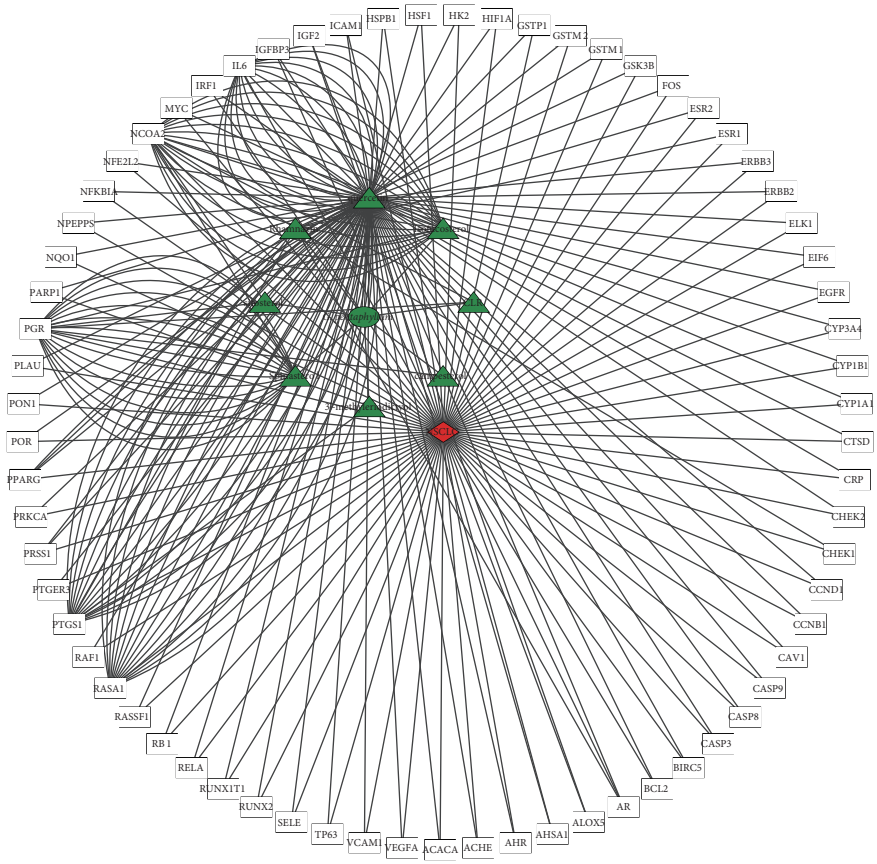
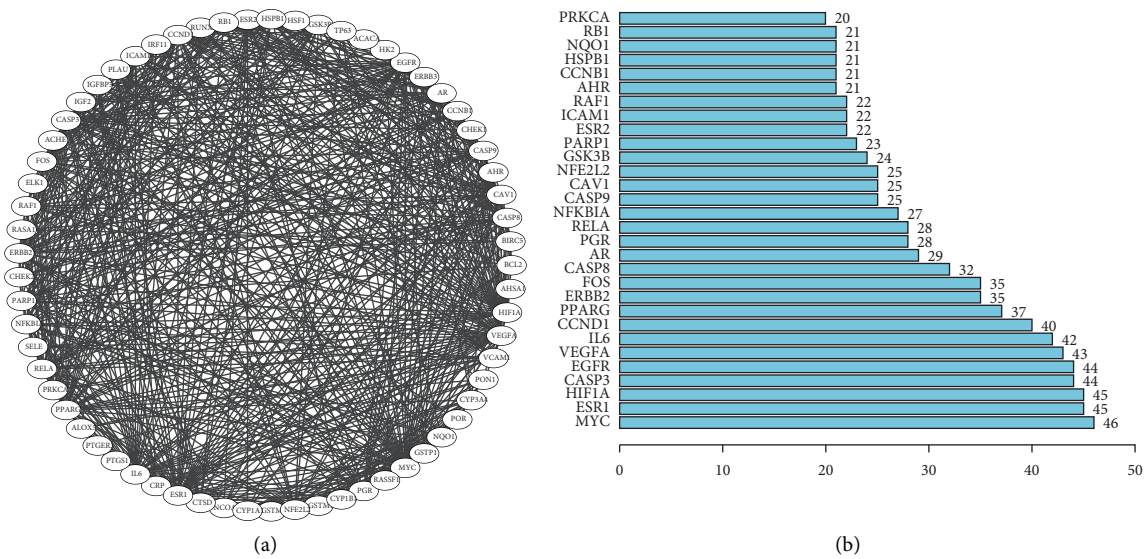


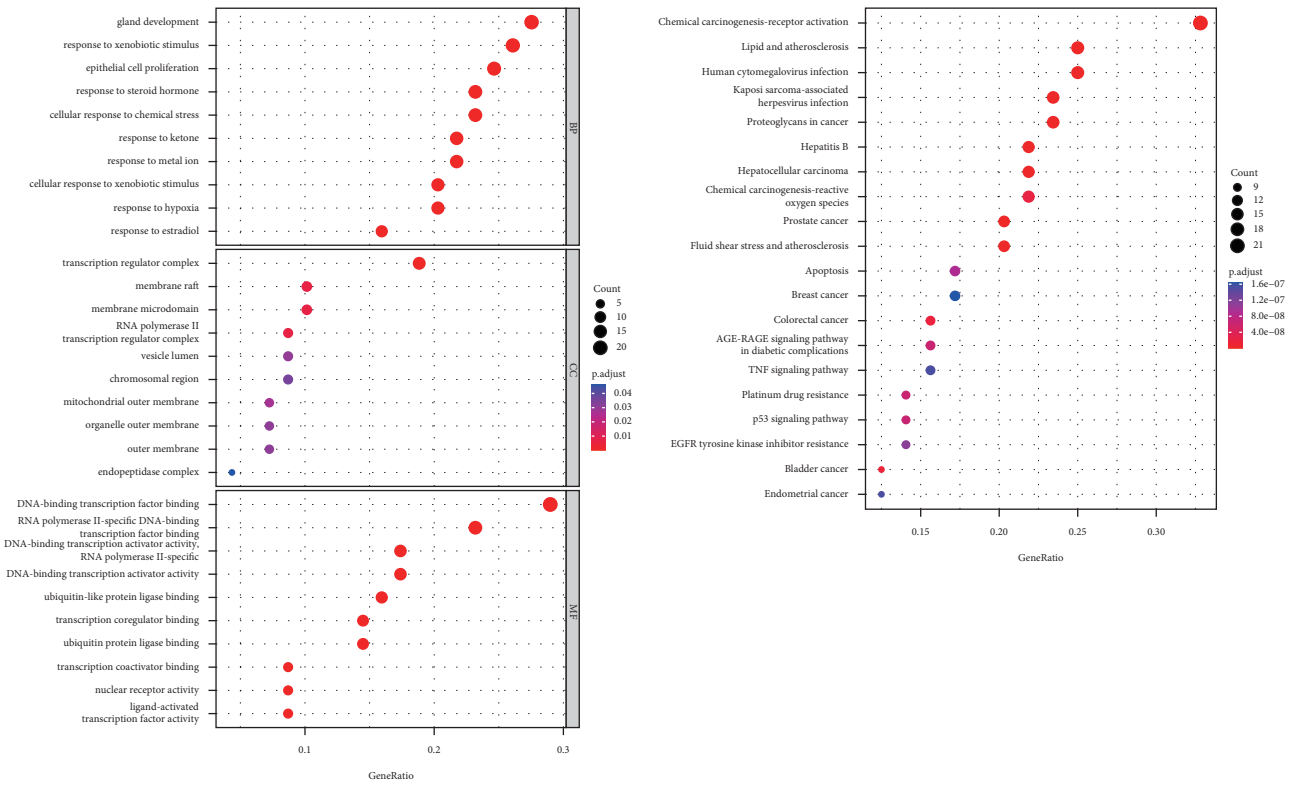
FIGURE 2: Disease-target-compound network based on 8 bioactive compounds and 69 common targets. A red node represents disease, green nodes represent bioactive compounds of G pentaphyllum, and nodes in the outer ring represent common targets.



(a) (b)

FIGURE 3: PPI network construction for disease-drug common targets (a) and their degree values (b) (here only listed targets with degree value more than 20).

core PPI network. The binding energy less than 0 indicates spontaneous binding of ligand and receptor, and smaller values reflect higher binding activity. The affinity energy ≤ −5 kcal/mol is considered high affinity. It was found that the binding energy of quercetin and MYC was −8.50 kcal/mol, rhamnazin and ESR1 was −8.40 kcal/mol, quercetin and HIF1A was −8.90 kcal/mol, suggesting that the 2 potential active compounds of *G. pentaphyllum*,



(a) (b)

Figure 4: Top 10 GO terms significantly enriched by disease-drug common targets at the levels of BP, CC, and MF (a) and KEGG pathways significantly enriched by disease-drug common targets (b). Larger circles reflect more enriched genes, and bluer indicates smaller p values.

quercetin and rhamnazin, have good binding ability with the targets MYC, ESR1, and HIF1A (Figure 5).

4. Discussion

TCM theory believes that the basic pathogenesis of lung cancer is attributed to the deficiency of the body's Yuan Qi with the excessiveness of pathological products (phlegm-blood stasis syndrome) within the human body and that "invigorating Qi for consolidation of the exterior" is an effective way to treat lung cancer [16]. With the substantial advancements in modern medicine, the mechanisms behind the therapeutic implications of TCM in lung cancer are involved in improving the body's immune function, inducing tumor cell apoptosis, and preventing tumor angiogenesis [17]. The active ingredients of *G. pentaphyllum* have been studied for their characteristics of clearing away heat and toxic materials, replenishing Qi and invigorating the spleen, and lung-moistening phlegm-transforming, which can be used to fight the basic pathogenesis of lung cancer [18–20]. Nevertheless, it is still a clinical challenge for the clinical translation of *G. pentaphyllum* for NSCLC treatment considering the complexity of the active ingredients and multiple targets of *G. pentaphyllum*. In the beginning, we searched the TCMSP database to collect putative molecules of *G. pentaphyllum* compounds and then searched the GeneCards and OMIM databases to collect therapeutic targets of NSCLC. Disease and drug common targets were acquired by Venn intersection and subjected to PPI analysis by functional enrichment analysis. The best binding mode of CS compounds and common target proteins was evaluated by molecular docking and analysis in AutoDockTools. In this work, the authors, with the help of a network pharmacology approach followed by molecular docking verification, attempt to elucidate the pharmacological mechanism of *G. pentaphyllum* on NSCLC treatment.

In the system of TCM, compounds fail to be delivered to the target organs to produce biological activities due to a lack of proper pharmacokinetic properties [21]. The network pharmacology approach integrates information from biological systems, drugs, and diseases, providing a systemic analysis of the pharmacokinetic properties of TCM. Usually, 30% of OB concomitant with 0.18 of DL was the lowest level to evaluate the pharmacokinetic actions of the compounds of herbal medicines. In our disease-target-compound network, 8 bioactive compounds in *G. pentaphyllum* stood out, which may responsible for the leading therapeutic effects of *G. pentaphyllum* on NSCLC, including *3′-methyleriodictyol*, *rhamnazin*, *sitosterol*, *spinasterol*, *campesterol*, *isofucosterol*, *CLR*, and *quercetin*. *Quercetin* ranked the highest with 107 targets of NSCLC, followed by the other three bioactive compounds, *isofucosterol*, *spinasterol*, and *rhamnazin*. *Quercetin* has a variety of biological properties, such as antioxidant, anti-inflammatory, and antiapoptosis [22–24], which has been widely investigated in human cancers, including lung cancer. It was reported that the antiproliferative

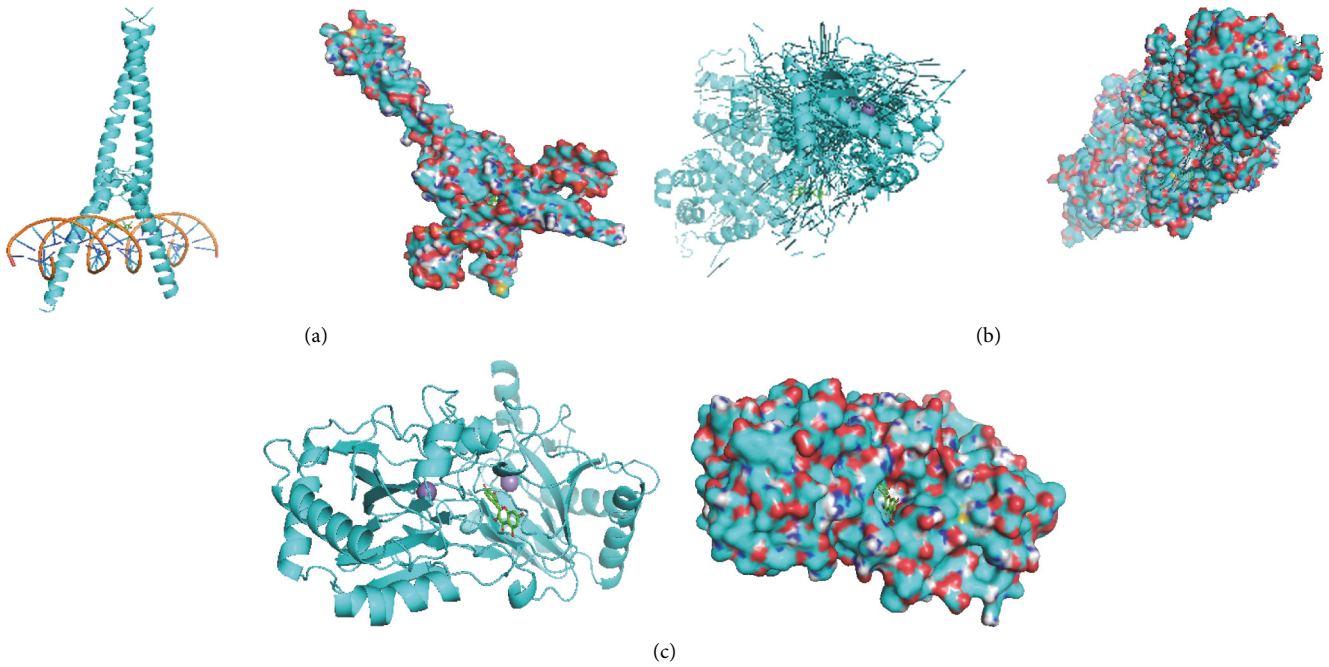


Figure 5: Docking analysis of *quercetin* and MYC (a), *rhamnazin* and ESR1 (b), *quercetin* and HIF1A (c).

effects on lung cancer cells by caspase-dependent DNA damage signaling [25]. More profoundly, Li et al. designed targeted delivery of *quercetin* by biotinylated mixed micelles and demonstrated a high accumulation of *quercetin*-loaded mixed micelles at the tumor site and showed good anticancer activity in the mouse model of NSCLC [26]. The antitumor functions of the other three bioactive compounds are also found in documented reports of lung cancer or other cancers. Yao et al. demonstrated that *rhamnazin* may exert a therapeutic effect on pulmonary fibrosis by alleviating inflammation, oxidation, and collagen deposition via the TGF-β/Smad axis [27]. The antitumor effects of *rhamnazin* were also proved in hepatocellular carcinoma [28]. Wahyuni et al. thought *spinasterol* might have activity against cancer cells in triple-negative breast cancer [29]. Ravikumar et al. reported the antiproliferative and proapoptotic activities of *spinasterol* [30]. However, at present, *isofucosterol* is still rarely reported for its anti-obesity effect rather than its antitumor effect [31].

Three candidate targets with higher degree values in the core PPI network, MYC, ESR1, and HIF1A, were subjected to further molecular docking and analysis, and it was revealed that the three core targets had good affinity with the active compounds of *G. pentaphyllum*, referring to *quercetin* and MYC, *rhamnazin* and ESR1, and *quercetin* and HIF1A. c-Myc regulates multiple genes, which are associated with cell proliferation in many cancers, including NSCLC [32]. Guo et al. demonstrated *quercetin* notably repressed cancer cell proliferation by downregulating c-Myc expression in pancreatic ductal adenocarcinoma [33]. Chen et al. demonstrated *quercetin* could block the Akt/mTOR/c-Myc axis to inhibit the epithelial-mesenchymal transition of cancer cells [34]. *Quercetin* induces mesenchymal-to-epithelial transition by changing the nuclear localization of β-catenin and regulating β-catenin target genes, including c-Myc in triple-negative breast cancer [35]. In addition to MYC, we also found a stable binding with *quercetin* and HIF1A. The overexpression of HIF1A was found to predict poor survival in lung cancer [36]. Hassan et al. found that *quercetin* could enhance the cytotoxic activity of gemcitabine or doxorubicin on cancer cells by inhibiting HIF1A expression [37]. Tumova et al. treated human umbilical vein endothelial cells with *quercetin* to modulate glucose uptake/metabolism by affecting the stability of HIF1α [38]. Fulvestrant, as an estrogen receptor antagonist, was demonstrated to repress the epithelial-mesenchymal transition process of lung cancer cells, reducing tumor resistance to the cytotoxic effect of antigen-specific T cells and natural killer effector cells [39], suggesting that the contribution of ESR1 expression on lung cancer progression. The mechanism of *rhamnazin* and ESR1 interaction in experimental models of lung cancer cells is not investigated in reported studies, which may be required for further profound functional validation. The importance of network pharmacology has been emphasized in medical research [40].

When interpreting our results, several limitations should be noted. First, the molecular mechanism by which *G. pentaphyllum* treats NSCLC is not completely characterized as the public databases we used in the study have been updated continuously. Second, only three key genes received molecular docking and a lack of functional studies may weaken the reliability of the clinical translation. Third, experimental validation in vivo and in vitro focusing on the suppressive effects of two potential active compounds of G. pentaphyllum, quercetin and rhamnazin, on NSCLC cells as well as the expressions of MYC, ESR1, and HIF1A is warranted to improve the preliminary nature of the study.

5. Conclusions

In conclusion, our study demonstrates that *G. pentaphyllum*, especially its main active compounds, *quercetin* and *rhamnazin*, may exert therapeutic effects on NSCLC through the modulation of multiple targets, such as MYC, ESR1, and HIF1A. The present work also supports that the network pharmacology prediction method with molecular docking verification may provide a preliminary but systemic exploration focusing on the pharmacokinetic properties and mechanism of TCM in human diseases, offering opportunities to develop micelles for targeted delivery of TCM to tumor sites.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Retraction

Retracted: Analysis of the Demand for Continuing Education of Nurses in the Department of Infectious Diseases and Its Influencing Factors

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
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(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] X. Pang, M. Zhang, and H. Pang, "Analysis of the Demand for Continuing Education of Nurses in the Department of Infectious Diseases and Its Influencing Factors," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 3743588, 5 pages, 2022.

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Research Article

Analysis of the Demand for Continuing Education of Nurses in the Department of Infectious Diseases and Its Influencing Factors

Xiaoqun Pang,[1] **Meiling Zhang**,[1] **and Huiyan Pang**[2]

[1]*Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-Sen University, Guangdong, Guangzhou 510630, China*
[2]*Department of Operating Theater, The Third Affiliated Hospital of Sun Yat-Sen University, Guangdong, Guangzhou 510630, China*

Correspondence should be addressed to Xiaoqun Pang; pangxq@mail.sysu.edu.cn

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Infection department is unique in working hours, environment, content, methods, and skills requirements, and continuing education plays an important role in stabilizing and improving the professional level of nurses in the infection department. Understanding the needs of nurses in the infection department for continuing education and the possible influencing factors of participating in continuing education and providing a management basis for managers in a targeted way can make the role of continuing education fully play. In this study, according to the characteristics of the Department of Infection, a questionnaire was designed to investigate the continuing education needs of nursing staff in the Department of Infection and analyze the influencing factors. The results show that the nursing staff in the infection department had a greater demand for continuing education. Age, professional title, working life, hospital level, and marital status were the risk factors that affected their demand for continuing education.

1. Introduction

In this era of continuous development and progress of society and information explosion, people are paying more attention to health. Unconsciously, patients and society have put forward higher requirements for the quality of care. In addition, with the continuous expansion of the hospital scale, the shortage of nursing staff is more obvious. Most hospitals recruit a large number of new nurses every year to meet the needs of improving the quality of nursing and adapting to the development of the hospital. However, almost all of the nursing staff have such shortcomings as lack of clinical knowledge, insufficient level of operation skills, insufficient clinical experience, lack of communication ability, poor psychological quality, and poor quality of care for high-risk patients, which have affected the patients' medical safety to a certain extent [1, 2]. The infectious disease department is a department with a special position. Due to the particularity of the working environment and working objects, the nurses of the infectious disease department have to face a wide variety of infectious diseases with various transmission routes for a long time [3]. At the same time, the patient's condition is prone to recurrence. So the nursing skills, service attitude, and details of the nursing staff are required to be higher [4]. However, now the main force of the hospital nursing team is the newly recruited nursing staff, and it is particularly important to strengthen their own learning and growth. Nursing staff in the infectious disease department need to continuously learn new knowledge, strengthen and improve their own protection, reduce the harm at work, and ensure the health of themselves and their families to a greater extent, which can effectively reduce the infection rate of patients and reduce the occurrence of nursing errors [5–7].

Continuing nursing education is lifelong nursing education, focusing on the learning of new nursing theories, new knowledge, new technologies, and new methods, which has become the best form of lifelong education and lifelong

learning for nurses. With the rapid development of science and technology and the continuous updating of nursing models, the connotation of nursing work has also undergone profound changes. It is necessary for in-service nurses to broaden their knowledge through continuous learning and update the nursing knowledge system in time to meet the needs of modern nursing work [8, 9]. Foreign studies have also pointed out that professional and effective continuing education is crucial to providing safe and high-quality care, regardless of age or seniority, only continuous learning can bring high-quality care to patients. Through the investigation, the nurses of the infection department affirmed the importance of continuing education [10]. However, there are differences in the degree of demand for continuing education among nurses of different ages and qualifications. Only by understanding these differences can we provide a management basis for managers in a targeted manner, and then the role of continuing education can be fully played. Therefore, in order to further understand the demand for continuing education of nurses in different infectious disease departments, our department has carried out relevant research, and the results are reported as follows.

2. Materials and Methods

2.1. General Information of the Respondents. We randomly selected 160 nurses from the infectious diseases department of 6 general hospitals of Grade III A and 4 hospitals of Grade II Grade A as the survey objects. The nurses participating in this survey are all working in the infectious disease department and have obtained the nurse practitioner qualification certificate.

The survey subjects were all female, with an average age of 28.21 ± 6.35 years and average working years in the infectious disease department 6.54 ± 3.02 years; 13 chief nurses, 20 chief nurses, 35 nurses, and 92 nurses; 75 students with a final degree of bachelor degree or above, 68 students from junior colleges, and 17 students from technical secondary schools; Among them, 102 were from third-class hospitals and 58 were second-class hospitals; marital status, 87 were married and 73 were unmarried.

2.2. Research Methods. On the basis of the literature review and characteristics of nursing work in the infectious diseases department, the questionnaire was formed after two rounds of expert evaluation [11]. The questionnaire set up 4 items about continuing education needs, a total of 40 items, and each item has 10 items. The four items are basic knowledge of infectious diseases, common occupational injuries, knowledge of infectious diseases, and disinfection and isolation protection of infectious diseases. Each item is a single-choice question. The options are very need, need, general, and no need, respectively, with 3, 2, 1, and 0 points, respectively. The total score is 120 points. The higher the score indicates the higher the demand. A total of 160 questionnaires were distributed and filled out by anonymous method. A total of 160 questionnaires were collected, and the collection rate and effective questionnaire rate were 100%.

2.3. Statistical Processing. The EPI INFO 6.0 software was used to establish the database, and all data were entered twice by a special person. SPSS 13.0 software was used to process and statistically analyze the obtained data, and descriptive statistics, univariate regression analysis, and other methods were used to analyze the data. $P < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1. Score of Nursing Staff's Demand for Continuing Education in the Infection Department. The average total score for continuing education needs of nurses in the infectious disease department was (89.24 ± 21.96) points, of which the basic knowledge direction of the infectious disease department was (15.36 ± 4.58) points, the common occupational injuries (24.87 ± 4.75) points, the knowledge of infectious diseases (12.71 ± 3.20) points, and disinfection and isolation protection of infectious diseases department (36.30 ± 7.68) points.

3.2. Continuing Education Needs of Nurses in the Infectious Disease Department. The survey results show that most of the personnel have a high demand for continuing education, and 69.17% of them have a score of 80 or more. The specific score distribution is shown in Table 1.

3.3. Univariate Analysis of Demand for Continue Education of Nursing Staff in the Infection Department. The results of the univariate analysis showed that in addition to educational background, age, professional title, working years, professional title, hospital level, marital status, and other factors had statistically significant differences in continuing education needs between groups. The younger the age, the shorter the working years, the lower the professional title, the lower the hospital level, and the greater the demand for unmarried persons ($P < 0.05$), see Table 2 for details.

3.4. Multifactor Analysis on Continue Education Demand of Nursing Staff in the Infection Department. The results of multivariate analysis showed that age, professional title, working years, professional title, hospital level, and marital status were the independent influencing factors of the nursing staff's demand for continuing education in the infectious disease department ($P < 0.05$), see Table 3 for details.

4. Discussion

The continuous development of nursing requires that the knowledge system of nurses is constantly updated. The knowledge obtained by school education alone is far from meeting the needs of nursing work, and continuing education as an important way to obtain new knowledge and skills for nurses in service plays a vital role in comprehensively improving the level of nurses' knowledge and skills. At the same time, continuing education for nurses is the need for the development of nursing disciplines and the

Table 1: Distribution of scores of continuing education needs of nurses in the infectious disease department.

Score	120~100	99~80	79~60	59~40	39 and below
n (%)	18 (15.00)	65 (54.17)	36 (30.00)	32 (26.67)	9 (7.50)

Table 2: Univariate comparison of continuing education needs among different factor groups.

Indexes	Number of cases	Score	x^2 value	P value
Age			19.768	0.000
> 25 year	83	76.21 ± 13.54		
< 25 year	77	103.28 ± 22.25		
Working years			11.052	0.005
≥ 5 years	78	90.90 ± 12.05		
< 5 years	72	99.84 ± 23.65		
Job title			13.214	0.001
Supervisor nurse and above	68	85.02 ± 17.39		
Nurse	92	95.13 ± 23.74		
Education			3.563	0.158
Bachelor's degree and above	75	87.87 ± 18.35		
College or technical secondary school	85	90.45 ± 22.69		
Hospital grade			16.768	0.000
Tertiary hospital	102	82.45 ± 22.08		
Grade II hospital	58	101.18 ± 23.19		
Marital status			8.254	0.012
Married	87	85.69 ± 19.68		
Unmarried	73	93.47 ± 24.09		

Table 3: Logistic regression analysis of continuing education demand.

Indexes	B	SE	Wald Chi-square value	P value	OR value
Age	1.765	0.712	15.432	0.017	12.078
Working years	0.952	0.386	9.675	0.048	8.513
Job title	1.172	0.432	10.765	0.035	9.875
Hospital grade	1.825	0.760	14.341	0.009	13.412
Marital status	2.449	0.911	16.349	0.000	16.454
Constant item	−3.203	0.658	11.231	0.003	—

self-realization of nurses, and it is also a part of lifelong education [12]. Serving nurses generally recognize the importance of continuing academic education. In recent years, with the reform of the medical and health system and the change of the hospital personnel system, education has become the primary condition for nurse employment. In-service nurses are generally aware of the importance of improving their academic qualifications and actively participate in continuing academic education. The ways of continuing academic education are flexible and diverse. Although self-study exams, college entrance examinations, correspondence courses, and online education are all types of national higher education exams, the advantages of self-study exams compared with other types of exams are obvious [13, 14]. Its advantages include quick effect, low cost, and little contradiction between engineering and learning. According to a survey, 65.6% of nurses choose self-study exams as a way to improve their academic qualifications for this reason [15].

The results of this study show that The average total score for continuing education needs of nurses in the infectious disease department was (89.24 ± 21.96) points, which indicates that there is a great demand for continuing education among nurses in the infectious disease department, especially in the disinfection and isolation protection of the infectious disease department and the common occupational injuries in the infectious disease department. As a nurse in the infectious disease department, they need to be in daily contact with biological specimens such as blood, body fluids, secretions, and excreta of infectious disease patients and are under the threat of various viruses. Secondly, the implementation of the strict disinfection system in the infectious disease department, and the various chemical preparations used in disinfection also threaten the health of nursing staff; Furthermore, the closed or semiclosed working environment of the infectious disease department makes it easy for nursing staff to feel depressed, and the worry about acquiring infectious diseases intensifies their psychological burden and damages their mental health [16]. Therefore, it is urgent to cultivate a team of nurses in infectious diseases with a solid theoretical foundation and good mental state through continuing education.

The demand for continuing education of nursing staff in the infection department was analyzed. The results showed that age, professional title, working years, professional title,

hospital grade, and marital status were all the influencing factors [17]. Newly recruited nursing staff often have their own weaknesses that are difficult to overcome, mainly reflected in the following points: First, the educational level is low, the foundation is poor, and there are obvious deficiencies in professional theory and logical thinking; they do not have the enthusiasm for active learning and mechanically execute the doctor's orders; Second, there are few opportunities for clinical practice before joining the job. When encountering special patients, they lack confidence and dare not take the initiative to undertake the operation. Over time, the technical operation ability is poor and nonstandard; Third, although they have some theoretical knowledge and nearly a year of internship experience, they are still unable to combine the knowledge they have learned with practice when they encounter emergencies; Nurses are not yet mature in their ability to judge changes in the condition. If they encounter a critically ill patient, they may be at a loss, be in a hurry, panic, and be afraid of facing the situation, and their emergency response ability is poor [18]. Fourth, after the newly recruited nurses started to work independently, due to their lack of knowledge and simple thinking, when faced with family members and patients who have problems or complaints, the nurses do not know if they can communicate effectively, which will make the relationship between nurses and patients tense, which is easy to cause. Nursing disputes arise. Coupled with the particularity of the diseases in our department, the difficulty of intravenous infusion in children with hand, foot, and mouth disease, and the weak protection knowledge and awareness of new nurses, junior nurses often feel physically and mentally exhausted.

In order to reduce the occupational risk of nurses in the infectious disease department, we should carry out corresponding continuing education programs for different groups of people. Continuing education should include the following: (1) Increase the self-protection awareness of nursing staff, adopt a mentoring model, and correct wrong nursing behaviors in a timely manner; (2) Continuously strengthen the professional training of nursing staff, and conduct targeted dissemination of professional knowledge of infection protection; (3) Implement a comprehensive nursing protection mechanism to effectively protect the personal safety of nursing staff [9, 10]. In addition, we should establish an assessment mechanism, and those who fail the assessment should be given counseling and training again, so as to ensure the quality of work and their own safety of the nurses in the infectious disease department [19].

In recent years, the continuous emergence of a variety of educational means has brought vitality to the continuing education of nursing, especially the application of various online education methods, breaking the original classroom teaching methods and emphasizing autonomous learning. Online education, as an extended mode of information distance education, effectively solves the requirements of traditional education mode for time and place. At the same time, online education pays more attention to students' autonomy, and it can also mobilize the classroom atmosphere. And online education has a variety of learning courses, with a wider knowledge coverage, which can better meet the on-the-job nurses' willingness to improve themselves through learning and make learning more efficient [20]. The survey found that most nurses can accept online education to complete on-the-job training, and support the application of online learning to on-the-job continuing education training. Online education can be used as a supplement to continuing education for working nurses and has been shown to be an effective alternative to nurse training. Teachers set clear learning and training tasks according to teaching goals, guide students to discover and analyze problems, and stimulate students' interest in learning; a massive network of teaching resources stimulates students' learning motivation so that students form the habit of autonomous learning and active exploration. In the process of knowledge transmission before class and knowledge expansion after class, students need to make learning plans according to the teaching objectives, and in the process of understanding and mastering the learning content [21]. This method can help nurses gradually develop the learning quality of independent thinking and active inquiry so that they can independently and effectively manage time and monitor the learning effect, and promote the improvement of self-monitoring ability. In the classroom learning process, it is necessary to fully understand the difficulties of knowledge, and fully review and review the knowledge that has been learned. By implementing the case teaching method, discussion teaching method, and group collaboration, group members can form a positive and stable team and establish a harmonious cooperative relationship, to improve the learner's team spirit, communication skills, and other nonintellectual factors. Due to its special working environment in the infectious disease department, nursing staff are in a high-risk working state for a long time, which seriously affects the physical and mental health of nursing staff and the quality of nursing work [22].

To sum up, nursing staff in the infection department had a greater demand for continuing education. Age, professional title, working life, professional title, hospital level, and marital status were the risk factors that affected their demand for continuing education. The deficiency of this study lies in the small sample size. In the future, the sample size can be expanded to further study nurses' demand for continuing education and its influencing factors.

Data Availability

The data can be obtained from the author upon reasonable request.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Retraction

Retracted: Study on the Changes and Significance of Immune State and Cycokines in Children with Adenovirus Pneumonia

Evidence-Based Complementary and Alternative Medicine

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[1] Y. Hou, J. Liu, Y. Li, and F. Chen, "Study on the Changes and Significance of Immune State and Cycokines in Children with Adenovirus Pneumonia," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2419454, 6 pages, 2022.

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Research Article

Study on the Changes and Significance of Immune State and Cycokines in Children with Adenovirus Pneumonia

Yue Hou, Jing Liu, Yanan Li, and Fang Chen

Department of Traditional Chinese Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China

Correspondence should be addressed to Fang Chen; cfedu417@163.com

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Objective. To observe the difference between peripheral blood T lymphocytes subsets and cycokines in children with severe adenovirus pneumonia and nonsevere adenovirus pneumonia, and to investigate their clinical value in the prognosis of severe pneumonia. *Methods*. 215 children with adenovirus pneumonia and 30 healthy volunteers (which was set as the control group) in our hospital from January 2017 to May 2019 were enrolled in the study. There were 47 children with severe pneumonia in the severe group and 168 nonsevere pneumonia children in the nonsevere group. The flow cytometry and ELISA methods were used to detect the serum levels of CD_3^+, CD_4^+, CD_8^+ T cells and interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ). *Results*. (1) The levels of CD_3 (%) T cells, CD_4 (%) T cells, and CD_4/CD_8 ratio values of children with adenovirus pneumonia were lower than these of normal children ($P < 0.05$). And the levels of CD_3 (%) T cells, CD_4 (%) T cells, and CD_4/CD_8 ratio values of children in the severe group were lower than these of children in the nonsevere group ($P < 0.05$). (2) The levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ values of children with adenovirus pneumonia were lower than these of normal children ($P < 0.05$). And the levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ of children in the severe group were higher than these of children in the nonsevere group ($P < 0.05$). (3) Among the 47 children with severe adenoviral pneumonia, 39 received systematic treatment in our hospital. According to the treatment effect, 39 children were divided into the effective group ($n = 25$) and the ineffective group ($n = 14$). (4) The CD3 (%), CD4 (%), and CD4/CD8 ratios of the children in the effective group were higher than those in the ineffective group ($P < 0.05$). (5) The levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ in the effective group were lower than those in the ineffective group ($P < 0.05$). *Conclusion*. The immunophenotype of peripheral blood T lymphocytes and cycokines could be helpful to judge the severity of adenovirus pneumonia, which could be used as the objective indexes to evaluate the prognosis of children with severe adenovirus pneumonia.

1. Introduction

Adenovirus is one of the most important pathogens causing severe pneumonia in children, and it is easy to cause multisystem complications. It is one of the main causes of death of an infant under 2 years old [1], which greatly increases the social medical burden. The onset of adenovirus pneumonia is acute, usually manifesting obvious symptoms of pneumonia 4-5 days after fever, and the course of the disease can be prolonged for several months, which can eventually lead to bronchiectasis, chronic obstructive pulmonary disease, and even death. However, due to the lack of typical clinical indications in the early stage, severe pneumonia can only be diagnosed when typical severe hypoxia, sepsis, and multiple organ dysfunctions occur, resulting in a high mortality rate in children [2]. Therefore, it is very important to find sensitive biomarkers to reflect the degree of disease progression as soon as possible and objectively for clinical individualized treatment and improving the prognosis of children with adenovirus pneumonia. As early as the 1970s, some scholars proposed that the lung tissue damage caused by adenovirus may be involved in immunological mechanisms [3]. In addition, adenovirus infection also involves a variety of inflammatory cells and inflammatory mediators. Chemokines and cytokines are the most important messengers of the immune system and play

an important role in maintaining the balance of immune responses [4]. If an immune imbalance occurs in the body, it may cause uncontrolled pulmonary inflammatory responses, resulting in multiple organ dysfunctions. This study intends to observe the immune typing of peripheral blood lymphocytes and differential changes in the levels of interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) in children with severe adenovirus infection to explore the infection mechanism of adenovirus from cytokine levels and whether it can help early diagnosis and prognosis prediction of severe adenovirus pneumonia. The research is reported as follows.

2. Materials and Methods

2.1. General Information. This study selected 215 children with pneumonia who were hospitalized in the Pediatrics Department of our hospital from January 2017 to May 2019. They were admitted to the hospital due to fever, cough, shortness of breath, chest tightness, dyspnea and other reasons. Among them, 126 were male and 89 were female, ranging in age from 2 months to 8 years, with an average age of (39.27 ± 10.62) months. Inclusion criteria: (1) Admission to the hospital within 3 days of acute onset; (2) Age $\leq$ 8 years old; (3) Meet the relevant diagnostic criteria of adenovirus pneumonia, the child developed acute fever, accompanied by respiratory, nervous, digestive and circulatory symptoms, their adenovirus was detected by respiratory immunofluorescence technique, the antigen was positive and/or the adenovirus PCR was positive [5]; (4) Complete clinical data and treatment process. Exclusion criteria: (1) Associated with other respiratory diseases such as bronchial asthma, pulmonary *tuberculosis*, malignant tumor; (2) Associated with definitely diagnosed immune system diseases; (3) Took glucocorticoids or immunosuppressants for nearly 3 months. According to the diagnostic criteria for severe pneumonia in the Guidelines for the Management of Community-Acquired Pneumonia in Children (2013 Revised Edition) issued by the Respiratory Group of the Pediatric Branch of the Chinese Medical Association in 2013 [6], they are divided into the severe group ($n = 47$) and the nonsevere group ($n = 168$) according to the severity of their illness. Infants with an axillary temperature greater than 38.5 C, poisoning symptoms, repeated high fever, more than 70 breaths per minute, older infants with a temperature greater than 38.5 C, and more than 50 breaths per minute, or complicated with any one of multiple organ function impairment, heart failure, respiratory failure, and shock, all of which can be considered as severe pneumonia.. In addition, 30 healthy children (whose age and gender ratio were matched with those of children with severe pneumonia) from the Pediatrics Department of our hospital during the same period were selected as the control group. This study complies with medical ethics requirements, and informed consent was signed by the families of the patients. There was no significant difference in general clinical data such as age, gender composition, and premature infants among the three groups ($P > 0.05$), as shown in Table 1.

2.2. Treatment. All the enrolled children were treated with antiviral therapy after admission and kept the airway open; children with bacterial infections need to be treated with antibiotics, and comprehensive supportive treatment was given according to the symptoms of the children, such as oxygen inhalation, sedation, and fever reduction, relieving spasm and asthma, relieving panic and protecting the organs, actively responding to the accompanying complications, and giving mechanically assisted ventilation to critically ill children.

2.3. Detection Indicators. Collection of blood samples: Blood samples of all the enrolled children were taken the next day after admission, 2 mL of fasting venous blood from children in the morning was aseptically drawn by pediatric professional nurses, and centrifuged at 3000 r/min for 10 min. The serum was taken and stored in a −80°C refrigerator for testing.

Detection of T cell subsets determined by flow cytometry. We added 100 μL of anticoagulant and 20 μL of RD1-CD_4, ECD-CD_8, and PE-CD_3 fluorescently labeled monoclonal antibodies and isotype control antibodies. We added 500 μL of hemolysin and acted for 20 min at room temperature in the dark. After lysing the red blood cells, we added a fixative for fixation. The proportion of positively expressed cells was calculated by MultiSET software, the negative control was used as the background parameter, the fluorescence compensation was adjusted, and the positive parameter value was set to obtain the proportion of each lymphocyte subsets CD_3, CD_4, and CD_8 and calculate the CD_4/CD_8 ratios. The MultiTEST kit was provided by BD Company in the United States.

Detection of inflammatory factors-related indicators (IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ) were detected by the ELISA antibody double sandwich method. Took out the kit and specimen from the refrigerator 20 minutes in advance and equilibrate to room temperature. We shook all reagents well before use and diluted the standards to different concentrations. We added the samples and standards of different concentrations (100 μL per well) to the corresponding wells and mark them. We strictly followed the operating instructions for testing and duplicated wells for samples (including standards) and blank wells. ELISA detection kits were purchased from Shanghai Jimian Industrial Co., Ltd.

2.4. Statistical Processing. The data were input into SPSS17.0 statistical software for processing and analysis; the measurement data were expressed as ($\overline{\chi} \pm s$); the data between two groups were compared by t-test; the data comparison between multiple groups was analyzed by one-way ANOVA; and the enumeration data were expressed as (%), and χ^2 test was used. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Comparison of Immune Typing of Peripheral Blood Lymphocytes in Children Tested. Comparing the peripheral blood CD_3 (%), CD_4 (%), and CD_4/CD_8 ratios of the three

Table 1: Analysis of general data of the selected children average age.

Group	Number of children (cases)	Average age ($\chi \pm s$, month)	Gender (cases)		Preterm infants [cases (%)]	Age ≤ 12 months [cases (%)]
			Male	Female		
Control group	30	37.73 ± 9.86	16	14	2 (6.67)	7 (23.33)
Severe group	47	38.29 ± 9.49	32	15	7 (14.89)	18 (38.30)
Nonsevere group	168	39.81 ± 9.05	94	74	17 (10.12)	48 (28.57)
F/χ^2	—	0.592	2.519		1.444	2.344
P value	—	0.554	0.284		0.486	0.310

Table 2: Comparison of immune typing of peripheral blood T lymphocytes in children ($\overline{\chi} \pm s$).

Group	Number of children (cases)	CD_3 (%)	CD_4 (%)	CD_8 (%)	CD_4/CD_8
Control group	30	67.27 ± 4.91	35.72 ± 3.79	24.45 ± 3.17	1.45 ± 0.18
Severe group	47	54.33 ± 5.26[a]	20.03 ± 5.14[a]	21.56 ± 2.91[a]	0.96 ± 0.22[a]
Nonsevere group	168	63.82 ± 6.37[ab]	31.19 ± 3.96[ab]	23.82 ± 3.40[b]	1.36 ± 0.21[ab]
F	—	8.859	9.512	5.228	7.041
P value	—	0.000	0.000	0.002	0.000

Note: Compared with the control group, [a]$P < 0.05$; compared with the severe group, [b]$P < 0.05$.

Table 3: Comparison of immune typing of peripheral blood T lymphocytes in children (pg/mL, $\overline{\chi} \pm s$).

Group	Number of children (cases)	IL-2	IL-4	IL-6	IL-10	TNF-α	IFN-γ
Control group	30	4.18 ± 2.33	2.54 ± 0.74	8.29 ± 2.67	8.41 ± 1.19	1.35 ± 0.67	2.84 ± 1.13
Severe group	47	94.25 ± 19.64[a]	2.62 ± 0.68	67.61 ± 10.23[a]	25.78 ± 6.34[a]	7.72 ± 2.50[a]	28.96 ± 9.49[a]
Nonsevere group	168	23.71 ± 6.95[ab]	2.55 ± 0.65	19.48 ± 5.11[b]	15.20 ± 4.72[ab]	2.41 ± 1.08[b]	11.27 ± 4.25[ab]
F		1001.219	0.221	1257.006	135.728	284.715	260.205
P value		0.000	0.802	0.000	0.000	0.000	0.000

Note: Compared with the control group, [a]$P < 0.05$; compared with the severe group, [b]$P < 0.05$.

groups of children, the variance analysis showed that the difference was statistically significant ($P < 0.05$). Compared with the control group, the CD_3 (%), CD_4 (%), and CD_4/CD_8 ratios of the children with adenovirus pneumonia were lower, Moreover, the peripheral blood CD_3 (%), CD_4 (%), CD_8 (%), and CD_4/CD_8 ratios of the children in the severe group were lower than those in the nonsevere group, as shown in Table 2.

3.2. Comparison of Peripheral Blood Cytokine Levels in Children. The serum levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ were compared among the three groups, and the variance analysis showed that the differences were statistically significant ($P < 0.05$). Compared with the control group, the levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ in the children with adenovirus pneumonia were increased, and the levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ of the children in the severe group were higher than those in the nonsevere group. In addition, the levels of IL-4 in the peripheral blood of the three groups of children were basically the same, and the difference was not statistically significant ($P > 0.05$), as shown in Table 3.

3.3. Treatment Results of Children with Severe Adenovirus Pneumonia. All children with severe adenovirus pneumonia were hospitalized for 7–45 days, with an average hospitalization of (18.43 ± 9.04) days. Among 47 children with severe adenoviral pneumonia, 39 children were treated with an auxiliary ventilator, and 8 children were not cured and discharged (their parents gave up treatment). The prognosis of 39 treated children after discharge is as follows There were 17 patients (43.59%) and 8 patients (20.51%) who were clinically cured and clinically improved, respectively, which were regarded as the effective treatment group, 14 cases (35.90%) were unhealed and died, regarded as the ineffective treatment group.

3.4. Differences in Immune Typing of Peripheral Blood Lymphocytes of Severe Adenovirus Pneumonia Children with Different Treatment Results. The CD_3 (%), CD_4 (%), and CD_4/CD_8 ratios of children with severe adenovirus pneumonia in the effective group and the ineffective group were compared. The CD_3 (%), CD_4 (%), and CD_4/CD_8 ratios of the children in the effective group were higher than those in the ineffective group, the difference was statistically significant ($P < 0.05$). There was no significant difference in peripheral blood CD_8 (%) between the two groups ($P > 0.05$). See Table 4.

3.5. Comparison of Peripheral Blood Cytokine Levels of Severe Adenovirus Pneumonia Children with Different Treatment Results. The levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ were compared between the effective group and the ineffective group. The levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ in the effective group were lower than those in the ineffective group, the difference was statistically significant

Table 4: Comparison of immune typing of peripheral blood T lymphocytes in severe adenovirus pneumonia children with different treatment results ($\overline{\chi} \pm s$).

Group	Number of children (cases)	CD_3 (%)	CD_4 (%)	CD_8 (%)	CD_4/CD_8
Effective group	25	59.24 ± 2.35	22.56 ± 2.49	21.76 ± 1.73	1.03 ± 0.12
Ineffective group	14	53.16 ± 2.71	19.02 ± 1.28	21.28 ± 2.20	0.92 ± 0.15
t	—	7.337	4.946	0.754	2.509
P value	—	0.000	0.001	0.456	0.017

Table 5: Comparison of peripheral blood cytokine levels of severe adenovirus pneumonia children with different treatment results (pg/mL, $\overline{\chi} \pm s$).

Group	Number of children (cases)	IL-2	IL-4	IL-6	IL-10	TNF-α	IFN-γ
Effective group	25	80.78 ± 9.69	2.68 ± 0.61	61.45 ± 12.38	22.17 ± 6.17	6.46 ± 1.53	19.58 ± 7.67
Ineffective group	14	108.92 ± 17.16	2.51 ± 0.48	73.22 ± 9.25	30.67 ± 4.33	10.02 ± 1.93	29.38 ± 7.96
t	—	6.575	0.897	3.099	4.553	6.343	3.777
P value	—	0.000	0.376	0.004	0.000	0.000	0.001

($P < 0.05$). There was no significant difference in peripheral blood IL-4 levels between the two groups ($P > 0.05$). See Table 5.

4. Discussion

Adenovirus is a double-stranded DNA virus first isolated from tonsil tissue. It is one of the most common pathogens that cause respiratory tract infections in children. One-third of children with adenovirus pneumonia may develop into severe pneumonia; it is easy to combine with multisystem complications and has a high mortality rate [7]. In this study, 215 children with adenoviral pneumonia hospitalized in the respiratory department and PICU of our hospital were randomly selected, of which 47 were severe children, and the incidence of severe pneumonia was 21.86%. Moreover, most of the children were aged less than 1 year, which may be related to the lack of adenovirus-specific antibodies and low immunity in children of this age. Because most children only show clinical symptoms such as fever and cough in the early stage of adenovirus infection, a small number of children will have shortness of breath, wheezing, cyanosis, etc., and pulmonary signs often appear later, and wet rales and pulmonary consolidation signs may appear after 3 days. Therefore, most parents of children may not choose to seek medical treatment for the first time. Therefore, we chose children who sought medical treatment within 3 days of onset as the objects. The main pathological changes of adenovirus pneumonia are extensive necrosis of bronchial epithelial tissue and alveolar interstitial inflammation. In severe cases, it can lead to bronchial lumen occlusion and even lead to other system dysfunctions [8]. However, the virulence of adenovirus and its metabolites is very small. Especially in the early stage of infection, adenovirus has little effect on the survival of cells [8]. Only when the inclusion body develops to a late stage will it have a certain killing effect on the host cell. In addition, adenoviruses only parasitize in bronchial mucosal epithelial cells and lung epithelial cells [9], so relying solely on the killing effect of adenoviruses on parasitic host cells cannot explain the multiple organ damage caused by adenovirus pneumonia, especially severe pneumonia. Immunological mechanisms and cytokines may play a key role in this. Based on the author's years of clinical experience and numerous research conclusions, the damage caused by the inflammatory response caused by adenovirus pneumonia may be greater than the damage caused by the virus replication itself, which may be one of the main factors affecting the clinical severity of adenovirus pneumonia [10].

In this study, we first compared the differences in peripheral blood lymphocyte typing and cytokine levels between children with severe adenovirus pneumonia, children with nonsevere adenovirus pneumonia, and normal children, and planned to analyze the immunology and inflammatory response to investigate the pathogenesis of severe adenovirus pneumonia. The results of the study showed that compared with the normal control group and the nonsevere group, the peripheral blood CD_3 (%), CD_4 (%), CD_8 (%), and CD_4/CD_8 ratios of the severe group were decreased, while the inflammatory factors of IL-2, IL-6, IL-10, TNF-α, and IFN-γ increased. It is suggested that during the acute attack of adenovirus pneumonia, the functions of CD_4^+T cells to promote cellular immunity and humoral immunity were significantly inhibited, and the functions of CD_8^+T cells to inhibit the proliferation and differentiation of immune cells were also affected. However, unlike the children with severe adenovirus pneumonia, the CD_8^+ T cell activity in the nonsevere adenovirus children was not statistically different from that in the normal children, and the decrease in CD_3 (%), CD_4 (%), and CD_4/CD_8 ratios did not obviously, the degree of inhibition and cytotoxicity of T cells in children with nonsevere adenovirus pneumonia was less than that in children with severe adenovirus pneumonia. Mature T cells in peripheral blood are mainly CD_3^+ T cells, CD_4^+ T cells can be divided into helper T cell 1 (Th1) subsets and Th2 subsets, while Th1/Th2 imbalance is related to viral infection. The function of CD8+ T cells is to directly kill the target antigen, mainly belonging to cytotoxic T lymphocytes, and the normal CD_4/CD_8 ratio maintains a dynamic balance within a certain range, but under the condition of virus infection, the CD_4/CD_8 imbalance, leading to immune dysfunction and reduced immune defense [11]. The CD_3

(%), CD_4 (%), CD_8 (%), and CD_4/CD_8 ratios of adenovirus-infected children were all decreased, indicating that the body's immune function was significantly inhibited and the immune system was unbalanced, resulting in adenovirus evasion of T lymphocyte-mediated immune attack. In addition, this study also found that the proportion of T lymphocyte subsets in children with severe adenovirus pneumonia was also closely related to prognosis. The immune function of the children in the severe group declined more seriously, resulting in continued uncontrolled infection.

In addition, cytokines secreted by T lymphocytes also play an important role in immune regulation. At present, the relatively mature T cells secreting cytokines are the Th1 subset and Th2 subset [12]. Th1 cells mainly secrete IL-2 and IFN-γ to mediate cellular immune responses, while Th2 cells mainly secrete IL-4, IL-6, IL-10, and other factors to mediate humoral immune responses [13]. IL-2 is the most active T cell growth factor at present, IFN-γ is a bridge connecting innate immunity and adaptive immunity and can also enhance the antiviral effect of type I interferon, which can promote the immune function of the body after virus infection recovery. In this study, the levels of inflammatory factors such as IL-2 and IFN-γ in the severe group were higher than those in the control group and nonsevere group, which may be related to the feedback regulation of inflammatory factors. IL-6 and IL-10 are a class of cellular inflammatory factors secreted by Th2 cells, macrophages, vascular endothelial cells, etc., which can inhibit the activation of Th1 cells and feedback regulate the release of various cytokines including IL-2 and IFN-γ [14]. IL-4 belongs to a class of typical chemokines that can mediate T cell activation and has certain antiviral effects [15]. However, in this study, the levels of IL-4 in peripheral blood of the three groups are basically the same, and the test results are not statistically significant, which may be due to the small sample size. In addition, TNF-α is secreted by activated macrophages, NK cells, and T cells and is involved in the initiation of inflammatory responses and the regulation of immune responses. The increased TNF-α level leads to the infiltration of local inflammatory cells and the release of inflammatory mediators, which is closely related to the severity of the inflammatory response, and high levels of cytokines, such as IL-2 and IFN-γ, can promote the secretion of TNF-α by mononuclear macrophages [16, 17].

In conclusion, the peripheral blood CD_3 (%), CD_4 (%), CD_8 (%), and CD_4/CD_8 ratios of children with severe adenovirus pneumonia were decreased, while the levels of IL-2, IL-6, IL-10, TNF- α, IFN-γ, and other cytokines all increased, indicating that the immune function of the body was suppressed. Adenovirus can evade the attack of T lymphocytes by stimulating the secretion of various cytokines, thereby strengthening the inflammatory response and causing damage to lung tissue. In addition to confirming that T cell subsets and cytokines such as IL-2, IL-6, IL-10, TNF-α, and IFN-γ are related to the severity of adenovirus pneumonia, this study is also expected to be a potential indicator for predicting the prognosis of children with severe adenovirus pneumonia.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest, financial or otherwise.

Acknowledgments

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Retraction

Retracted: Investigation on Depression of College Students Majoring in Physical Education and Nonphysical Education: A StudyBased on the Age Region and Gender of 374 Students

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] X. Ding and N. Tang, "Investigation on Depression of College Students Majoring in Physical Education and Nonphysical Education: A StudyBased on the Age Region and Gender of 374 Students," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 9106594, 5 pages, 2022.

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Research Article

Investigation on Depression of College Students Majoring in Physical Education and Nonphysical Education: A Study Based on the Age Region and Gender of 374 Students

Xiaofen Ding[1] and Nian Tang[2]

[1]*School of Physical Education, Hunan First Normal University, Changsha 410205, Hunan, China*
[2]*College of Physical Education, Huzhou University, Huzhou 314000, Zhejiang, China*

Correspondence should be addressed to Nian Tang; tangnian@zjhu.edu.cn

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In the research on the relationship between depression and college students' major, there are some differences in the degree of depression between sports major and nonsports major students. Based on these results, we assume that there is the possibility of emotional differences between professional and nonprofessional sports. A total of 374 samples of students majoring in physical education and nonphysical education at the same university were analyzed by using the methods of literature review and data analysis. A total of 188 subjects, including 121 males and 253 females (186 majoring in sports and nonsports), were asked to fill in the SDS (Self-Rating Depression Scale). SDS is widely used in rough screening, emotional state evaluation, investigation, and scientific research of outpatients in clinical psychology departments. The research obtained the difference in depression degree in the whole sample and further compared the depression degree of students of different ages and native places. Statistical analysis was performed on all data using SPSS 23.0 software. Basic data description, paired chi-square analysis, and covariance analysis were used. The results show that in this sample, the maximum value (minimum/maximum value) of one item of the total depression score of nonphysical education students exceeds the average value by 3 standard deviations, and this shows that the general level of depression scores of non-PE majors is high; most non-PE majors are in mild depression, which is equal to the number of PE majors who are in a normal mood; and nonsports majors in cities are more likely to have mild depression.

1. Introduction

Depression has become a more prevalent mental illness than many people imagine [1], with core symptoms of marked and persistent sadness [2], loss of interest, and lack of energy [3]. Suicide is one of the most serious consequences for people with depression and has become the second leading cause of death among young people aged 15–29 years [4, 5]. The population at this age, most of which are in the student stage, especially college students, is the main component [6].

College students with depression usually felt hopeless and helpless [7], and adverse childhood experiences (ACEs) were recognized as long-distance risks of depression in adulthood [8, 9]; smartphone addiction [10, 11] and epidemic [12, 13]are also important causes of depression among college students, depression and race of college students [14], gender [15], and professional [16, 17].

A cross-sectional study has been widely used in studies related to depression and college students' majors [18–20]. There is a difference in the degree of depression between sports majors and nonsports majors. The incidence of depression among nonsports majors is significantly higher than that of sports majors [21]. Students who major in physical education are active, enthusiastic, and energetic. Regular physical exercise can effectively reduce the risk of depression [22]. Physical exercise and suicide behavior were negatively correlated, and the frequency of physical exercise had the greatest effect, followed by the duration and intensity of physical exercise [23].

Compared with college students who do not often engage in sports dancing, college students who often practice sports dancing are less prone to depression [24]. The combination of life and death education (LDE) and dance exercise therapy (DMT) can prevent and relieve depression in college students. We assume that there is the possibility of emotional differences between professional and nonprofessional sports. In the study of the relationship between depression and college students' major, there is a certain difference in the degree of depression between sports major and nonsports major students. On this basis, using the method of literature and data analysis, the paper analyzes the sample of 374 sports and nonsports major students at the same university. A total of 188 subjects, including 121 males and 253 females (186 sports and nonsports majors), were required to fill in the SDS. SDS is widely used in screening, emotional state evaluation, investigation, and scientific research of outpatients in clinical psychology departments. The study revealed differences in depression levels across the sample and further compared the levels of depression among students of different ages and origins.

2. Objective and Methods

2.1. General Description. A total of 374 college students (121 males and 253 females, including 186 PE majors and 188 non-PE majors) in Hunan First Normal University were investigated using the self-rating depression scale (SDS). We will publish the questionnaire online, please fill in the questionnaire at the link. A total of 488 copies were received. After screening, the anonymous questionnaire that was filled in less than one minute was deleted, and 374 people remained. SDS has been widely used in clinical psychology all over the world. After more than 20 years of localized revision in China, it has been applied to the rough screening of outpatients in clinical psychology departments, as well as the assessment and general investigation of adult emotional states, and has also been widely used in scientific research.

2.2. Statistical Analysis. Statistical analysis was performed on all data using SPSS 23.0 software. Basic data description, paired chi-square analysis, and covariance analysis were used.

3. Results and Discussion

Table 1 provides the analysis of the basic situation of PE major students and non-PE major students, including the students' native place and gender. Table 1 shows that more than 50% of the samples are "rural" in terms of the native regions of PE students. In addition, the proportion of urban samples is 41.40%. The proportion of "female" in the sample was 57.53%. The proportion of male samples was 42.47%. From the perspective of non-PE major students' native regions, more than 50% of the samples are "rural." The proportion of urban samples is 44.15%. The proportion of "women" is 77.66%.

All the samples were investigated with Zun's depression questionnaire, and the scores were calculated. Describe the overall situation of the data according to the mean or median of two groups: PE students and non-PE students. It could be seen from Table 2 that the maximum value of the total depression score of non-PE majors in one item exceeded the average value by 3 standard deviations, indicating that the data fluctuated greatly. Compared with the average value, the median was more suitable for describing the overall level. The maximum (minimum/maximum) of the total depression scores of non-PE majors in one item of data exceeded the average by 3 standard deviations. This indicates that the overall level of the depression total score of non-PE major students is higher.

According to the results of the Chinese norm, the demarcation value of the SDS standard score was 53 points, of which 53–62 points were classified as mild depression, 63–72 points as moderate depression, and above 73 points as severe depression. The sample score is judged according to the standard.

Table 3 shows that the paired chi-square test is used to study the relationship between depression of PE major students and depression of non-PE major students. The number of categories compared in this pair was greater than 2 (i.e., paired multiclass), and therefore, the study was conducted using the Bowker test. Significant differences between paired data at the 0.05 level ($\text{chi} = 178.103$, $p \leq 0.001 < 0.05$) were noted. The mild depression of non-PE majors was the same as the normal mood of PE majors, as shown in Table 4.

This study explored the correlation between milder depressive emotions presented by nonphysical education majors and "region of origin" and "gender." Considering the potential interfering factors, the influence of "native place" on "depressed mood" and "age" and "gender" was likely to be the influencing factor, belonging to the interfering items. Therefore, it needs to be taken into account in the analysis. After analysis, the term of "gender" has no relationship with the term of "native place" for the term of "depressed mood," so it was excluded. We used covariance analysis, and the interference term, also known as the "covariate," is here the "age" term.

Table 5 shows the results of the parallelism test. In this case, only the significance of the interaction items should be concerned. The "Native area of non-PE major students * age of non-PE major students" in the table was the interaction term of independent variable x and covariate. The data results showed that through the parallelism test ($F = 0.041$, $P = 0.072 > 0.05$), the premise assumption of covariance analysis was met, and thus, it indicated that covariance analysis could be further conducted.

Table 6 shows the results of the covariance analysis. The square value of R in the above table is 0.005, which means that the native place and geographical source of non-PE students can explain 0.5% of the mild depression of non-PE students. Further expand the mean comparison of native regions to get Table 7.

Table 7 shows that the average depression score of the sample of non-PE major from rural areas is 48.21, which is less than 49.07 of the urban groups, indicating that in this sample, the urban non-PE major students are more prone to mild depression.

Table 1: Basic information.

Name	Option	Frequency	Percentage (%)
Native place of sports major students ($n = 186$)	Rural area	109	58.60
	Urban area	77	41.40
Sports major student gender ($n = 186$)	Woman	107	57.53
	Man	79	42.47
Native place of non-PE major students ($n = 188$)	Rural area	105	55.85
	Urban area	83	44.15
Gender of non-PE major students ($n = 188$)	Woman	146	77.66
	Man	42	22.34

Table 2: Basic indicators.

Name	Sample size	Minimum value	Maximum	Average value	Standard deviation	Median
Total depression score of physical education major students	186	20.000	60.000	39.828	9.017	39.000
Total depression score of nonphysical education major students	188	27.000	79.000	48.590	6.417	48.000

Table 3: Paired chi-square analysis results.

match	Name	Depression among nonphysical education major students			Amount to	χ^2	P
		Moderate depression	Normal	Mild depression			
Depression of physical education major students	Normal	0	153	18	171	178.103	≤0.001**
	Mild depression	2	0	13	15		
	Moderate depression	0	0	0	0		
Amount to	2	153	31	186	—	—	—

* $p < 0.05$. ** $p < 0.01$.

Table 4: Comparison of depression among PE majors and non-PE majors.

	Depression of physical education major students		Depression among nonphysical education major students	
	n	Percentage	n	Percentage
Normal	171	91.94	2	1.08
Mild depression	15	8.06	153	82.26
Moderate depression	0	0.00	31	16.67
Summarize	186	100.00	186	100.00

Table 5: Parallelism test of covariance analysis.

Difference source	Sum of squares	df	Mean square	F	P
Intercept	3041.268	One	3041.268	74.385	≤0.001**
Area of origin of non-PE major students	122.760	One	122.760	3.003	0.085
Age of non-PE major students	1.673	One	1.673	0.041	0.840
Area of origin of non-PE major students ∗ age of non-PE major students	134.245	One	134.245	3.283	0.072
Residual	7522.915	184	40.885		

R^2, 0.023. * $p < 0.05$.** $p < 0.01$.

Table 6: Covariance analysis results.

Difference source	Sum of squares	*df*	Mean square	*F*	*P*
Intercept	3881.870	One	3881.870	93.788	≤0.001**
Area of origin of non-PE major students	29.152	One	29.152	0.704	0.402
Age of non-PE major students	7.797	One	7.797	0.188	0.665
Residual	7657.160	185	41.390		

R^2, 0.005. $^*p < 0.05$.$^{**}p < 0.01$.

Table 7: Native areas of non-PE major students.

Item	Average value	Standard deviation	*n*
Rural area	48.21	7.08	105
Urban area	49.07	5.47	83

4. Conclusions

In this sample, the following conclusions are made:

(1) The maximum (minimum/maximum) of the total depression score of non-PE students exceeds the average by 3 standard deviations. This indicates that the overall level of the depression total score of non-PE major students is higher.

(2) Most of the nonphysical education students were in mild depression, and the number of these nonphysical education students was the same as that of the normal students.

(3) Urban non-PE majors were more likely to have mild depression.

5. Discussion

We assume that there is the possibility of emotional differences between students majoring in physical education and nonphysical education majors. In the study of the relationship between depression and college students' majors, there are some differences in the degree of depression between physical education majors and nonphysical education majors.

Obviously, the innovation of the research still needs to be improved. As a cross-sectional study, we only discussed the situation of a sample in a university. In this sample, most of the nonphysical education majors were in mild depression, and the number of these nonphysical education majors was the same as those in normal mood. This may be due to significant data bias. Because there are twice as many women as men in this sample, and in a previous 17-year-old study of depression among Chinese college students, women were more likely to be depressed [25], so there is such a significant difference.

It should also be noted that urban non-PE majors were more likely to have mild depression. This is inconsistent with the existing research reports in academic circles in China and Western countries [26, 27]. Previous studies found that rural college students were more likely to commit suicide, and depression was the root cause of suicide. The reason for this is that we may use a cross-sectional design, and the sample size is too small for our student sample to represent the sample of college students from other universities in China. We cannot exclude unmeasured confounding factors at this time. The sample size can be further expanded in future studies to explore the reasons for this situation.

Data Availability

The data used to support the findings of this study are included within the supplementary file.

Ethical Approval

When the research questionnaire is distributed, the purpose, social value, and benefit of the research are informed in the lead of the questionnaire. There is also the scope of collected information, risks that may involve privacy, and treatment measures. They left the signatures and contact information of the researchers and the institutions they rely on. If the residents surveyed agree to fill out the questionnaire, fill it out and submit it. If residents do not agree to be investigated, they refuse to fill out the questionnaire.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

XD conceptualized and designed the study and wrote the manuscript NT read and revised the manuscript and contributed to project management. XD collected and analyzed data. All authors approved the submitted version.

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Supplementary Materials

Raw data for the analysis. (*Supplementary Materials*)

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Research Article

Therapeutic Effects of the Proximal Femoral Nail for the Treatment of Unstable Intertrochanteric Fractures

Yuwei Cai,[1] Wenjun Zhu,[1] Nan Wang,[2] Zhongxiang Yu,[1] Yu Chen,[1] Shengming Xu,[1] and Juntao Feng[1]

[1]*Department of Orthopedics, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200120, China*
[2]*Department of Traditional Chinese Medicine, Shanghai YangZhi Rehabilitation Hospital (Shanghai Sunshine Rehabilitation Center), School of Medicine, Tongji University, Shanghai 201619, China*

Correspondence should be addressed to Shengming Xu; smmu2004@126.com and Juntao Feng; fengjuntao101125@163.com

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Objective. The aim of this study was to analyze the clinical effect of the proximal femoral nail on elderly patients with unstable intertrochanteric fracture and the effect of the proximal femoral nail on serum levels of matrix metalloproteinases (MMPs) and osteoprotegerin (OPG). *Methods*. The elderly patients with unstable intertrochanteric fracture of the femur admitted to our hospital from January 2017 to January 2021 were studied. 100 patients were randomly divided into two groups: the control group ($n = 50$) and the observation group ($n = 50$). The patients in the control group were treated with a proximal femoral locking compression plate. The patients in the observation group were treated with the proximal femoral antirotation intramedullary nail. The clinical therapeutic effects of the two groups and the changes in serum MMPs and OPG levels before and after treatment were analyzed. *Results*. Compared with the control group, the operation time, postoperative landing time, and fracture healing time of the observation group were significantly shortened, and intraoperative blood loss was significantly reduced ($P < 0.05$). Compared with the control group, the total effective rate of patients in the observation group was significantly higher ($P < 0.05$). After treatment, the levels of CRP, IL1β, IL2, MMP-2, MMP-6, TIMP-1, and RANKL decreased significantly in both groups ($P < 0.05$), while the levels of OPG increased significantly ($P < 0.05$). Compared with the control group, the changes in the above indexes were more obvious in the observation group ($P < 0.05$). *Conclusion*. The proximal femoral antirotation intramedullary nail has a better therapeutic effect on elderly patients with unstable intertrochanteric fracture, and the level of MMPs and OPG may be related to the treatment process.

1. Introduction

Intertrochanteric fractures of the femur are common surgical fractures with high morbidity rates [1, 2]. In order to improve the mobility of the lower extremities and improve the prognosis of patients, patients with intertrochanteric fractures should receive immediate surgery and actively perform lower extremity functional exercises [3]. The proximal femoral anti-rotation intramedullary nail is a common method for the treatment of femoral intertrochanteric fractures, with the advantages of less trauma and easy operation [4]. Matrix metalloproteinases (MMPs) regulate the remodeling process of the extracellular matrix and are also widely involved in the process of bone tissue injury and healing [5]. The receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG) is a key signal transduction pathway of bone metabolism and is closely related to the pathological and physiological processes of bone tissue [6]. However, there is no relevant report on the level of MMPs during the treatment of elderly unstable intertrochanteric fractures with proximal femoral antirotation intramedullary nails. This study analyzed the

clinical effect of the proximal femoral antirotation intramedullary nail on elderly patients with unstable intertrochanteric fractures and the effect on serum levels of MMPs and OPG in order to provide a reference for clinical treatment.

2. Materials and Methods

2.1. Research Objects. Elderly patients with unstable femoral intertrochanteric fractures admitted to our hospital from January 2017 to January 2021 were selected as the research subjects. Inclusion criteria were as follows: all patients met the diagnostic criteria for unstable intertrochanteric fractures [7] and were diagnosed by X-ray; there is a clear history of trauma; hip pain, swelling, lower extremity dysfunction; patient has severe lower extremity deformity and valgus, and local tenderness is obvious; clinical data are complete. Exclusion criteria are as follows: combined with severe bone disease; severe metabolic dysfunction; patients with concurrent malignant tumors; patients taking drugs that affect bone metabolism within the past 3 months; patients with incomplete clinical data or who disagree with this study. 100 patients were randomly divided into two groups according to the treatment method. Control group ($n = 50$): 24 males and 26 females; aged 61–72 years, mean 66.5 ± 8.5 years old; 28 patients with EvansIII (intertrochanteric fractures combined with greater trochanteric fractures with displacement, no posterolateral support, and comminuted posterior fracture); and 22 patients with EvansIV (combined lesser trochanter fracture with displacement and no medial support). Observation group ($n = 50$): 23 males and 27 females; aged 61–72 years, mean 66.8 ± 8.8 years old; 29 patients with EvansIII; and 21 patients with EvansIV. There was no statistical difference in general data such as gender and average age between the two groups ($P > 0.05$).

2.2. Treatment Methods. The patients in the control group were treated with the proximal femoral locking compression plate. The patients were in a supine position, continuous epidural anesthesia was administered, a soft pillow was placed on the affected buttocks, and the surgical incision was selected at 2.9 ± 1 cm above the apex of the greater trochanter, extending laterally. Separate the skin and subcutaneous tissue of the patient, expose the fracture end, use Kirschner wire fixation after satisfactory reduction and traction, insert screw-type screws through C-arm fluoroscopy, lock the screws at the distal end, and move the affected limb.

The patients in the observation group were treated with the proximal femoral antirotation intramedullary nail. The patients were in a supine position, continuous epidural anesthesia was administered, adduction of the affected limb about 15° in neutral position, reduction under C-arm fluoroscopy, and longitudinal incision about 1 cm above the greater trochanter, and an open 5.5 ± 0.5 cm. The needle was placed at the apex of the tuberosity, and after reaming, the proximal antirotation intramedullary nail was inserted and screwed into the helical blade and distal locking nail.

2.3. Observation Indicators and Methods

2.3.1. Analysis of Clinical Treatment Effect of the Two Groups of Patients. In this study, the operation time, intraoperative blood loss, postoperative landing time, and fracture healing time of the two groups of patients were analyzed, and the total effective rate of the treatment was also analyzed. The treatment effect is divided into four categories. Cure: at the follow-up after 12 months of treatment, the Harris score of the hip joint of the patient is more than 90 points. Significant effect: at the follow-up after 12 months of treatment, the Harris score of the hip joint of the patient is more than 80 points. Valid: at the follow-up after 12 months of treatment, the Harris score of the hip joint of the patient is more than 70 points. Invalid: at the follow-up after 12 months of treatment, the Harris score of the hip joint of the patient is not more than 70 points. Total effective rate = (cure + significantly effect + valid)/total number of cases × 100%.

2.3.2. Biochemical Index Analysis. Before and after treatment, 5 ml of fasting venous blood was collected in the morning. Serum MMPs (including MMP2, MMP6, and its inhibitor TIMP1), RANKL/OPG levels, CRP, Interleukin (IL)1β, and IL2 before and after treatment were analyzed by enzyme-linked immunosorbent assay. MMP2 and MMP6 detection kits were purchased from Cell Signaling. TIMP1 detection kit was purchased from R&D company. RANKL detection kit was purchased from Santa Cruz company. The OPG, CRP, IL1β, and IL2 detection kit was purchased from Abcam Company. All detection operations were performed in accordance with the kit instructions.

2.3.3. Patient Follow-Up. All patients were followed up for more than 12 months. After discharge, the patients were investigated by telephone and clinic every 2 months, and the complications of patients during this period were counted.

2.4. Statistical Analysis. SPSS 20.0 statistical software was used to analyze the data. Measurement data were expressed as mean ± standard deviation ($\overline{x} \pm s$), t-test was used for comparison between the two groups, count data was expressed as percentage, and the chi-square test was used for comparison between the two groups. $P < 0.05$ means the difference is statistically significant.

3. Results

3.1. Analysis of the Surgical Conditions of the Two Groups of Patients. The study found that compared with the control group, the operation time, postoperative landing time, and fracture healing time of the observation group were significantly shortened, intraoperative blood loss was significantly reduced, and the difference between the two groups was statistically significant ($P < 0.05$), as shown in Table 1.

3.2. Analysis of the Improvement Effect of Hip Joint Function in the Two Groups of Patients. The study found that compared

Table 1: Analysis of the surgical conditions of the two groups of patients.

Group	n	Operation time (min)	Intraoperative blood loss (ml)	Postoperative landing time (d)	Fracture healing time (weeks)
Control group	$n = 50$	78.43 ± 10.44	116.56 ± 12.56	10.43 ± 1.43	13.34 ± 3.21
Observation		49.56 ± 9.56^a	97.21 ± 8.48^a	6.68 ± 1.90^a	11.19 ± 3.09^a
Groupt	$n = 50$	1.865	2.334	1.762	1.856
P		<0.05	<0.05	<0.05	<0.05

Note. Compared with the control group, $^aP<0.05$.

with the control group, the total effective rate of patients in the observation group was significantly higher, and the difference between the two groups was statistically significant ($P < 0.05$), as shown in Table 2.

3.3. Changes of Serum MMPs Levels in the Two Groups of Patients before and after Treatment. The study found that there was no statistical difference in the levels of MMP2, MMP6, and TIMP1 between the two groups before treatment ($P > 0.05$). After treatment, the levels of MMP2, MP6, and TIMP 1 in the two groups of patients were lower than those before treatment, and compared with the control group, the decreases in the observation group were more significant ($P < 0.05$), as shown in Table 3.

3.4. Changes of Serum RANKL/OPG Levels in the Two Groups of Patients before and after Treatment. The study found that there was no significant difference in RANKL/OPG between the two groups before treatment ($P > 0.05$). After treatment, OPG level in two groups increased, while RANKL level decreased. Compared with the control group, the change trend in the observation group was more significant ($P < 0.05$), as shown in Table 4.

3.5. Changes of Serum Interleukin and C-Reactive Protein Levels in the Two Groups of Patients before and after Treatment. The study found that there was no significant difference in the levels of CRP, IL1β, and IL2 between the two groups before treatment ($P > 0.05$), and the above indicators were significantly decreased after treatment ($P < 0.05$), and compared with the control group, the above indicators of the observation group were decreased more significantly ($P < 0.05$), as shown in Table 5.

3.6. Complications. No serious complications occurred in the two groups after treatment.

4. Discussion

Elderly unstable femoral intertrochanteric fracture is a common clinical disease and frequently occurring disease, which brings a heavy burden to patients and families. Currently, surgery is usually used for the treatment of femoral intertrochanteric fractures. In this study, it was found that the clinical effect of the proximal femoral antirotation intramedullary nail was better. It is suggested that the proximal antirotation intramedullary nail has a good therapeutic effect on elderly patients with unstable femoral intertrochanteric fracture, and the recovery of MMP and OPG/RANKL levels may be related to the treatment process. Although it is generally believed that proximal femoral anti-rotation intramedullary nails and locking compression plates affect the efficacy of unstable intertrochanteric fractures mainly due to biomechanical rather than biological factors, through this study we confirmed that biological factors, especially changes in the levels of MMPs and their inhibitors, may be involved in the above-mentioned treatment process.

The abnormal expression of MMPs and their inhibitors is involved in the pathological process of a variety of bone tissues and is closely related to the clinical treatment effects [8]. Many clinical medications for bone or joint diseases achieve their therapeutic effects by interfering with MMP levels. Both Polygonatum preparation and celecoxib can improve the joint function score of patients and knee joint function by reducing the content of MMP-13 in their serum, and the reduction of MMP-13 is also related to reducing inflammatory responses and protecting chondrocytes [9, 10]. Drug treatment of knee osteoarthritis can effectively reduce the levels of inflammatory factors such as serum metalloproteinases, thereby improving knee joint mobility and quality of life [11]. When calcitriol is used in the treatment of knee osteoarthritis, it can inhibit MMP by inhibiting MMP-1, MMP-3, and MMP-13 gene expression, thereby reducing the severity of arthritis in patients, reducing pain in patients, and improving the living conditions of patients [12]. This study also found that the levels of MMP2, MMP6, and their inhibitor TIMP1 were significantly reduced in the two groups after treatment, and compared with the control group, the above indicators in the observation group changed more significantly, suggesting that the better therapeutic effect of the proximal bone antirotation intramedullary nail on elderly patients with unstable intertrochanteric fractures may be related to the regulation of abnormal levels of MMPs. Therefore, in addition to the influence of biomechanical factors, biological factors, especially MMPs and their inhibitors, play a key role in the effect of the proximal femoral antirotation intramedullary nail and locking compression plate on the efficacy of unstable intertrochanteric fractures. However, the changes in the above cytokines in patients treated with the proximal femoral antirotation intramedullary nail were more obvious than in those treated with a locking compression plate. Although the changes of the above factors were analyzed in this paper, the regulatory pathways upstream of these factors have not been effectively explored. Future work will focus on the analysis of changes from upstream cytokines.

Table 2: Analysis of the improvement effect of hip joint function in the two groups of patients.

Group	n	Cured	Significantly effect	Valid	Invalid	Total efficiency (%)
Control group	50	17	10	18	5	45 (90.0%)
Observation group	50	22	14	13	1	49 (98.0%)
X^2						2.996
P						<0.05

Table 3: Changes of serum MMP levels in the two groups of patients before and after treatment.

Group		MMP2 (mg/L)	MMP6 (mg/L)	TIMP1 (mg/L)
Control group ($n = 50$)	Before treatment	34.52 ± 9.23	24.76 ± 5.60	23.65 ± 7.12
	After treatment	29.45 ± 7.09^{b}	19.78 ± 4.81^{b}	19.60 ± 4.65^{b}
Observation group ($n = 50$)	Before treatment	35.09 ± 10.11	25.01 ± 6.33	23.98 ± 8.33
	After treatment	25.53 ± 4.59^{ab}	14.54 ± 4.62^{ab}	14.36 ± 3.35^{ab}

Note. Compared with the control group in the same period, $^{a}P<0.05$; compared with before treatment, $^{b}P < 0.05$.

Table 4: Changes of serum RANKL/OPG levels in the two groups of patients before and after treatment.

Group		OPG (ng/L)	RANKL (ng/L)
Control group ($n = 50$)	Before treatment	301.33 ± 32.76	14.47 ± 3.88
	After treatment	335.76 ± 27.89^{b}	11.09 ± 4.21^{b}
Observation group ($n = 50$)	Before treatment	300.98 ± 19.88	15.01 ± 4.09
	After treatment	387.95 ± 25.66^{ab}	8.13 ± 1.44^{ab}

Note. Compared with the control group in the same period, $^{a}P<0.05$; compared with before treatment, $^{b}P < 0.05$.

Table 5: Changes of serum CRP, IL1β, and IL2 levels in the two groups of patients before and after treatment.

group		CRP (mg/L)	IL1β (ng/L)	IL2 (ng/L)
Control group ($n = 50$)	Before treatment	54.54 ± 7.66	47.87 ± 9.44	51.43 ± 8.89
	After treatment	43.43 ± 6.89^{b}	40.54 ± 5.21^{b}	43.56 ± 7.33^{b}
Test group ($n = 50$)	Before treatment	54.09 ± 7.32	48.01 ± 8.33	52.01 ± 9.21
	After treatment	25.64 ± 4.22^{ab}	33.13 ± 5.65^{ab}	32.34 ± 6.66^{ab}

Note. Compared with the control group in the same period, $^{a}P<0.05$; compared with before treatment, $^{b}P < 0.05$.

The occurrence, development, and treatment of many bone and joint diseases are related to MMPS, RANKL, and OPG. Yougui Pill can delay cartilage degeneration by inhibiting the activity of MMPs and the expression of inflammatory factors. The RANKL/OPG signaling pathway is also closely related to the process of bone metabolism [13, 14]; the effect of traditional Chinese medicine treatment on the levels of serum OPG and RANKL in patients with rheumatoid arthritis of the wind-cold-dampness-type is the key to clinical efficacy [15]. Serum RANKL and OPG levels in patients with ankylosing spondylitis (AS) are significantly correlated with enthesopathy, and they can be used as reliable indicators for predicting the presence of enthesopathy in AS patients, especially the presence of bone erosion [16]. At the same time, percutaneous vertebroplasty can effectively treat senile osteoporotic thoracolumbar fractures and can also significantly reduce the levels of OPG and RANKL and promote bone healing [17]. In this study, after treatment, the levels of RANKL in the two groups were significantly decreased and the level of OPG was significantly increased, indicating that the proximal bone antirotation intramedullary nail has a good therapeutic effect on elderly patients with unstable femoral intertrochanteric fractures, and its effect may be related to the regulation of abnormal levels of MMPs and OPG. Previous studies have also found that interleukin and C-reactive protein are also closely related to the pathology and recovery process of fractures [18, 19]. Incision infection after calcaneal fracture affects the clinical treatment effect, and serum IL-2, IL-6, and CRP levels increase in patients with postoperative incision infection after bone fracture [20]. Closed negative pressure drainage combined with astragalus injection irrigation in the treatment of traumatic suppurative osteomyelitis can effectively improve the patient's limb function, improve treatment efficiency, and reduce complications and hospitalization costs, which may be related to the inhibition of CRP and IL-6 secretion [21, 22]. At the same time, the abnormal recovery of interleukin and C-reactive protein levels has a certain correlation with the recovery of fractures [23–26]. Lugua polypeptide can increase bone mineral density, improve red blood cell-related, bone metabolism and inflammatory indexes in patients with osteoporotic fractures [27], the increase of serum IL-6 level is involved in the injury of elderly femoral neck fracture and acute trauma in the early stage of surgery, and inflammatory response participates in the bone remodeling of postoperative fracture

healing [28]. This study also confirmed that the levels of interleukin and CRP in the two groups of patients were significantly reduced after treatment, and the changes in the above indicators in the observation group were more obvious, suggesting that the proximal bone antirotation intramedullary nail is more effective in regulating the abnormally elevated inflammation level in elderly patients with unstable femoral intertrochanteric fractures, which may be related to the regulation of abnormal levels of MMPs and OPG. In future studies, we will further analyze whether MMPs and OPG are risk factors for unstable intertrochanteric fractures and analyze the correlation between them, so as to provide a reference for clinically relevant disease prevention and treatment.

In conclusion, the proximal femoral antirotation intramedullary nail has a good therapeutic effect on elderly patients with unstable intertrochanteric fractures, and the changes in MMPs and OPG levels may be related to the treatment process.

Data Availability

The raw data supporting the conclusion of this article will be available by the authors without undue reservation.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Authors' Contributions

Yuwei Cai and Wenjun Zhu contributed equally to this work.

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Research Article

Clinical Significance of Neuregulin 4, Afamin, and SERPINB1 in Gestational Diabetes Mellitus and Their Relationship with Insulin Resistance

Qian Li,[1] Chunmei Li,[1] Jing Jin,[2] Yang Shen,[1] and Mei Wang[2]

[1]*Department of Obstetrics and Gynecology, Dongxihu People's Hospital, Wuhan, China*
[2]*Endocrine Department, Dongxihu People's Hospital, Wuhan, China*

Correspondence should be addressed to Mei Wang; wang03dongxihu@163.com

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Objective. This study aims to explore the serum levels of neuregulin 4 (NRG4), afamin (AFM), and serpin family B member 1 (SERPINB1) in gestational diabetes mellitus (GDM) patients and their relationship with insulin resistance. *Method*. Serum levels of AFM, SERPINB1, and NRG4 were measured in GDM ($n = 58$), and non-GDM women ($n = 60$) using enzyme-linked immunosorbent assay (ELISA) kits. Besides, the serum insulin and glucose levels were also measured followed by calculating the homeostatic model assessment of insulin resistance (HOMA-IR). The correlation was performed using the Pearson analysis. *Results*. The increased serum levels of AFM and SERPINB1 were revealed in GDM patients as compared with non-GDM women, accompanied by the lower NRG4 serum level. ROCs for AFM concentrations showed an AUC of 0.629 (95% CI: 0.527~0.731), 0.832 (95% CI: 0.754~0.909) for the SERPINB1 serum level, and 0.626 (95% CI: 0.524~0.728) for the NRG4 serum level. The threshold was 108.05 mg/L, 8.75 ng/mL, and 96.25 ng/mL of AFM, SERPINB1, and NRG4. Moreover, the combined ROC of AFM, SERPINB1, and NRG4 serum levels showed higher sensitivity (72.41%) and specificity (85.00%) for the diagnosis of GDM (AUC = 0.839; 95% CI: 0.764~0.913). In GDM patients, the Pearson analysis revealed a significant correlation between AFM and SERPINB1 ($r = 0.776$), AFM and NRG4 ($r = -0.799$), as well as SERPINB1 and NRG4 ($r = -0.783$). Moreover, AFM and SERPINB1 serum concentrations in GDM patients were positively related to insulin levels, fasting glucose levels, and HOMA-IR values. However, the SERPINB1 serum level was negatively correlated with serum insulin and glucose levels and HOMA-IR. *Conclusion*. Abnormal serum levels of NRG4, AFM, and SERPINB1, as highly sensitive diagnostic tools, are closely related to insulin resistance in GDM patients.

1. Introduction

As hyperglycemia and glucose intolerance are first recognized in the second or third trimester of pregnancy, gestational diabetes mellitus (GDM) is not attributable to previous diabetes, which can cause several risks for pregnant women and their fetus, including an increased risk of developing type 2 diabetes and other obesity-related disorders [1, 2]. Insulin resistance is an important physiological process essential during pregnancy to ensure sufficient fetal nutrition, and the physiological changes in insulin are excessive in women with GDM, usually as a result of β-cell impairment [2]. GDM complicates approximately 1~14% of all pregnancies worldwide with higher rates in Asia [3]. In mainland China, the incidence of GDM is 14.8%, which is similar to the reported incidence of GDM in Hong Kong (14.4%) [4].

At present, blood glucose screening is the most common method for the diagnosis of GDM in the middle and late stages of pregnancy. However, once diagnosed, there is little time left to treat GDM, leading to a negative impact on the fetus. Therefore, the identification of biomarkers for diagnosis and appropriate treatment of GDM is crucial in preventing maternal and neonatal complications [5, 6]. Neuregulins (NRGs) family (NRG1-4) is a signal protein containing epidermal growth factor-like domains, acting on

tyrosine kinase receptors of the ErbB family (ErbB1-4), which participates in a variety of biological processes by mediating cell-cell interactions [7], such as stimulation, proliferation, apoptosis, migration, and differentiation [8]. As ligands for receptor tyrosine kinases of the ErbB family, NRGs have been found to be involved in the development of nervous systems, such as schizophrenia [9], organ systems such as heart and breast [10], and human diseases such as diverse cancers [11]. Neuregulin 4 (NRG4) is a specific ligand of ErbB4 and is mainly expressed and secreted by brown adipocytes [12]. Brown adipose tissue maintained body temperature higher than ambient temperatures and its activation alleviated obesity, with approximately 2.5–5% of contribution rate to human resting metabolic rate [13, 14]. As an 87,000-dalton protein, afamin (AFM) is a novel human serum protein that belongs to the albumin family localized on chromosome 4 and has specific binding properties for vitamin E [15]. An increased level of AFM was observed during persistent pregnancy secondary to hormonal changes [16]. It has been shown to play a vital role in the prevalence and incidence of type 2 diabetes mellitus [17]. Currently, the generation of insulin-secreting cells from human pluripotent stem cells [17] or the promotion of pancreatic β cell proliferation [18] contributed to reversing diabetes. Pancreatic β cells in response to insulin resistance were partially mediated by liver-derived protein [19]. As a liver-derived secretory protein, SERPINB1 was reported to promote pancreatic β-cell proliferation [20].

In this retrospective study, we collected clinical data of 60 non-GDM and 58 GDM women, evaluated the maternal circulating levels of NRG4, AFM, and SERPINB1 during pregnancy in GDM, and identified their diagnostic values.

2. Methods and Materials

2.1. Study Participants. Overall, all women ($n = 118$) over 18 years of age underwent a 75 g oral glucose tolerance test (OGTT) [21] in the second trimester (24~28 weeks), and all did not receive medications that interfered with glucose or lipid metabolism before blood sampling. According to the result of OGTT screening, GDM was diagnosed if the subjects had fasting glucose ≥5.1 mmol/L, 1-hour glucose ≥10.0 mmol/L, and/or 2-hour glucose ≥8.5 mmol/L. There were 58 pregnant women diagnosed with GDM and the other women were not diagnosed with GDM ($n = 60$). Maternal prepregnancy body mass index (BMI) was calculated as weight/height^2 (kg/m^2) [22]. The gestational age was calculated according to the date of the last trustworthy menstrual period, which was then confirmed by the earliest pregnancy scanning [23].

2.2. Sample Size. We calculated the sample size by the G* Power software (latest ver. 3.1.9.7) using t tests (means: the difference between two independent means) [24]. We input the β/α ratio, effect size, and total sample size for the two groups in the main window, and the result showed a power of 0.927.

2.3. Exclusion Criteria. Exclusion criteria were as follows: (1) multiple pregnancy; (2) pregestational diabetes; (3) preexisting glucose intolerance; (4) pregnancy-induced hypertensive disease; (5) parathyroid and bone metabolism abnormalities; (6) syphilis, Hepatitis B virus, or HIV carrier; (7) acute or chronic inflammation; (8) allergic diseases; (9) smoking, alcohol use, or drug use; (10) a history of fetal anomalies; (11) premature rupture of membranes; and (12) a history of insulin therapy.

2.4. Sample Collection. An overnight fasting venous blood sample was collected from all study participants through venipuncture. The serum was obtained by centrifugation (5000 rpm for 15 min), and its aliquots were frozen and kept at −80°C until analysis. The serum levels of glucose and insulin were assessed using a human glucose assay kit (Catalog No. KA0831, Bio-Techne China Co. Ltd. Shanghai, China) and a human Insulin Quantikine Enzyme-linked immunosorbent assay (ELISA) kit (DINS00, Bio-Techne China Co. Ltd. Shanghai, China). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting glucose (mmol/L) × fasting insulin (IU/mL)/22.5 [25].

2.5. Detection of AFM, SERPINB1, and NRG4 Serum Levels. The serum level of NRG4 (Catalog No. ABIN6968855, Antibodies-online GmbH, Aachen, Germany), AFM (Catalog No. ABIN6730921, Antibodies-online GmbH, Aachen, Germany), and SERPINB1 (Catalog No. ABIN6959408, Antibodies-online GmbH, Aachen, Germany) was measured using human ELISA kits. The interassay and interassay CV %, standard curve range, and sensitivity are listed in Table 1.

2.6. Statistical Analysis. Statistical package program SPSS 20 (Armonk, NY: IBM Corp.) was used to interpret the data with $P < 0.05$ as statistically significant. After the assessment for normality of data distribution using the Shapiro–Wilk test (data not shown), all the continuous variables in our study with normal distribution expressed as mean ± SD were performed using Student's t-test. Correlations were analyzed by the Pearson analysis.

3. Result

3.1. Subject Baseline Characteristics. The characteristics of 60 non-GDM and 58 GDM women are summarized in Table 2. For both groups, average ages, gestational age, and BMI were similar, with a mean of 29.5 ± 2.27 years in non-GDM and 29.57 ± 2.94 years in GDM women ($P = 0.891$), a mean of 26.05 ± 1.35 weeks in non-GDM and 25.78 ± 1.36 weeks in GDM cases ($P = 0.274$), as well as an average of 24.95 ± 2.42 kg/m^2 in non-GDM and 25.04 ± 2.15 kg/m^2 in GDM subjects ($P = 0.831$). Moreover, no significant difference was observed regarding to HbA1C% ($P = 0.399$), SBP ($P = 0.486$), DBP ($P = 0.975$), gravidity ($P = 0.599$), and parity ($P = 0.813$), indicating the patients were compared. Besides, GDM women had significantly serum insulin

Table 1: Detailed information on enzyme-linked immunosorbent assay (ELISA) kits.

Gene	Full names	Intra-assay CV%	Interassay CV%	Standard curve range	Sensitivity
NRG4	Neuregulin 4	<8	<10	0.781~50 ng/mL	0.469 ng/mL
AFM	Afamin	<10	<12	3.12~200 ng/mL	1.450 ng/mL
SERPINB1	Serpin family B member 1	<10	<12	0.31~20 ng/mL	0.115 ng/mL

Neuregulin 4 (NRG4), afamin (AFM), serpin family B member 1 (SERPINB1), and coefficient of variation (CV).

Table 2: Demographic, clinical, and biochemical characteristics of study groups.

	GDM	Non-GDM	t	P
Age (years)	29.5 ± 2.27	29.57 ± 2.94	0.138	0.891
Gestational age (weeks)	25.78 ± 1.36	26.05 ± 1.35	1.099	0.274
BMI (kg/m^2)	25.04 ± 2.15	24.95 ± 2.42	0.213	0.831
Newborn weight (g)	3.03 ± 0.53	2.9 ± 0.51	1.294	0.198
HbA1C%	5.00 ± 0.64	4.91 ± 0.56	0.847	0.399
SBP (mmHg)	106.4 ± 8.47	105.3 ± 9.80	0.700	0.486
DBP (mmHg)	74.53 ± 8.72	74.48 ± 8.72	0.032	0.975
Gravidity	2.14 ± 1.13	2.25 ± 1.17	0.528	0.599
Parity	0.98 ± 0.71	1.02 ± 0.83	0.237	0.813
Fasting glucose (mmol/L)	7.8 ± 1.15	7.08 ± 0.57	4.353	<0.001
Fasting insulin (IU/mL)	9.66 ± 4.36	8.29 ± 1.74	2.250	0.026
HOMA-IR	3.42 ± 1.72	2.61 ± 0.6	3.415	0.001

Gestational diabetes mellitus (GDM), body mass index (BMI), hemoglobin A1C (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), and homeostatic model assessment of insulin resistance (HOMA-IR).

and glucose levels and HOMA-IR compared with non-GDM women (all $P < 0.05$).

3.2. Comparison of AFM, SERPINB1, and NRG4 Serum Levels in GDM and Non-GDM Women. As illustrated in Figure 1, the increased serum levels of AFM (97.44 ± 42.83 vs. 78.62 ± 36.32 mg/L, $t = 2.579$, $P = 0.011$) and SERPINB1 (12.16 ± 5.02 vs. 6.37 ± 2.89 ng/mL, $t = 7.707$, $P < 0.001$) in GDM patients as compared with non-GDM women. Besides, GDM patients had lower NRG4 serum level than the non-GDM cases (84.86 ± 33.33 vs. 102.00 ± 46.00 ng/mL, $t = 2.311$, $P = 0.023$).

3.3. The Diagnostic Effect of AFM, SERPINB1, and NRG4 Serum Levels in GDM. ROCs for AFM concentrations showed an AUC of 0.629 (95% CI: 0.527~0.731, Figure 2(a)), 0.832 (95% CI: 0.754~0.909, Figure 2(b)) for the SERPINB1 serum level, and 0.626 (95% CI: 0.524~0.728, Figure 2(c)) for the NRG4 serum level. The threshold of AFM, SERPINB1, and NRG4 were 108.05 mg/L, 8.75 ng/mL, and 96.25 ng/mL, respectively, for distinguishing between women who developed GDM, and those who did not with the sensitivity of 44.38%, 75.86%, and 66.67%, as well as the specificity of 85.00%, 81.67%, and 62.07% (Table 3). Moreover, the combined ROC of AFM, SERPINB1, and NRG4 serum levels showed higher sensitivity (72.41%) and specificity (85.00%) for the diagnosis of GDM (AUC = 0.839; 95% CI: 0.764~0.913, Figure 2(d), Table 3).

3.4. Correlation among AFM, SERPINB1, and NRG4 Serum Levels in GDM. To find the correlation among AFM, SERPINB1, and NRG4 serum levels in GDM, the Pearson analysis was then performed, and the result revealed a significant correlation between AFM and SERPINB1 ($r = 0.776$, $P < 0.001$), AFM and NRG4 ($r = -0.799$, $P < 0.001$), as well as SERPINB1 and NRG4 ($r = -0.783$, $P < 0.001$) in serum of GDM patients (Figure 3).

3.5. Correlation between AFM, SERPINB1, and NRG4 Serum Levels and Insulin Resistance. Moreover, AFM and SERPINB1 serum concentrations in GDM patients were positively related to insulin levels, fasting glucose levels, and HOMA-IR values (all $P < 0.05$). In terms of the NRG4 serum level, it was shown to be negatively correlated with serum insulin and glucose levels and HOMA-IR (all $P < 0.05$, Figure 4, Table 4).

4. Discussion

Women with GDM run a higher risk of developing maternal and perinatal complications including preeclampsia [26], type 2 diabetes mellitus after delivery [27], hypertension, and cardiovascular disease [28], and their infants are more likely to have adverse outcomes, such as neonatal hypoglycemia and polycythemia [29]. Therefore, a novel diagnosis for GDM is extremely important for the health of pregnant women and their fetuses.

AFM is a vitamin E-binding protein mainly secreted by the liver and exhibited antioxidant properties against related injuries and disease [30]. AFM has been reported to be increased in maternal serum during pregnancy and related to pregnancy-related complications. A pilot study presented by Hubalek et al. [31] revealed that in the first trimester, pregnant women with preeclampsia showed significantly higher median serum concentrations of AFM than that in

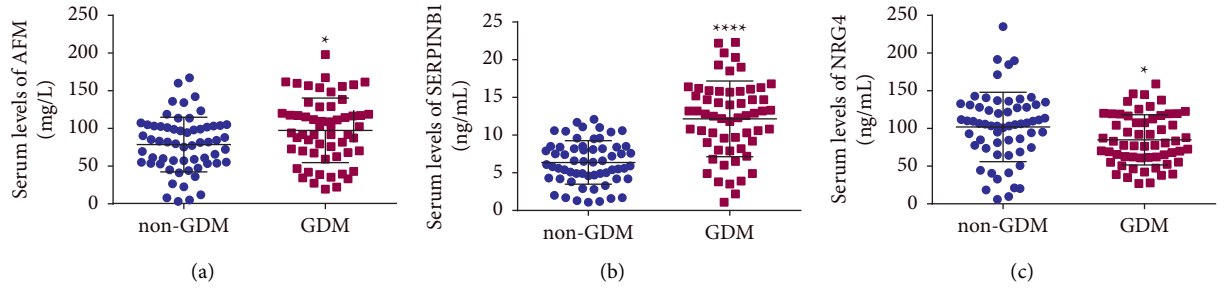

Figure 1: NRG4, AFM, and SERPINB1 serum levels were detected using ELISA. The increased serum levels of afamin (AFM, (a)) and serpin family B member 1 (SERPINB1, (b)) in gestational diabetes mellitus (GDM) patients as compared with non-GDM women accompanied by reduced neuregulin 4 (NRG4, (c)). $^{*}P < 0.05$ and $^{****}P < 0.001$ when compared to the non-GDM group.

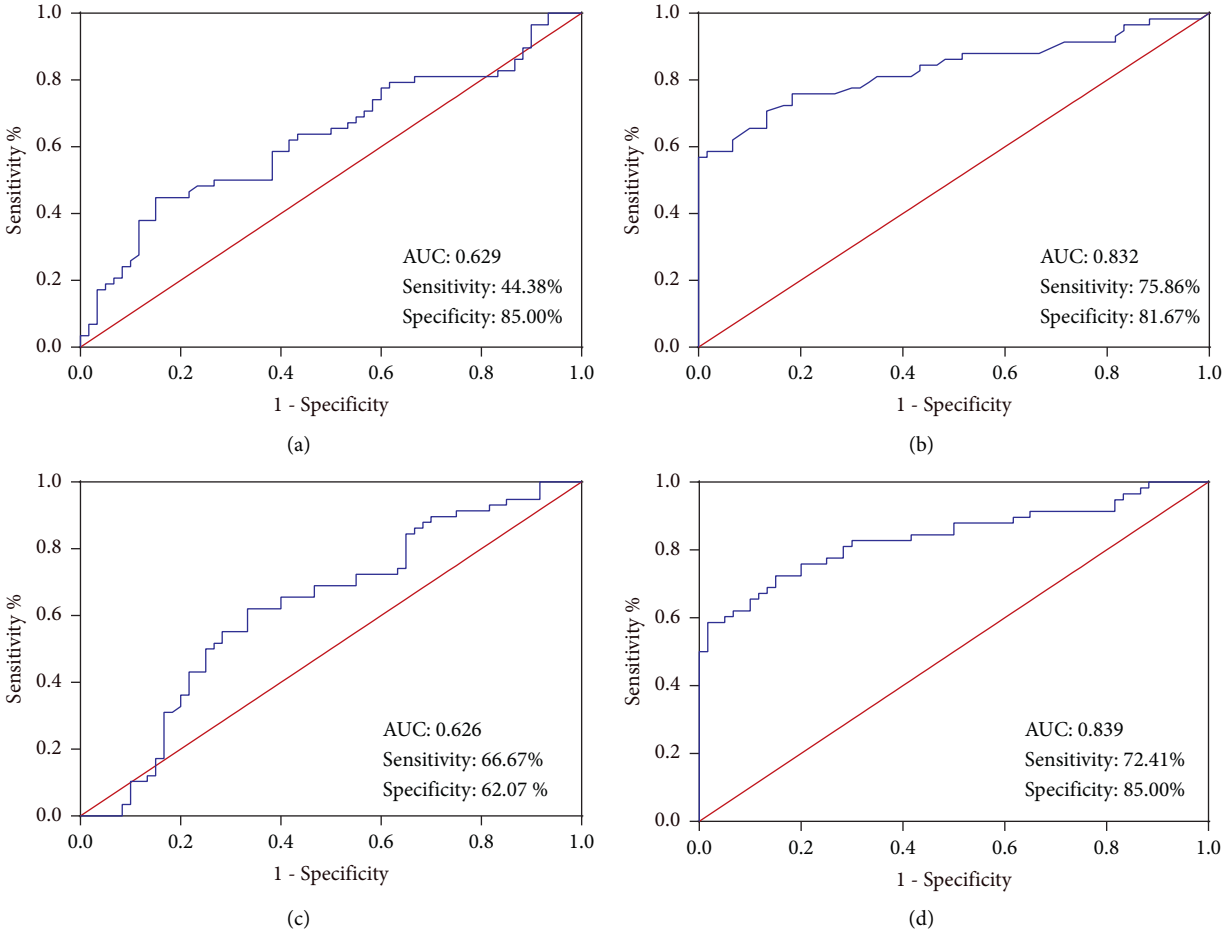

Figure 2: The diagnostic effect of AFM, SERPINB1, and NRG4 serum levels in GDM. ROCs for afamin (AFM) concentrations showed an AUC of 0.629 (95% CI: 0.527~0.731, (a)) of 0.832 (95% CI: 0.754~0.909, (b)) for the serpin family B member 1 (SERPINB1) serum level, of 0.626 (95% CI: 0.524~0.728, (c)) for the neuregulin 4 (NRG4) serum level, and of 0.839 (95% CI: 0.764~0.913, (d)) for the combined detection of AFM, SERPINB1, and NRG4 serum levels.

Table 3: Results of ROC analyses.

Parameter	AUC (95% CI)	Threshold	Sensitivity (%)	Specificity (%)
AFM	0.629 (0.527~0.731)	108.05 mg/L	44.83	85.00
SERPINB1	0.832 (0.754~0.909)	8.75 ng/mL	75.86	81.67
NRG4	0.626 (0.524~0.728)	96.25 ng/mL	66.67	62.07
Combined	0.839 (0.764~0.913)	0.538	72.41	85.00

Neuregulin 4 (NRG4), afamin (AFM), serpin family B member 1 (SERPINB1), receiver operating characteristic (ROC), and area under the ROC curve (AUC).

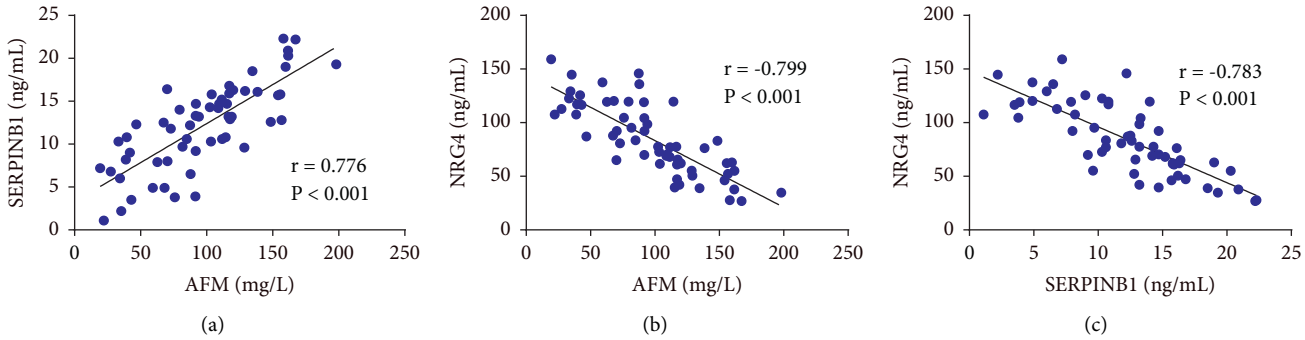

Figure 3: Pearson analysis revealed a significant correlation between AFM and SERPINB1 (a), AFM and NRG4 (b), as well as SERPINB1 and NRG4 (c) in serum of GDM patients. Gestational diabetes mellitus (GDM), neuregulin 4 (NRG4), afamin (AFM), serpin family B member 1 (SERPINB1), and homeostatic model assessment of insulin resistance (HOMA-IR).

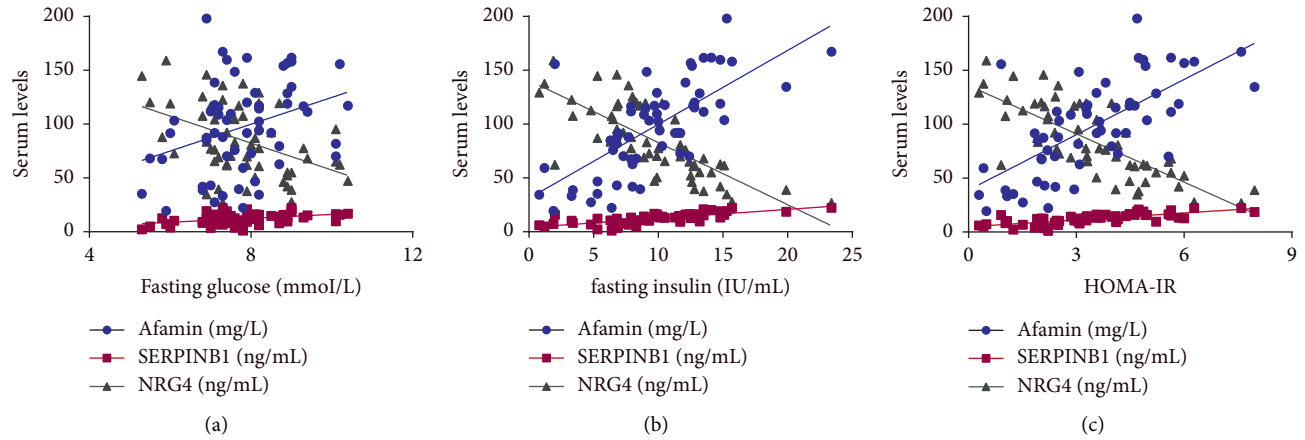

Figure 4: Correlations between AFM, SERPINB1, and NRG4 serum levels and insulin resistance in GDM patients. Gestational diabetes mellitus (GDM); neuregulin 4 (NRG4), afamin (AFM), serpin family B member 1 (SERPINB1), and homeostatic model assessment of insulin resistance (HOMA-IR).

Table 4: Correlations between AFM, SERPINB1, and NRG4 serum levels and insulin resistance in GDM patients.

Parameter	*AFM (mg/L)*		*SERPINB1 (ng/mL)*		*NRG4 (ng/mL)*	
	R	*P*	*r*	*P*	*r*	*P*
Fasting glucose (mmol/L)	0.334	0.010	0.420	0.001	−0.432	0.001
Fasting insulin (IU/mL)	0.699	<0.001	0.727	<0.001	−0.755	<0.001
HOMA-IR	0.688	<0.001	0.737	<0.001	−0.773	<0.001

Neuregulin 4 (NRG4), afamin (AFM), serpin family B member 1 (SERPINB1), and homeostatic model assessment of insulin resistance (HOMA-IR).

pregnant healthy controls. Another study also indicated that compared to healthy pregnant women, elevated first-trimester serum AFM levels were observed in pregnant women with preeclampsia and GDM [32]. In our study, we included a total of 118 pregnant women consisting of GDM women and non-GDM women, and they were between 24 and 28 weeks of gestation (second trimester). The serum levels of AFM, SERPINB1, and NRG4 were determined, and it was observed that GDM patients revealed significantly higher serum levels of AFM than that non-GDM patients. Our results were a little different from another study, which suggested no significant difference in third-trimester AFM levels between GDM and non-GDM groups was discovered [33]. Furthermore, we performed ROCs to predict if AFM can be used as an indicator for GDM diagnosis, and the data showed AFM was with AUC of 0.629 (95% CI: 0.527~0.731), specificity of 85.00%, and 108.05 mg/L as the threshold for distinguishing GDM patients from non-GDM patients. During pregnancy, the risk of pregnancy complications including GDM is associated with insulin resistance and insulin secretion [34]. Biochemical variables were evaluated in our study in response to the correlation between these and AFM, and we discovered that serum AFM level was significantly positively related to insulin levels, fasting glucose levels, and HOMA-IR values. Although there was no direct evidence supporting our above finding, other GDM studies confirmed that significantly higher levels of fasting blood glucose, fasting insulin, and HOMA-IR were revealed in

pregnant women with GDM than that in controls [25]. Akbas et al. also demonstrated that these three biomarkers were increased in GDM patients compared to the controls, and serum cortistatin related to GDM was negatively correlated with these biomarkers [21].

NRG4 is a novel adipokine, which is primarily expressed in brown adipose tissue, and acts as a vital role in regulating metabolic homeostasis and maintaining energy. Previous evidence proved that NRG4 has been involved in several disorders related to obesity [35] and GDM [36]. Attique et al. concluded that NRG4 concentration declined in GDM females compared to the healthy group ($P < 0.04$) and showed a weak association with HOMA-IR but the significant inverse association with insulin, indicating a potential role of NRG4 in regulating insulin sensitivity, and its possibility as a biomarker of GDM [37]. During the second and third trimesters, Zhang et al. indicated the females in the control group exhibited significantly higher serum NRG4 concentration than the GDM females and NRG4 concentration was negatively related to fasting glucose and HOMA-IR [38]. These findings were similar to ours, which suggested that NRG4 expression decreased in GDM patients than that in non-GDM patients, and the difference was statistically significant. Moreover, there were negative relations between NRG4 levels and three biomarkers including insulin levels, fasting glucose levels, and HOMA-IR values. The ROCs data proved that NRG4, with an AUC of 0.626, a sensitivity of 66.67%, and a specificity of 62.07%, might be a potential biomarker of GDM diagnosis.

As a member of the clade B of SERPINS, the role of inflammation and cell migration of intracellular protein SERPINB1 has been widely explored [39, 40]. Recently, SERPINB1 has attracted attention in the treatment of diabetes mellitus treatment due to its role in inducing β-cell proliferation [41]. A small sample size of the study showed that elevated serum level of SERPINB1 was revealed in the patients with type 2 diabetes compared to the healthy controls, and SERPINB1 was significantly negatively correlated with serum low-density lipoprotein cholesterol [42]. In the present study, compared to non-GDM women, GDM women presented higher serum levels of SERPINB1. Furthermore, SERPINB1 showed an AUC of 0.832, a sensitivity of 75.86%, and a specificity of 81.67% for distinguishing between women with and without GDM. Kamal et al. demonstrated that higher SERPINB1 was associated with β-cell dysfunction and abnormal glycolipid, but no correlation was found between SERPINB1 and HOMA-IR both in non-type 2 diabetes and subjects with type 2 diabetes [41]. In our study, SERPINB1 serum concentration in GDM patients was positively related to insulin levels, fasting glucose levels, and HOMA-IR values.

In conclusion, our results show differences in the AFM, SERPINB1, and NRG4 serum levels between GDM and control pregnant group during pregnancy with high diagnostic values, which all were correlated with serum insulin and glucose levels and HOMA-IR.

To our knowledge, our study is one of the first to investigate the levels of the novel markers AFM, SERPINB1, and NRG4 in the GDM population. The combined ROC of AFM, SERPINB1, and NRG4 serum levels showed higher sensitivity and specificity for the diagnosis of GDM and provided a comprehensive overview of potential serum protein biomarkers for early GDM prediction.

However, a further study based on larger subjects is necessary to verify our results, and it still remains unclear whether these three serum levels can be used as biomarkers for the early screening of GDM. Moreover, the circulating concentrations in serum and plasma of AFM, SERPINB1, and NRG4 in different trimesters of pregnant women would be further explored in the future as time and funding permit.

Data Availability

The data used to support the findings of this study are included in the article.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Authors' Contributions

Qian Li and ChunMei Li contributed to this work equally.

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Retraction

Retracted: Effects of Positive Psychological Nursing Combined with Free Posture on the Prognosis of Primipara with Singleton Spontaneous Delivery

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] X. Zhao, J. He, and J. Liu, "Effects of Positive Psychological Nursing Combined with Free Posture on the Prognosis of Primipara with Singleton Spontaneous Delivery," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 6393050, 5 pages, 2022.

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Research Article

Effects of Positive Psychological Nursing Combined with Free Posture on the Prognosis of Primipara with Singleton Spontaneous Delivery

Xuefei Zhao, Jianjun He, and Jue Liu

The Second Affiliated Hospital, Department of Obstetrics and Gynecology, Hengyang Medical School, University of South China, Hengyang, Hunan 421001, China

Correspondence should be addressed to Jue Liu; liujue9570@163.com

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Objective. To explore the effects of positive psychological nursing combined with free posture on the prognosis of primipara with singleton spontaneous delivery. *Methods*. 106 cases of primipara with singleton spontaneous delivery who were admitted to the obstetrics department of our hospital from January 2017 to December 2019 were selected as the research subjects and they were divided into the observation group and control group according to the random number table method and maternal willingness, with 53 cases in each group. The control group received routine nursing, and the observation group was given positive psychological nursing combined with free posture on the basis of the control group. The stress degree during delivery (Hamilton anxiety scale (HAMA) and Hamilton depression scale (HAMD)), the time of first stage of labor, the time of second stage of labor, the time of third stage of labor, pain level during the active period of the first stage of labor, and delivery outcomes were observed and compared between the two groups. *Results*. The degree of anxiety and depression during childbirth in the observation group was significantly lower than that in the control group ($P < 0.05$). The time of first stage of labor and the time of second stage of labor in the observation group were shorter than those in the control group ($P < 0.05$), and there was no significant difference in the time of the third stage of labor ($P > 0.05$). The pain degree in the active stage of the first stage of labor in the observation group was lower than that in the control group ($P < 0.05$). The pain degree in the active stage of the first stage of labor in the observation group was lower than that in the control group ($P < 0.05$). *Conclusion*. Positive psychological nursing combined with free posture for primipara with singleton spontaneous delivery can shorten the stages of labor, reduce the pain, relieve psychological stress, and improve the delivery outcomes.

1. Introduction

Parturients, especially primiparas, face enormous pain and psychological pressure during childbirth. Severe labor pains can lead to uncoordinated uterine contractions, prolonged labor, and fetal distress. It will cause anxiety and depression in parturients, resulting in maternal endocrine dysfunction [1]. Due to excessive pain during labor, women tend to shout, which can easily lead to hyperventilation and increase oxygen consumption, further affecting the labor process. Therefore, positive and effective psychological nursing for primiparas is helpful to relieve their psychological pressure and negative emotions [2]. Childbirth pain affects the entire production process of the parturient and may have a negative impact on the fetus. In order to relieve the discomfort of the parturient during the labor process, it is of great significance to choose an appropriate delivery position [3]. Based on this, this study implemented positive psychological nursing and free posture for singleton primiparous women and achieved satisfactory results. The report is as follows.

2. Materials and Methods

2.1. General Information. 106 cases of primipara with singleton spontaneous delivery who were admitted to the obstetrics department of our hospital from January 2017 to

December 2019 were selected as the research subjects, and they were divided into the observation group and control group according to the random number table method and maternal willingness, with 53 cases in each group. Inclusion criteria include the following: all primiparas; those with single fetus in head position and full-term pregnancy; those with prenatal amniotic fluid volume, pelvis, fetal weight, biparietal diameter, and other indicators meet the conditions of natural childbirth; and those who gave informed consent to this study. Exclusion criteria include the following: those with pregnancy complications such as gestational hypertension and cardiopulmonary insufficiency; those who do not cooperate well with puerpera and have a history of mental illness or family mental illness; those who have high-risk pregnancy factors; and those who have severe liver and kidney dysfunction and coagulation dysfunction. There was no statistical significance in general clinical data between the two groups ($P > 0.05$), which were comparable, as shown in Table 1.

2.2. Methods. The puerpera in the control group were given routine midwifery care: when the cervix of the puerpera was opened to 2 cm, the puerpera entered the delivery room, and the midwives perform routine intrapartum monitoring and corresponding delivery guidance for the puerpera. On the basis of this, the puerpera in the observation group implemented positive psychological nursing with free posture as follows: ① positive psychological induction: with the increased stimulation of uterine contractions and lack of knowledge of childbirth, primiparas usually have varying degrees of anxiety and tension, which affects the process of natural childbirth. Prenatal education is provided to puerpera, so that parturients can fully understand the delivery environment and the attending doctor and play delivery videos for the puerpera to prepare them psychologically. Midwives stay by the bedside, actively communicate with parturient; inform them of uterine contraction rhythm, pain intensity and duration; explain knowledge of childbirth cooperation, factors determining childbirth, and perineal incision and protection for pregnant women; provide language, eye encouragement, and appropriate psychological counseling; describe the signs of the second stage of labor for the puerpera, instruct them to correctly match the luck of uterine contractions, take deep breaths with the rhythm during uterine contractions, change to shallow breathing according to the rhythm of uterine contractions, and massage the abdomen from inside out when the uterine contractions are stronger; after uterine contractions, guide the patient into a state of total relaxation, pay close attention to the status of the labor process and fetal heart sounds, pay attention to the maternal mood at any time, and give the maternal affirmation to maintain a good psychological state. ② Music therapy distraction: play music for the patient according to the parturient's preference, choose light music that is relaxing, soothing, and pleasant, and the volume should be controlled within 70 dB. From the second stage of labor, play it to the third stage of labor and try to keep the music without pause. ③ Positive psychological suggestion: according to maternal needs, adjust indoor temperature, humidity, and light to enhance maternal comfort; use authoritative language to eliminate maternal concerns about childbirth and enhance confidence in natural childbirth; psychological comfort to the puerpera when there are changes in the intensity of uterine contractions, abnormal fetal position, and slow dilation of the cervix during the production process; regardless of whether the labor progresses smoothly or not, parturients are encouraged to actively respond in a relaxed, gentle, and pleasant way, and at the same time, close observation of physical signs is carried out. If any abnormality occurs, report to the responsible physician immediately. ④ Free posture pain relief delivery: during the first stage of labor, after a correct assessment by the midwives, the puerpera can freely choose the delivery position, and the principle is to give priority to be comfortable and safe. Sitting, lying down, crouching, standing, and other positions are acceptable. When the position of the puerpera changes, the medical staff massages the puerpera with moderate intensity to promote the opening of the cervix of the puerpera. After waiting for the puerpera to enter the second stage of labor, switch to the supine position for delivery. The medical staff pays close attention to the status of the puerpera during the labor process and provides real-time delivery guidance.

2.3. Observation Indicators. The degree of stress during labor, the duration of the first, second, and third stages of labor, the degree of pain in the active phase of the first stage of labor, and the delivery outcome were observed and compared between the two groups. ① Stress degree [4]: the degree of stress response during childbirth was assessed by Hamilton anxiety scale (HAMA) and Hamilton depression scale (HAMD). All items of the HAMA and HAMD are scored on a five-point scale from 0 to 4 points. The higher score showed more severe anxiety/depression. Cronbach's α coefficient of HAMA is 0.798 and Cronbach's α coefficient of HAMD is 0.784. ② Pain level [5]: the pain visual analog scale was used to evaluate the pain level in the active phase of the first stage of labor. The basic method was to use a walking scale about 10 cm, with 10 scales on the one side and "0" points on both ends. 0 point is no pain; 10 points is the most severe pain that is unbearable. Turn the scaled side away from the puerpera and ask the puerpera to mark the corresponding position on the ruler that can represent the degree of pain. The doctor evaluates the score according to the position marked by the puerpera, and 0–2 points are 1st grade, 3–5 points are 2nd grade, 6–8 points are 3rd grade, and >8 points are 4th grade. ③ Delivery outcome: the two groups were compared for postpartum hemorrhage, amniotic fluid contamination, and neonatal asphyxia rate.

2.4. Statistical Methods. Statistical software SPSS 17.0 professional statistical software was used to analyze the data. Enumeration data were expressed as percentages, and the χ^2 test was used for comparison between groups. Measurement data were expressed as mean ± standard deviation, and the t

Table 1: Comparison of clinical data between the two groups (M ± SD, $n = 53$).

Group	Age (year)	Gestational week (week)	Weight (kg)	Educational level		
				Junior high school and below	High school	College and above
Observation group	24.40 ± 2.50	38.81 ± 0.80	57.62 ± 7.74	13 (24.53)	24 (45.28)	16 (30.19)
Control group	24.75 ± 3.25	38.77 ± 0.75	58.34 ± 9.31	11 (20.75)	27 (50.94)	15 (28.30)
t or χ^2 value	0.621	0.266	0.433	0.113		
P value	0.536	0.791	0.666	0.910		

test was used for comparison between groups. $P < 0.05$ was regarded as a statistically significant difference.

3. Results

3.1. Comparison of Stress Levels. The degree of anxiety and depression during childbirth in the observation group was significantly lower than that in the control group ($P < 0.05$), as shown in Table 2.

3.2. Comparison of Labor Time. The time of the first stage of labor and the second stage of labor in the observation group were shorter than those in the control group ($P < 0.05$), and there was no significant difference in the time of the third stage of labor ($P > 0.05$), as shown in Table 3.

3.3. Comparison of Pain Levels in the Active Phase of the First Stage of Labor. The pain degree in the active stage of the first stage of labor in the observation group was lower than that in the control group ($P < 0.05$), as shown in Table 4.

3.4. Comparison of Maternal Delivery Outcomes. The postpartum hemorrhage, amniotic fluid contamination, and neonatal asphyxia rate in the observation group were lower than those in the control group ($P < 0.05$), as shown in Table 5.

Table 2: Comparison of maternal stress levels between the two groups (score, $n = 53$).

Group	HAMA	HAMD
Observation group	8.53 ± 2.46	7.03 ± 2.52
Control group	11.25 ± 2.93	12.05 ± 3.13
t value	5.176	9.095
P value	0.001	0.001

Table 3: Comparison of labor time between the two groups ($n = 53$).

Group	Process of childbirth (h)		
	1st stage	2nd stage	3rd stage
Observation group	9.17 ± 1.85	0.91 ± 0.17	0.17 ± 0.08
Control group	13.15 ± 2.17	1.43 ± 0.29	0.17 ± 0.07
t value	10.161	11.262	0
P value	0.001	0.001	1.000

Table 4: Comparison of the degree of pain in the active phase of the first stage of labor between the two groups (n (%), $n = 53$).

Group	Grade 1	Grade 2	Grade 3	Grade 4
Observation group	8 (15.09)	40 (75.47)	3 (5.66)	2 (3.77)
Control group	4 (7.55)	13 (24.53)	23 (43.40)	13 (24.53)
χ^2 value	5.392			
P value	0.001			

4. Discussion

Fear of pain and lack of awareness of childbirth knowledge can cause obvious psychological pressure on primiparas, which is not conducive to smooth delivery, and may even have adverse effects on the fetus in the uterus.

Due to the lack of production experience, primiparas are usually worried about accidents during natural childbirth. In addition, the neuroendocrine regulation makes the parturient more sensitive to the pain of uterine contractions, which can cause secondary uterine atony, prolonged labor, and increase the number of voluntary and involuntary labor [6]. Childbirth is not only a process of physical stress but also a process of psychological stress, and parturients are usually accompanied by different degrees of psychological stress and negative emotions [7]. Because vaginal delivery itself has certain risks, various physiological and psychological factors may affect the delivery process and threaten the safety of the parturient and baby [8]. According to relevant surveys, more than 25% of puerpera have anxiety, about 20% have depression, and the rate is even higher in primiparas [9]. Strong negative emotions can enhance the activity of the adrenal cortex system, which can cause a large increase in the concentration of catecholamines in the maternal body, disrupt the neuroendocrine regulation function, affect smooth muscle contraction, cause secondary uterine atony, and aggravate maternal pain. Negative emotions may prolong the labor process and increase the risk of postpartum hemorrhage [10]. Therefore, it is necessary to carry out effective psychological nursing for primipara. On the basis of understanding the physiological and psychological changes of the puerperium during childbirth, medical personnel need to educate the puerperium, enhance the confidence of the puerpera, and guide the puerpera to relieve pain by diverting attention and controlling emotions, such as slow breathing during contractions. For parturients with excessive psychological pressure, they should pay close attention to their emotional changes and provide timely psychological counseling. In the first stage of labor, the intensity and frequency of uterine contractions gradually increase. At this time, the parturient's mood fluctuates greatly, and she is

Table 5: Comparison of maternal delivery outcomes between the two groups (n (%), $n = 53$).

Group	Postpartum hemorrhage	Amniotic fluid contamination	Neonatal asphyxia
Observation group	1 (1.89)	2 (3.77)	1 (1.89)
Control group	8 (13.21)	8 (13.21)	7 (11.56)
χ^2 value	5.950	3.975	4.867
P value	0.015	0.046	0.027

often anxious or even noisy. Nursing staff should increase patience and adopt methods such as chatting to divert parturient's attention to reduce parturient's negative emotions; the second stage of labor is a key stage of natural labor. Frequent uterine contractions increase the pain. At this time, giving parturient music therapy is helpful to guide the parturient to relax physically and mentally and maintain a good state of mind. After the fetus and placenta are delivered in the third stage of labor, the pain of uterine contractions is relieved; while sharing the joy with the parturient and her family, it is also necessary to praise and comfort the parturient to avoid postpartum hemorrhage caused by emotional fluctuations.

There are usually two positions for natural childbirth for puerpera: supine position for labor and semirecumbent position for labor. However, due to the long labor process, the puerpera are prone to orthostatic hypotension, causing dizziness during labor and increasing maternal discomfort [11]. When primiparas give birth naturally, the parturient can freely choose the most comfortable position for delivery, which can help to eliminate negative emotions such as tension and anxiety [12]. Free posture delivery can increase the pressure of the fetal head on the cervix, which is conducive to cervical dilation, shortens the labor process, and reduces maternal and neonatal birth injury [13]. At the same time, when the fetus is squeezed through the birth canal, it can promote the discharge of amniotic fluid accumulated in the lungs and reduce the risk of neonatal asphyxia [14]. The results of this study showed that the degree of anxiety and depression during childbirth in the observation group was significantly lower than that in the control group, the time of the first and second stages of labor was shorter than that of the control group, and the pain degree in the active phase of the first labor was lower than that of the control group. The postpartum hemorrhage, amniotic fluid contamination, and neonatal asphyxia rate in the observation group were lower than those in the control group, and the differences were statistically significant. The first stage of labor is the longest, and it is also the period when the parturient complains of the most severe pain. The second stage of labor has strong uterine contractions, and the maternal fear expands which may cause uterine smooth muscle tension and increase pain [15]. Pain is not just a physical problem. Psychological factors can also increase the intensity of pain [16]. By improving childbirth care and implementing positive psychological care and free posture, it can help relieve maternal pain in labor. By enabling primiparas to establish a comprehensive and accurate cognition of the progress of the labor process and delivery cooperation, it enables them to cooperate more actively and scientifically with the labor process. When maternal emotional state is relatively stable, abnormal uterine contraction caused by psychological factors can be avoided, and labor stagnation or extension can be avoided, which is conducive to the smooth completion of natural delivery.

In conclusion, the implementation of positive psychological nursing and free posture for singleton primipara vaginal delivery can shorten the labor process, reduce the physical and mental pain of the puerperium, relieve psychological stress, and ensure the safety of parturient and child, which is of great significance for reducing the rate of unindicated cesarean section, saving medical resources, and reducing doctor-patient disputes, and it is worthy of clinical application.

Data Availability

The data used to support this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Retraction

Retracted: Protective Role of Amiodarone on Reperfusion Arrhythmia in Patients of Acute Myocardial Infarction with Percutaneous Coronary Intervention Treatment

Evidence-Based Complementary and Alternative Medicine

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[1] J. Wang, J. Leng, X. Sun et al., "Protective Role of Amiodarone on Reperfusion Arrhythmia in Patients of Acute Myocardial Infarction with Percutaneous Coronary Intervention Treatment," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2597173, 5 pages, 2022.

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Research Article

Protective Role of Amiodarone on Reperfusion Arrhythmia in Patients of Acute Myocardial Infarction with Percutaneous Coronary Intervention Treatment

Jianying Wang,[1] Jinchang Leng,[1] Xiaowei Sun,[1] Kun Peng,[1] Xaojuan Ma,[1] Shiqin Huang,[1] and Fang Wang[2]

[1]*Department of Infomation, Medical Supplies Center of PLA General Hospital, Beijing 100039, China*
[2]*Department of Pharmacy, Medical Supplies Center of PLA General of PLA General Hospital, Beijing 100039, China*

Correspondence should be addressed to Fang Wang; luckada@sohu.com

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With the development and popularity of percutaneous coronary intervention (PCI), ischemia-reperfusion injury (IRI) has attracted more and more clinical attention. Reperfusion arrhythmia (RA), one of the common manifestations during and after PCI, can affect the postoperative cardiac function of patients with acute myocardial infarction (AMI). Therefore, effective intervention on RA has important clinical significance. This study observed the effect of amiodarone on reperfusion arrhythmia (RA) after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) and explored its possible mechanism. The results showed that amiodarone had good clinical efficacy in the prevention of RA in patients with AMI after PCI, and it could reduce the levels of serum IL-6, hs-CRP, CK-MB, and cTnI in patients and reduce the damage caused by reperfusion, thereby reducing the occurrence of RA.

1. Introduction

Percutaneous coronary intervention (PCI) is currently the most important method for the treatment of acute myocardial infarction (AMI). However, after vascular recanalization, it will cause ischemia-reperfusion injury (IRI) to the myocardium, resulting in arrhythmia, heart failure, cardiogenic shock, and other symptoms, which seriously affect the prognosis of patients with AMI [1]. Reperfusion arrhythmia (RA), as one of the common manifestations during and after PCI, has an impact on the recovery of postoperative cardiac function, and prevention of this disease will help to improve the prognosis of patients and restore cardiac function [2]. Amiodarone multichannel blockers have the pharmacological effects of all antiarrhythmic drugs in class I to IV, as well as mild noncompetitive α and β-adrenergic receptor blockade and mild antiarrhythmic drugs in class I and class IV [3]. In clinical practice, amiodarone not only has a certain effect on the ventricular premature beat, ventricular tachycardia, and ventricular fibrillation after myocardial infarction and heart failure but also has a certain effect on reducing mortality [4]. Therefore, this study aimed to observe the effect of preoperative amiodarone on postoperative RA in patients with AMI undergoing emergency PCI and to explore its mechanism.

2. Materials and Methods

2.1. Research Objects. According to the following inclusion and exclusion criteria, patients with AMI who received emergency PCI in our hospital from August 2017 to February 2018 were selected as the research subjects. After review and approval by the hospital ethics committee, a total of 264 patients with AMI were included in this study, and the patients were randomly divided into the control group (conventional PCI group) with 132 cases and the study group (amiodarone intervention group) with 132 cases according to the random number table method. The clinical data of the patients and the number of diseased coronary arteries and infarct sites were recorded.

2.2. Inclusion Criteria. Inclusion criteria are as follows: (1) meet the diagnostic criteria of the Chinese Medical Association for AMI [5]; (2) perform PCI within 24 hours after onset; (3) Killip grade 1–2; (4) sinus rhythm, and before treatment not taking antiarrhythmic drugs; and (5) the patient's family signed informed consent.

2.3. Exclusion Criteria. Exclusion criteria are as follows: (1) with mechanical complications such as ventricular septal perforation and valve prolapse; (2) with severe systemic diseases; (3) with peripheral vascular disease and aortic aneurysm; (4) with coagulation disorders etc.; (5) there was bradyarrhythmia before treatment; (6) a pacemaker had been installed; and (7) proximal right coronary artery occlusion.

2.4. Treatment Methods. All patients received emergency PCI, while the control group received conventional treatment, including aspirin, clopidogrel or ticagrelor, beta-blockers, and statins. On the basis of the conventional PCI group, the amiodarone intervention group was given amiodarone hydrochloride injection before the operation, and the injection was continuously pumped at the speed of 1 mg/min until 4 hours after the operation. If there was tachycardia and the blood pressure dropped during the treatment, the infusion was stopped.

Interventional treatment methods: preoperative aspirin 300 mg plus clopidogrel 600 mg or ticagrelor 180 mg, coronary angiography via the femoral artery or radial artery, and unfractionated heparin if the infarct-related vascular (IRA) lesions are clearly shown. Stents were placed directly after 100 U/kg anticoagulation, and stents were placed after balloon dilation for subtotal occlusion or total occlusion of IRA. TIMI blood flow grade III with lumen stenosis <30% indicates successful stent placement. After the operation, the patients continued to take dual antibacterial drugs, were routinely given statins and other drugs, and were given ACEI or β-blockers according to their condition.

2.5. Observation Indicators

2.5.1. Occurrence of Reperfusion Arrhythmia. The patients received continuous ECG monitoring during and after the operation, and the observation time for RA was within 4 hours after the opening of IRA. More than one min, tachyarrhythmias such as ventricular premature beats, ventricular tachycardia, atrial fibrillation, and ventricular fibrillation occur [6].

2.5.2. Laboratory Examination. 5 ml of fasting venous blood was drawn from all patients at the time of admission and 24 hours after the operation. The levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin -6 (IL-6) were detected by nephelometry and enzyme-linked immunosorbent assay (ELISA). The myocardial troponin I(cTnI) level was detected by the chemiluminescence method. The creatine kinase isoenzyme (CK-MB) level was detected by the rate method.

2.6. Statistical Methods. Statistical analysis was performed using SPSS 22.0 software. Measurement data were expressed as mean ± standard deviation ($\overline{x} \pm S$). If it conformed to normal distribution and homogeneity of variance, the t-test was used for comparison between the two groups; if it did not conform to normal distribution, the rank sum test was used. Enumeration data were expressed as absolute numbers or percentages (%), and the χ^2 test or rank sum test was used. Differences were considered significant at $P < 0.05$.

3. Results

3.1. Comparison of General Data of the Two Groups of Patients. In the routine PCI group, there were 84 males (63.6%) and 48 females (36.4%), with an average age of 59.3 ± 8.0 years and a body mass index (BMI) of 24.2 ± 3.5 kg/m^2; the amiodarone intervention group included 87 males (65.9%) and 45 females (34.1%), with an average age of 57.6 ± 6.6 years and a body mass index of 24.8 ± 2.4 kg/m^2. There were no significant differences in age, gender, BMI, history, infarct location, and number of stenotic or occluded coronary branches between the two groups of AMI patients ($P > 0.05$), as shown in Table 1.

3.2. The Occurrence of Reperfusion Arrhythmia. A total of 137 cases (51.9%) of RA occurred after PCI, including 89 cases (67.4%, 89/132 cases) in the conventional PCI group and 48 cases (36.4%, 48/132 cases) in the amiodarone intervention group. Ventricular arrhythmias are most common, ventricular tachycardia and ventricular premature beats are more common, and bradyarrhythmias and ventricular fibrillation are rare. Compared with the conventional PCI group, the incidence of RA in the amiodarone intervention group was lower, and the difference was significant ($P < 0.01$). Among them, the incidence of ventricular fibrillation and defibrillation in the intervention group was lower than that in the conventional group. In addition, the incidence of premature ventricular contractions and ventricular tachycardia in the intervention group was also lower than that in the conventional PCI group, and the differences were statistically significant ($P < 0.05$). Bradyarrhythmia were rare in both groups, with 18 (13.6%) and 12 (9.1%), respectively, as shown in Table 2.

3.3. Laboratory Tests. After PCI, the levels of serum IL-6 and hs-CRP in the two groups were increased compared with those before treatment, while the levels of cTnI and CK-MB were decreased compared with those before treatment, and the difference was statistically significant ($P < 0.05$). Compared with the control group, the levels of IL-6, hs-CRP, cTnI, and CK-MB in the amiodarone intervention group were significantly lower after treatment, and the difference was statistically significant ($P < 0.05$), as shown in Table 3.

Table 1: Comparison of the general conditions of the two groups of patients ($\overline{x} \pm S$, n (%)).

General conditions	Regular PCI group ($n = 132$)	Amiodarone intervention group ($n = 132$)	χ^2/t value	P value
Age (year)	59.3 ± 8.0	57.6 ± 6.6	1.883	0.061
Gender (male)	84 (63.6)	87 (65.9)	0.149	0.699
Body mass index (kg/m^2)	24.2 ± 3.5	24.8 ± 2.4	−1.624	0.106
Diabetes	61 (46.2)	64 (48.5)	0.137	0.712
Hypertension	98 (74.2)	91 (68.9)	0.913	0.339
Hyperlipidemia	73 (55.3)	70 (53.0)	0.137	0.711
History of smoking	88 (66.7)	91 (68.9)	0.156	0.693
Infarct site				
Extensive, anterolateral sidewall	114 (86.4)	119 (90.2)	0.914	0.339
Inferior wall, posterior wall, right ventricle	18 (13.6)	13 (9.8)		
The number of coronary arteries with lesions				
1 artery	71 (53.8)	75 (56.8)	5.158	0.161
2 arteries	41 (31.1)	38 (28.8)		
3 arteries	20 (15.2)	19 (14.4)		

Table 2: Comparison of the incidence of reperfusion arrhythmia in the two groups of patients (n, %).

	Regular PCI group ($n = 132$)	Amiodarone intervention group ($n = 132$)	χ^2 value	P value
Incidence of arrhythmia	89 (67.4)	48 (36.4)	25.506	<0.001
Premature ventricular contractions	29 (22.0)	16 (12.1)	4.527	0.033
Ventricular tachycardia	22 (16.7)	11 (8.3)	4.190	0.041
Ventricular fibrillation	10 (7.6)	2 (1.5)	5.587	0.018
Sinus bradycardia	11 (8.3)	7 (5.3)	0.954	0.329
High-grade atrioventricular block	7 (5.3)	5 (3.8)	0.349	0.555
Various cardiac arrhythmias	10 (7.6)	7 (5.3)	0.566	0.452

Table 3: Comparison of serum IL-6, hs-CRP, cTnI, and CK-MB levels in the two groups of patients before and after treatment ($\overline{x} \pm S$).

Group	Time	IL-6 (pg/ml)	Hs-CRP (mg/L)	cTnI (ng/mL)	CK-MB (U/L)
Regular PCI group ($n = 132$)	Before treatment	4.09 ± 0.36	7.02 ± 1.03	13.11 ± 2.02	243.15 ± 21.46
	After treatment	5.05 ± 0.31$^{\triangle}$	8.12 ± 1.20$^{\triangle}$	8.43 ± 1.85$^{\triangle}$	186.67 ± 25.32$^{\triangle}$
Amiodarone intervention group ($n = 132$)	Before treatment	4.01 ± 0.42	7.23 ± 1.05	12.98 ± 2.10	245.92 ± 23.17
	After treatment	4.76 ± 0.29$^{*\triangle}$	7.64 ± 1.12$^{*\triangle}$	6.31 ± 1.79$^{*\triangle}$	112.33 ± 27.83$^{*\triangle}$

Note. Compared with the conventional PCI group after treatment, $^{*}P < 0.05$; compared with the same group before treatment, $^{\triangle}P < 0.05$.

4. Discussion

As a common treatment for AMI, PCI can open narrowed or occluded blood vessels, increase myocardial blood supply, and significantly improve myocardial diastolic and systolic function [7]. However, while blood reperfusion increases blood supply, it may also aggravate myocardial damage and cause IRI, which manifests as severe or even fatal arrhythmia, heart failure, or cardiogenic shock [8]. With the development and popularization of PCI, IRI has received more and more clinical attention, but its mechanism has not yet been fully clarified. Studies have shown that calcium ion overload, the production of a large number of oxygen free radicals, and the secretion of endothelial factors by vascular endothelial cells may be related to this pathophysiological process [9]. In addition, the activation of neutrophils, the increase of myocardial automaticity, and the Vf threshold of ischemic myocardium, the decline of myocardial electrolytes, myocardial electrolyte disturbance, etc. may be involved in the occurrence of IRI [10]. RA is one of the common manifestations of IRI. The occurrence of RA will not only aggravate the damage to the ischemic myocardium but also have a serious impact on hemodynamics. If it is not terminated in time, it may lead to further deterioration of cardiac function and further increase the mortality rate. Therefore, early treatment and prevention of ventricular arrhythmia after myocardial infarction has become an important measure to reduce its mortality [11]. Therefore, effective intervention for RA has important clinical significance.

Amiodarone is a class III antiarrhythmic drug that can delay ischemic myocardial conduction and reduce the action potential of ischemic and nonischemic myocardium, thereby reducing reentrant excitation and triggered activity and helping to inhibit the occurrence of arrhythmia [12]. Clinical studies have shown that in acute myocardial ischemia or myocardial infarction, amiodarone can increase the activity of ion channels without aggravating the deterioration of cardiac function and has no effect on myocardial ischemia [13, 14]. All kinds of arrhythmia combined in the blood have a better effect. In this study, the incidence of RA in the conventional PCI group and the amiodarone intervention group was 67.4% and 36.4%, respectively. The incidence of RA in the AMI patients with amiodarone intervention was

significantly lower, and the proportion of various ventricular arrhythmias, especially the occurrence of ventricular fibrillation, was significantly lower than that of the conventional group. This suggests that amiodarone has a better preventive effect on the occurrence of RA, especially ventricular arrhythmia, thereby reducing the risk of ventricular tachycardia.

In IRI, amiodarone not only acts as an antiarrhythmic but also protects cardiomyocytes [15]. After the occurrence of AMI, the permeability of the myocardial cell membrane increases, causing the intracellular CK-MB and cTnI to leak out, resulting in an increase in the concentration of CK-MB and cTnI in the blood of patients, so the levels of the two are more sensitive indicators to reflect the degree of myocardial injury [16]. Animal experiments have shown that amiodarone can reduce serum CK-MB and cTnI levels in rats with myocardial ischemia-reperfusion, suggesting that it can alleviate acute myocardial ischemia-reperfusion injury in rats [17]. In this study, the serum cTnI and CK-MB levels in the amiodarone intervention group after PCI were significantly lower than those in the routine PCI group, suggesting that in patients with AMI undergoing emergency PCI, the use of amiodarone intervention can reduce myocardial injury.

Activation of neutrophils is an important pathway for IRI. IL-6 is a cytokine that mediates inflammatory responses, and inhibiting the release of inflammatory factors can reduce the accumulation of neutrophils in microvessels, thereby reducing myocardial damage [18]. In addition, according to research, hs-CRP content was significantly negatively correlated with the prognosis of PCI patients [19]. In this study, the levels of serum IL-6 and hs-CRP in patients after PCI were higher than those before treatment, indicating that reperfusion activated neutrophils and caused a large number of inflammatory factors to be released. The levels of serum IL-6 and hs-CRP in AMI patients treated with amiodarone after PCI were significantly lower than those in the conventional PCI group, indicating that amiodarone can improve the level of inflammatory factors, thereby effectively reducing IRI. In addition to the above mechanisms, amiodarone also can inhibit Na^+/Ca^{2+} exchange protein, thereby reducing calcium overload during blood reperfusion.

In conclusion, amiodarone can protect ischemic myocardium in various ways. Preoperative amiodarone intervention in patients with AMI can reduce the levels of serum IL-6, hs-CRP, CK-MB, and cTnI after PCI, reduce the damage caused by reperfusion, thereby reducing the occurrence of RA and providing a basis for preventing the occurrence of RA after PCI [20].

Data Availability

The raw data supporting the conclusion of this article will be available by the corresponding author without undue reservation.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Retraction

Retracted: Balloon Eustachian Tuboplasty and Grommet Insertion: A Combined Surgical Treatment for Chronic Suppurative Otitis Media with Eustachian Tube Dysfunction

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] S. Lu, J. Xu, H. Lu, and W. Chi, "Balloon Eustachian Tuboplasty and Grommet Insertion: A Combined Surgical Treatment for Chronic Suppurative Otitis Media with Eustachian Tube Dysfunction," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 9516029, 7 pages, 2022.

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Research Article

Balloon Eustachian Tuboplasty and Grommet Insertion: A Combined Surgical Treatment for Chronic Suppurative Otitis Media with Eustachian Tube Dysfunction

ShuXuan Lu, Jin Xu, HongYi Lu, and WanLei Chi

Otolaryngological Department, TongDe Hospital of Zhejiang Province, Hangzhou, China

Correspondence should be addressed to WanLei Chi; chiwanlei2022@163.com

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Objectives. This study aims to evaluate the effectiveness of Balloon Eustachian tuboplasty (BET) and grommet insertion in patients having chronic suppurative otitis media combined with eustachian tube dysfunction (CSOM-ETD). *Methods*. We evaluated the data of CSOM-ETD patients ($n = 96$) from January 2019 to January 2021, who were divided into the following groups: 48 cases underwent BET (BET group) and 48 cases underwent BET plus Grommet insertion (BET + Grommet group). The air-bone gap (ABG), Eustachian Tube Dysfunction Questionnaire (ETDQ-7) score, Eustachian tube inflammation scale, Chronic Otitis Media Outcome Test 15 (COMOT-15), Valsalva maneuver, and patient satisfaction were evaluated after surgery. *Results*. The postoperative ABG in the BET + Grommet group was better than that in the BET. In addition, the ABG was improved obviously in the BET + Grommet group at 6 and 12 months after the corresponding surgery. Moreover, the Eustachian tube inflammation scale, ETDQ-7, and COMOT-15 scores were reduced after the treatment with the combination of BET and Grommet insertion at 6 and 12 months. The postoperative ETDQ-7 score, Eustachian tube inflammation scale, and COMOT-15 score were lower in the BET + Grommet group than that in the BET group. The percentage of patients who could perform a positive Valsalva maneuver was significantly higher in the BET + Grommet group than that in the BET group at 6 months and 12 months after surgery with increased patient satisfaction. *Conclusion*. Our results demonstrate that BET plus Grommet insertion showed better treatment efficacy for patients with CSOM-ETD than BET alone via improving the Eustachian tube function hearing outcome and quality of life with less Eustachian tube inflammation.

1. Introduction

Otitis media (OM), characterized by infection, inflammation, and the production of persistent effusions in the middle ear, mainly includes acute otitis media (AOM), chronic otitis media with effusion (COME; glue ear), and chronic suppurative otitis media (CSOM) [1,2]. CSOM (sometimes referred to chronic OM [3]) is a chronic polymicrobial infection with perforation of the tympanic membrane [4,5], thus being the common and major cause of persistent or intermittent ear discharge, as well as acquired hearing impairment and disability [2,6]. The hearing loss had a negative impact on the quality of life via affecting the speech and language skills, employment prospects, and children's psychosocial and cognitive development [2]. Moreover, mortality was increased due to complications of CSOM, for instance, the intracranial complications (brain abscess and meningitis) are the most common causes of death in CSOM patients [7]. Worth mentioning, eustachian tube dysfunction (ETD) was reported to impair pressure equilibration in the middle ear and perturb the middle ear aeration, thus resulting in the classic symptoms of CSOM, which is found in 70% of patients undergoing middle ear surgery [8]. Therefore, finding an effective therapy for patients having CSOM combined with ETD (CSOM-ETD) is urgent and necessary.

Balloon Eustachian tuboplasty (BET), as a second-line treatment in cases in which adenoidectomy and paracentesis have failed, is a treatment option used to solve ETD [9,10]. Besides, it has been also widely used as a surgical approach

for OM [11,12], which, however, did not achieve significant symptom improvement with an effective rate of only 66% [13]. A previous study showed that simultaneous BET and hearing reconstruction surgery can effectively improve the hearing degree in CSOM-ETD patients with better Eustachian tube function [14]. Moreover, BET could be used as an adjunctive procedure in the treatment of CSOM with obstructive Eustachian tube dysfunction (OETD) [15]. The Grommets insertion (also known as ventilation or tympanostomy tubes) as one of the most common surgical procedures for OM [16,17] cannot directly resolve ETD being associated with several complications, such as infection, persistent perforation, and tympanosclerosis [18]. According to a previous study, the BET combined with grommet insertion could effectively reduce the complications for patients with chronic dilation Eustachian tube dysfunction (CDETD) [19]. Therefore, we performed this retrospective study to determine the combined effectiveness of BET and grommet insertion in CSOM-ETD patients via evaluating the hearing ability, eustachian tube function, Eustachian tube inflammation, quality of life, and patient satisfaction.

2. Materials and Methods

2.1. Demographic Data of Subjects. A total of 96 ears from 96 patients having CSOM combined with ETD (CSOM-ETD) were observed from January 2019 to January 2021 with the age ranged from 23 to 61 years, who were divided into the following groups: 48 cases underwent BET (BET group), and 48 cases underwent BET plus grommet insertion (BET + -Grommet group).

2.2. Inclusion and Exclusion Criteria. All CSOM-ETD subjects fulfilled the following inclusion criteria: (1) The patients were diagnosed as CSOM, a perforated tympanic membrane with persistent drainage from the middle ear lasting >6~12 weeks [20]; (2) Patients were identified as severe ETD according to the Eustachian Tube Dysfunction Questionnaire (ETDQ-7, a seven-question survey, Table 1) with the total score of ≥14.5 (mean score ≥2.1) and the symptoms lasting more than 3 months [15,21]. Exclusion criteria: (1) Patients had previously undergone treatment; (2) Patients were due for revision procedure; (3) Patients had a congenital ear anomaly, a history of ear surgery within the past 6 months, a history of head and neck cancer, acute otitis media, refractory chronic rhinosinusitis, recent use of ototoxic medications, or pregnancy.

2.3. Surgical Procedure. All patients performed BET surgery under general anesthesia. In brief, a balloon catheter (20 mm in length and 3 mm in width) was introduced into the cartilaginous part of the Eustachian tube endoscopically through the nasal cavity, which was inflated with distilled water to achieve a pressure of 10 bars for maintaining 2 minutes. In the BET + Grommet group, the patients also performed bilateral insertion of ventilation tubes in the tympanic membranes. All patients were followed up for 12 months.

2.4. Hearing Test Using Air-Bone Gap (ABG). Using a Madsen OB922 pure-tone audiometer (Otometrics, Taastrup, Denmark), the air and bone conduction thresholds were measured at frequencies of 500 Hz, 1 kHz, 2 kHz, and 4 kHz, followed by calculating the air-bone gap (ABG). Surgical success was defined as an ABG ≤20 dB [22].

2.5. Chronic Otitis Media Outcome Test 15 (COMOT-15). The disease-specific quality of life (QoL) was measured using COMOT-15 (total score: 0~100) [23], which consists of three subscales called ear symptoms, hearing function, and mental health, as well as two other questions: (1) an overall evaluation of the impact of CSOM on QoL and (2) the frequency of doctor visits as a result of CSOM in the previous 6 months. Higher scores in the COMOT-15 overall score correlate with a poorer QoL.

2.6. Eustachian Tube Inflammation Scale. Using nasal endoscopy, the assessment of Eustachian tube inflammation from normal to severely inflamed mucosa (Grade 1–4) was based on mucosal inflammation within the nasopharyngeal orifice and lumen, as well as the Eustachian tube function according to a previous study [24].

2.7. Positive Valsalva Maneuver and Subjective Satisfaction. When performing the Valsalva maneuver, the patient could find the "pop" sound in their ears which indicated positive Valsalva maneuver. At 6 months and 12 months postoperatively, patients were asked for their opinion on the surgery based on the satisfied or dissatisfied [25].

2.8. Statistical Analysis. All two-sided P values are regarded as statistical significance at the 0.05 level. The descriptive statistics presented as means ± SD and categorical variables as counts (n) and percentages (%) were analyzed using SPSS Statistics. The χ^2 test was performed to compare categorical variables between groups, and the Student's t-test to compare descriptive statistics. The paired t-test was performed to compare pre and postoperative data.

3. Results

3.1. General Characteristics of the CSOM-ETD Patients in the Two Groups. Demographic data for CSOM-ETD patients in the BET group and the BET + Grommet group are shown in Table 2, which showed no significance of age (42.52 ± 10.90 years vs. 40.27 ± 12.05 years, $P = 0.340$), gender ($P = 0.683$), and ear sides ($P = 0.100$) between the two groups.

3.2. Improvement of ABG after the Treatment with the Combination of BET and Grommet Insertion. We determined the postoperative ABG and the improvement in ABG after surgery (Table 3 and Figure 1). The average preoperative ABG was 24.19 ± 12.8 dB in the BET group and 25.50 ± 10.51 dB in the BET + Grommet group with no significant difference ($P = 0.584$). Moreover, the postoperative ABG in the BET + Grommet group (6 months:

Table 1: Evaluation of Eustachian tube function by the Eustachian Tube Dysfunction Questionnaire (ETDQ-7).

Symptom	No problem	Moderate problem	Severe problem
Pressure in the ears?			
Pain in the ears?			
A feeling that your ears are clogged?			
Ear symptoms when you have a cold or sinusitis?	1~2	3~5	6~7
Cracking or popping sounds in the ears?			
Ringing in the ears?			
A feeling that your hearing is muffled?			
Patients with ETD	ETDQ-7 total score of 14.5 (mean item score 2.1)		

18.06 ± 10.34 dB; 12 months: 15.40 ± 10.12 dB) was better than that in the BET group (6 months: 23.31 ± 10.56 dB; 12 months: 22.29 ± 10.65 dB, both $P < 0.05$). In addition, the ABG was obviously decreased in the BET + Grommet group at 6 and 12 months after the corresponding surgery (both $P < 0.05$). A postoperative ABG of ≤20 dB was observed in 43.75% (6 months) and 45.83% (12 months) patients in the BET group and 54.17% (6 months) and 66.67% (12 months) patients in the BET + Grommet group.

3.3. Improvement of ETDQ-7, Eustachian Tube Inflammation Scale, and COMOT-15 after the Treatment with the Combination of BET and Grommet Insertion. As illustrated in Table 4 and Figure 2, the preoperative ETDQ-7 scores (BET + Grommet group: 27.19 ± 6.11; BET group: 26.4 ± 5.56) and Eustachian tube inflammation scale (BET + Grommet group: 2.98 ± 0.81; BET group: 3.08 ± 0.74) showed no significant difference between the two groups (both $P > 0.05$). The Eustachian tube inflammation scale in the BET + Grommet group (6 months: 1.92 ± 0.87; 12 months: 1.48 ± 0.50) and the BET group (6 months: 2.56 ± 1.17; 12 months: 2.04 ± 0.82) was decreased at 6 and 12 months after surgery (all $P < 0.05$). Moreover, the ETDQ-7 scores were reduced after the treatment with the combination of BET and Grommet insertion at 6 months (21.77 ± 6.34) and 12 months (18.04 ± 6.38, both $P < 0.05$). The postoperative ETDQ-7 score and Eustachian tube inflammation scale were lower in the BET + Grommet group than the BET group (all $P < 0.05$). In addition, 6 and 12 months after surgery, there were only one (2.08%) and three (6.25%) patients in the BET group, but 12.50% (6/48) and 31.25% (15/48) in the BET + Grommet group who achieved a normal ETDQ-7 score of less than or equal to 14.

3.4. Improvement of QoL after the Treatment with the Combination of BET and Grommet Insertion. Based on the result of COMOT-15 score (Table 4 and Figure 2), we found no significant difference in preoperative QoL between the BET + Grommet group (40.60 ± 15.92) and the BET group (40.79 ± 15.49, $P = 0.954$), which was improved in both groups after the treatments at 6 months (BET + Grommet group: 33.42 ± 15.58; BET group: 39.98 ± 15.03) and 12 months (BET + Grommet group: 30.60 ± 15.89; BET group: 38.38 ± 15.54, all $P < 0.05$). Besides, the combination of BET and Grommet insertion had better effect on improving the QoL of CSOM-ETD patients than those receiving BET alone (both $P < 0.05$).

Table 2: General characteristics of the CSOM-ETD patients in the two groups.

	BET group	BET + Grommet group	P
Age (years)	42.52 ± 10.90 (25~60)	40.27 ± 12.05 (23~61)	0.340
Gender			
Male	25	22	
Female	23	26	0.683
Ear sides			
Left	17	26	
Right	31	22	0.100

Table 3: The preoperative and postoperative air-bone gap (ABG) of the CSOM-ETD patients in the two groups.

Groups	Preoperative	Postoperative	
		6 months	12 months
BET group	24.19 ± 12.8	23.31 ± 10.56	22.29 ± 10.65
BET + Grommet group	25.50 ± 10.51	18.06 ± 10.34*	15.40 ± 10.12*
P	0.584	0.016	0.002

Note: *$P < 0.05$, the intragroup comparison with preoperative data.

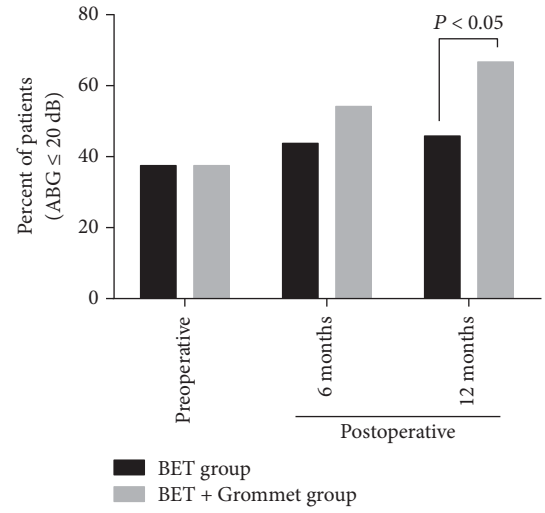

Figure 1: The comparison of hearing outcome after surgery between the BET ($n = 48$) and the BET + Grommet group ($n = 48$). Note: patients with postoperative air-bone gap (ABG) ≤ 20 dB were considered as functionally successful.

Table 4: Improvement of ETDQ-7, Eustachian tube inflammation scale, and COMOT-15 after the treatment with the combination of BET and Grommet insertion.

	Preoperative	Postoperative	
		6 months	12 months
ETDQ-7 scores			
BET group	26.4 ± 5.56	24.75 ± 5.88	22.23 ± 6.34*
BET + Grommet group	27.19 ± 6.11	21.77 ± 6.34*	18.04 ± 6.38*#
P	0.509	0.019	0.002
Eustachian tube inflammation scale			
BET group	3.08 ± 0.74	2.56 ± 1.17*	2.04 ± 0.82*#
BET + Grommet group	2.98 ± 0.81	1.92 ± 0.87*	1.48 ± 0.50*#
P	0.513	0.003	<0.001
COMOT-15 scores			
BET group	40.79 ± 15.49	39.98 ± 15.03*	38.38 ± 15.54*#
BET + Grommet group	40.60 ± 15.92	33.42 ± 15.58*	30.60 ± 15.89*#
P	0.954	0.038	0.0173

Note: *$P < 0.05$, the intragroup comparison with preoperative data; #$P < 0.05$, intragroup comparison with the postoperative data at 6 months.

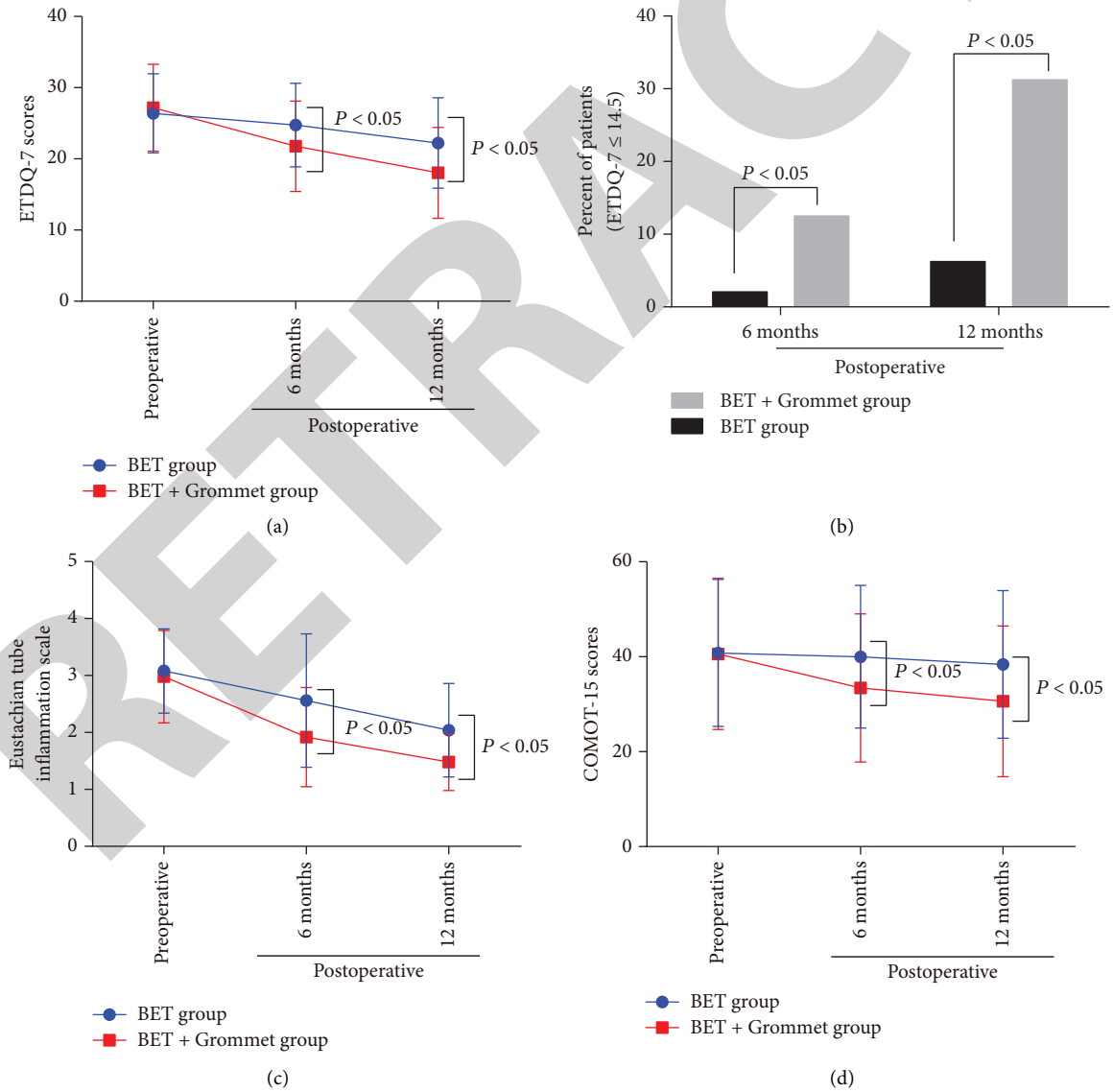

Figure 2: Comparison of postoperative ETDQ-7, Eustachian tube inflammation scale, and COMOT-15 between the BET ($n = 48$) and the BET + Grommet group ($n = 48$). (a, b) Comparison of postoperative ETDQ-7 between the BET + Grommet group and the BET group. Patients were identified as ETD according to the ETDQ-7 with the total score of ≥14.5. (c) Comparison of Eustachian tube inflammation scale between the two groups. (d) Comparison of postoperative quality of life (QoL) between the BET + Grommet group and the BET group.

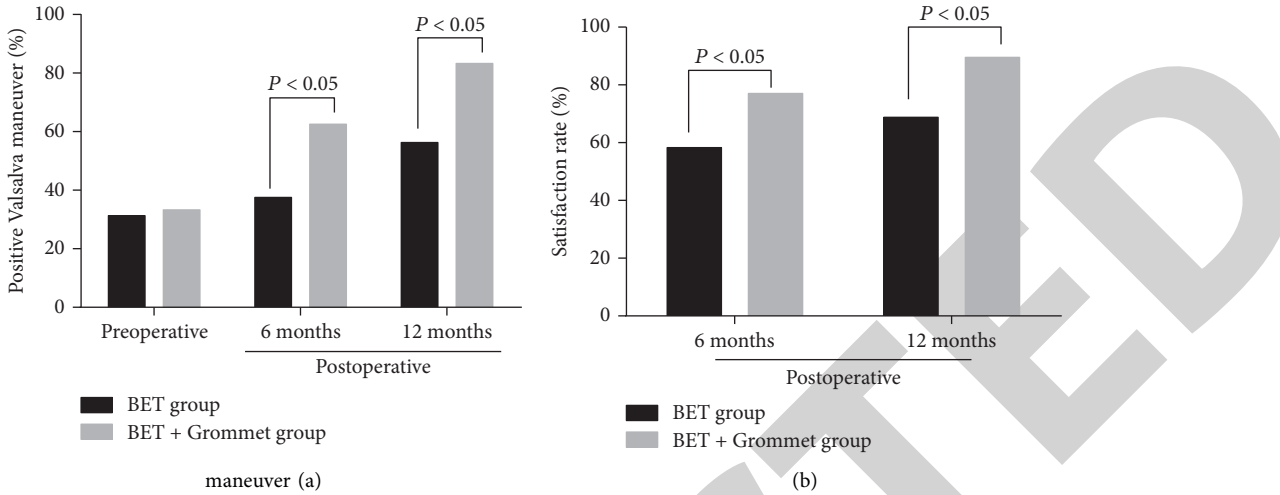

Figure 3: Comparison of positive Valsalva maneuver (a) and patient satisfaction (b) between the BET ($n = 48$) and the BET + Grommet group ($n = 48$).

3.5. Comparison of Positive Valsalva Maneuver and Patient Satisfaction in the Two Groups. The percentage of patients who could perform a positive Valsalva maneuver was significantly higher in the BET + Grommet group than in the BET group at 6 months (62.50% vs. 37.50%) and 12 months (83.3% vs. 56.25%) after surgery (Figure 3(a)). Additionally, the percentage of satisfactory outcomes in the BET + Grommet group vs the BET group were 58.33% and 77.08% at 6 months after surgery, as well as 68.75% and 89.58% at 12 months after surgery, respectively (Figure 3(b)). Furthermore, only few complications were seen during these the procedures, namely, only two patients in the BET group kept slight tenderness, which was relived at 6 and 12 months postoperatively, indicating there was no difference regarding to the adverse events between the two groups.

4. Discussion

Grommet insertions are traditional treatment for ETD and/or recurrent/chronic otitis media because of the persistent middle ear fluid, frequent ear infections, or ear infections that persist after antibiotic therapy, to re-establish ambient-middle ear pressure, resolving inflammation, clearing effusions, and improve hearing, thus being the most commonly performed ambulatory procedure [26–28]. BET as a minimally invasive intervention first described in 2010 has been successfully investigated by randomized control trials and clinical studies in the past decade [29,30]. Considering BET surgery did not achieve significant symptom improvement of OM, the combination treatment with BET and Grommet insertion has been evaluated in OM [12,31,32] and ETD [19].

As demonstrated by Chen S et al., at 12 months after the operation, the ABG an important indicator of hearing status [33] in children having otitis media with effusion treated with BET combined with myringotomy and Grommet insertion was smaller than those treated with myringotomy alone [34]. Moreover, the average ABG improvement was found in patients with CSOM and OETD treating with the combination of tympanoplasty and BET when compared with the control subjects enrolled for tympanoplasty [15], suggesting both Grommet insertion and BET could improve the hearing ability. In our study, the ABG was decreased obviously in the BET + Grommet group at 6 and 12 months after the surgery, and the postoperative ABG in the BET + Grommet group was better than that in the BET group. Additionally, based on the Japan Clinical Otology Committee criteria [35], a postoperative ABG of ≤20 dB for calculating hearing improvement was observed in 43.75% (6 months) and 45.83% (12 months) patients in the BET group and 54.17% (6 months) and 64.58% (12 months) patients in the BET + Grommet group. All mentioned above indicating the combination of BET and Grommet insertion could significantly increase the hearing function.

It has generally been considered that surgery for improving hearing can be considered only when eustachian tube function becomes normal [36]. COME patients treated with BET and grommet insertion was reported to have an improvement in eustachian tube function and structure [12,32]. In a previous study, the ETDQ-7 score with total score of ≥14.5 (mean score of ≥2.1) showed 100% sensitivity and 100% specificity for categorizing a patient as having ETD [37]. At 6 and 12 months after surgery, there were only 2.08% and 6.25% patients in the BET group who achieved a normal ETDQ-7 score ≤14.5, respectively, but 12.50% and 31.25% in the BET + Grommet group. In addition, ETDQ-7 and COMOT-15 scores were reduced after the treatment with the combination of BET and Grommet insertion at 6 and 12 months with the improvement of Valsalva maneuver. The postoperative ETDQ-7 and COMOT-15 scores were lower in the BET + Grommet group than the BET group accompanied by higher positive Valsalva maneuver, indicating the significant efficacy of this combination for the treatment of ETD. Because mucosal inflammation is the most common cause for ETD [24], a scale for Eustachian tube mucosal inflammation was determined, and the result revealed that the alleviated inflammation in both BET + Grommet group and BET group at 6 and 12 months after

surgery, especially in the BET + Grommet group. These results suggested that the combination treatment could alleviate ETD via attenuating the inflammation status, thus improving the HoL of CSOM-ETD patients.

It was considered that BET plus Grommet Insertion can be used as an appropriate approach for the treatment of COME with ETD, which is the main strength of our study. However, this study has several limitations. Firstly, similar to previous studies in this field, this retrospective study did not involve a control group, thus causing lower credibility of our results, which should be verified by the randomized controlled trial. Secondly, follow-up was limited to only 12 months after surgery in the current study, the treatment effect should be compared over a longer time span with a large cohort of patients.

In conclusion, BET plus Grommet insertion showed better treatment efficacy for patients with CSOM-ETD than BET alone via improving the Eustachian tube function and hearing outcome with less Eustachian tube inflammation, as well as increasing patient satisfaction.

Data Availability

The data supporting the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

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Retraction

Retracted: Analysis of the Efficacy of Multidrug Combination Chemotherapy Regimens for Osteosarcoma and the Management of Chemotherapeutic Reactions

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] D. Tian, K. Feng, X. Wu, C. Gao, and L. Hu, "Analysis of the Efficacy of Multidrug Combination Chemotherapy Regimens for Osteosarcoma and the Management of Chemotherapeutic Reactions," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 6510429, 6 pages, 2022.

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Research Article

Analysis of the Efficacy of Multidrug Combination Chemotherapy Regimens for Osteosarcoma and the Management of Chemotherapeutic Reactions

Dawei Tian,[1,2] Kun Feng,[2] Xiaobao Wu,[1] Chao Gao ,[1] and Lixin Hu [1]

[1]*Department of Orthopedics, Sinopharm Dongfeng General Hospital of Hubei University of Medicine, Shiyan 442000, Hubei, China*
[2]*Department of Postgraduate Training Base, Sinopharm Dongfeng General Hospital of Jinzhou Medical University and Hubei University of Medicine, Shiyan 442000, Hubei, China*

Correspondence should be addressed to Chao Gao; xm1234560613@163.com and Lixin Hu; wwwhulixin@163.com

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Purpose. To analyse the efficacy of high-dose methotrexate + adriamycin + cisplatin (HD-MTX + ADR + PDD, MAP) regimens applied to osteosarcoma and the pretreatment and resolution of chemotherapeutic reactions. *Methods*. The clinical data of 21 patients with osteosarcoma in our hospital from January 2015 to January 2018 were retrospectively analysed. All patients were treated with the MAP protocol, 21 days for 1 cycle, and treated with artificial joint replacement or amputation after 3~4 cycles of treatment. The tumour tissue necrosis rate, limb preservation success rate after treatment, and chemotherapy response during chemotherapy were counted and analysed for all patients. A local recurrence rate, a distant metastasis rate, and an overall survival rate were recorded during the 3-year follow-up period. *Results*. After treatment, the percentage of tumour tissue necrosis ≥90% was 85.71% (18/21) and the percentage of successful limb preservation was 57.14% (12/21) in 21 patients with osteosarcoma. During chemotherapy, all 21 patients with osteosarcoma experienced various degrees of chemotherapy reactions, mainly bone marrow suppression of 100% (21/21), gastrointestinal reactions of 100% (21/21), liver function impairment of 66.67% (14/21), and cardiotoxicity of 52.38% (11/21), all of which improved and completed treatment after treatment. During the 3-year follow-up period, the 21 patients with osteosarcoma had a local recurrence rate of 9.52% (2/21), a distant metastasis rate of 28.57% (6/21), and an overall survival rate of 80.95% (17/21). *Conclusion*. With stringent protection and relief measures, patients with osteosarcoma treated with the MAP regimen have promising near-term outcomes, with high survival rates over 3 years and tolerable chemotherapy responses. The clinical trial is registered under L2015093.

1. Introduction

Osteosarcoma is a primary malignant tumour of bone tissue, which originates from the mesophyll tissue of undifferentiated bone. The main feature is the presence of spindle-shaped stromal cells that produce bone-like tissue, and fibrous and cartilaginous tissue can also be seen in the tumour tissue. It can occur anywhere in the body, with 80% to 90% occurring in long tubular bones, commonly in the actively growing distal femur, proximal tibial epiphysis, and, to a lesser extent, the proximal humerus, accounting for approximately 11.7% of primary bone tumours in humans [1, 2]. Osteosarcoma mostly occurs in young and middle-aged people aged 15 to 25 years old. Clinical manifestations include swollen and painful limbs, high local temperature, varicose veins, mental decrepitude, weight loss, loss of appetite, motor impairment, and other typical symptoms, showing rapid progression, poor treatment effect, and high mortality rate [3, 4].

Currently, preoperative neoadjuvant chemotherapy combined with surgical resection is more common in the treatment of osteosarcoma, with a five-year tumour-free

survival rate of 50–70% and a local recurrence rate of 5–10% in patients [5, 6]. However, for patients with lung metastases present at the time of initial diagnosis, the 2-year tumour-free survival rate is only 28% if there are ≥3 metastases [7]. In recent years, the recommended drugs for neoadjuvant chemotherapy in osteosarcoma are high-dose methotrexate (HD-MTX), adriamycin (ADR), cisplatin (PDD), and ifosfamide (IFO), administered mainly in combination or in sequential doses, which can significantly improve the prognosis of patients with nonmetastatic osteosarcoma [8]. However, in view of the late development of chemotherapy for osteosarcoma in China, chemotherapy for osteosarcoma mostly refers to foreign chemotherapy schemes. Clinical research [9] shows that the efficacy of these schemes applied to domestic patients is limited. Therefore, it is necessary to explore and formulate chemotherapy schemes suitable for domestic patients.

This study analyses the efficacy of the application of the HD-MTX + ADR + PDD (MAP) regimen for the treatment of osteosarcoma and the pretreatment and resolution of chemotherapeutic reactions. Details are as follows.

2. Materials and Methods

2.1. General Data. Retrospective analysis of the clinical data of 21 patients with osteosarcoma in our hospital from January 2015 to January 2018: inclusion criteria: ① pathologically confirmed untreated primary osteosarcoma. ② No previous history of tumours. ③ Stages I and II, as determined by Enneking staging. ④ No other conditions that might interfere with chemotherapy. ⑤ The patient's clinical profile was complete. ⑥ All patients were treated in our hospital with the MAP protocol combined with prosthetic arthroplasty or amputation. The general clinical information of the 21 patients with osteosarcoma is shown in Table 1.

Table 1: General clinical information of 21 patients with osteosarcoma (*n*, %).

Clinical information	*n*	Percentage
Gender		
Male	12	57.14
Female	9	42.86
Age/years		
< 15	1	4.76
15~25	18	85.72
> 25	2	9.52
Type of pathology		
Common type	19	90.48
Telangiectatic type	1	4.76
Chondroblastoma-like osteosarcoma	1	4.76
Enneking staging		
I	8	38.10
II	13	61.90
Tumour location		
Upper tibia	10	47.62
Lower femur	6	28.57
Upper femur	3	14.29
Humerus	1	4.76
Upper ulna	1	4.76
Alkaline phosphatase (AKP) levels		
Normal	7	33.33
Rise	14	66.67
Preoperative chemotherapy cycle		
3 cycles	15	71.43
4 cycles	6	28.57

2.2. Chemotherapy Regimens. MAP regimen: MTX (Yue Kang Pharmaceutical Group Co., Ltd., Approval No. H20113120) at 10–12 g/m^2 was administered intravenously for 6 h on the first day and 6 hours after the intravenous infusion of MTX; 25 mg of calcium folinate (Jiangsu Hengrui Pharmaceutical Co., Ltd., Approval No. H20000584) was injected intramuscularly for rescue, once every 6 hours for a total of 14–16 times; ADR (Hanhui Pharmaceutical Co., Ltd., Approval No. H33021980) at 50 mg/m^2 was applied in 2 divided doses on days 6 and 7; PDD (Qilu Pharmaceutical Co., Ltd., Approval No. H37021357) at 80–100 mg/m^2 was applied in 2 divided doses on day 6 and 7; intravenous rehydration was 3,000 ml per day during MTX treatment and the patient was advised to drink plenty of fluids to promote adequate hydration; the patient was also given 5% sodium bicarbonate (Shandong Shenglu Pharmaceutical Co., Ltd., Approved No. H37021234) 250 ml intravenously twice/day, and took sodium bicarbonate tablets (Hebei Sangshi Pharmaceutical Co., Ltd., Approved No. H13022430) of 1.0 g orally 3 times/day and allopurinol (Chongqing Qingyang Pharmaceutical Co., Ltd., Approval No. H50020548) of 100 mg orally 3 times/day to alkalinize the urine and supplemented with acid-suppressing (e.g., proton pump inhibitor) antiemetic drugs (e.g. metoclopramide and 5-hydroxytryptamine inhibitor) orally, and urine was monitored daily to maintain pH between 7 and 9 for a total of 5 d. During the treatment of PDD and ADR, at least 2500 ml of intravenous fluids were replenished every day, diuretics were used, and blood routine and liver and kidney functions were tested on the 5th day after MTX chemotherapy and the 2nd day after all chemotherapies. 21 days was one cycle. After 3~4 cycles of treatment, the lesion location was reexamined. After MRI and plain film evaluation, artificial joint replacement or amputation was performed.

2.3. Assessment Indicators. The tumour tissue necrosis rate, limb preservation success rate after treatment, and chemotherapy response during chemotherapy were counted and analysed for all patients. Tumour tissue necrosis rate: this was determined according to the Huvos rating system [10], and through the pathological examination of osteosarcoma, the tumour tissue necrosis rate (the largest cross-section of the tumour after decalcification of the postoperative specimen was taken, and the two pathologists jointly judged) and the limb salvage success rate were used to evaluate the overall treatment effect. If the patient had ≥90% tumour tissue necrosis on postoperative pathology, the original regimen of chemotherapy was continued for 3 cycles, if <90%, then high-dose MTX and PDD combined with IFO relief chemotherapy were used

instead. Chemotherapy reactions include bone marrow suppression, gastrointestinal reactions, oral ulcers, hepatic and renal impairment, cardiotoxicity, neurotoxicity, and allergic reactions. The grading criteria for chemotherapy drug toxicities 0–IV were determined according to the WHO standards [11].

Patients' local recurrence rates, distant metastasis rates, and overall survival rates were recorded during the 3-year follow-up period. Local recurrence rate: local recurrence at the primary site of the tumour, usually due to the growth of untreated residual living tumour cells. Distant metastasis rate: the rate of metastasis to the lung, bone, and abdomen. Overall survival rate: follow-up the survival rate of all patients from the beginning of chemotherapy (MAP regimen, surgery) to 1, 2, and 3 years after the end of treatment, including the survival rate with tumour.

2.4. Statistical Methods. SPSS 22.0 software was used. Count data were expressed as ratio (%), and the χ^2 test was used for comparison, while the measurement data were expressed as mean ± standard deviation ($x \pm s$) and compared using the t-test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Analysis of the Recent Outcome of 21 Patients with Osteosarcoma. After treatment, the percentage of patients with tumour tissue necrosis ≥90% was 85.71% (18/21) in 21 patients with osteosarcoma whose pathological type was common, 14.29% (3/21) in patients with tumour tissue necrosis <90%, 57.14% (12/21) in patients with successful limb preservation, and 42.86% (9/21) in patients with failed limb preservation, as seen in Table 2.

3.2. Analysis of Chemotherapy Reactions during Chemotherapy in 21 Patients with Osteosarcoma. During chemotherapy, all 21 patients with osteosarcoma experienced various degrees of chemotherapy reactions, mainly bone marrow suppression of 100% (21/21), gastrointestinal reactions of 100% (21/21), liver function impairment of 66.67% (14/21), and cardiotoxicity of 52.38% (11/21), as seen in Table 3.

3.3. Analysis of the Management of Chemotherapy Reactions in 21 Patients with Osteosarcoma

3.3.1. Hematotoxicity. Haematological toxicity appeared 4–5 days after MTX chemotherapy or 7 days after the end of the whole course of treatment. Treatment was mainly by subcutaneous injection of granulocyte-colony-stimulating factor and granulocyte-macrophage colony stimulating factor, and, if necessary, by transfusion of component blood. We add imipenem and cilastatin sodium for injection and fluconazole for grade IV leukopenia with infection or hyperthermia, along with bedside isolation, ultraviolet disinfection, and treatment in a separate ward or transfer to a laminar flow room. Prompt treatment of ordinary patients with bone marrow suppression of grade II or higher was done. Patients with previous myelosuppression of grade III or higher were treated prophylactically 48 hours after the administration of chemotherapy drugs. After 3~5 days of treatment, the patients recovered gradually, and in severe cases, they recovered to normal in 7~14 days.

Table 2: Recent outcome of 21 patients with osteosarcoma (n, %).

Result	N	Percentage
Tumour tissue necrosis		
≥90%	18	85.71
< 90%	3	14.29
Limb preservation results		
Success	12	57.14
Failure	9	42.86

3.3.2. Gastrointestinal Reactions. Most of them occurred 2–5 days after chemotherapy, vomiting also occurred on the day of administration. Central antiemetic drugs were continuously given until the reaction disappeared, and severe vomiting was temporarily treated with a metoclopramide needle. Patients with frequent diarrhoea were treated with Smecta. Patients with oral ulcers were treated with Kangfuxin gargle, Xilei powder for external use, and compound vitamin B and zinc gluconate tablets orally. Patients with gastrointestinal bleeding were treated with antacids, hemostasis, and blood transfusion. We apply medication promptly after the onset of symptoms and it is cured within 5 days.

3.3.3. Hepatotoxicity. Most of them occurred 2 to 5 days after chemotherapy and were mostly transient liver function abnormalities that recovered quickly after stopping the drug. For those who still had liver damage after stopping the drug, glycine was given continuously to protect the liver and it is cured in 3–6 days.

3.3.4. Cardiotoxicity. It appeared 1 month after chemotherapy. Two of the cases with grade III cardiotoxicity were both sinus tachycardia and one was with T-wave changes. Medication was started after the onset of symptoms and both improved after 2 weeks of treatment with betaloc tablets.

3.3.5. Nephrotoxicity. All cases in this group had mild haematuria and proteinuria, without elevated creatinine or urea nitrogen. All improved after regular review.

3.3.6. Skin Toxicity. The rash appeared on the same day or 3 to 5 days after the drug was administered and was cured 3 to 5 days after antiallergic treatment. Pigmentation appeared in the first month of chemotherapy and gradually faded away about six months after chemotherapy was stopped. Hair loss started 1 month after chemotherapy and could not be graded as all patients were asked to shave their hair at the start of chemotherapy, total hair loss was 100%, and hair regrowth started 1 month after the end of chemotherapy.

Table 3: Chemotherapy reactions during chemotherapy in 21 patients with osteosarcoma (n, %).

Chemotherapy reactions	Grade				
	I	II	III	IV	Total
Hematotoxicity					
Leukopenia	1 (4.76)	5 (23.81)	9 (42.86)	6 (28.57)	21 (100.00)
Decreased haemoglobin	2 (9.52)	4 (19.05)	11 (52.38)	4 (19.05)	21 (100.00)
Decreased platelets	1 (4.76)	1 (4.76)	5 (23.81)	7 (33.33)	14 (66.66)
Gastrointestinal reactions					
Nausea, vomiting	6 (28.57)	9 (42.86)	3 (14.29)	3 (14.29)	21 (100.00)
Oral mucositis	6 (28.57)	3 (14.29)	4 (19.05)	1 (4.76)	14 (66.67)
Gastrointestinal bleeding	3 (14.29)	1 (4.76)	1 (4.76)	0 (0.00)	5 (23.81)
Diarrhoea	1 (4.76)	1 (4.76)	0 (0.00)	0 (0.00)	2 (9.52)
Hepatotoxicity					
Elevated alanine transaminase	6 (28.57)	8 (38.10)	0 (0.00)	0 (0.00)	14 (66.67)
Cardiotoxicity					
Cardiac damage	6 (28.57)	3 (14.29)	2 (9.52)	0 (0.00)	11 (52.38)
Nephrotoxicity					
Haematuria, proteinuria	4 (19.05)	1 (4.76)	0 (0.00)	0 (0.00)	5 (23.81)
Skin toxicity					
Rash	4 (19.05)	2 (9.52)	0 (0.00)	0 (0.00)	6 (28.57)
Pigmentation	2 (9.52)	1 (4.76)	0 (0.00)	0 (0.00)	3 (14.29)

3.3.7. MTX Poisoning. Two cases (9.52%) of MTX toxicity were seen in this group, with clinical manifestations appearing 3 days after the use of HD-MTX, and their various complications were managed symptomatically according to the different symptoms described previously. In 2 cases of poisoning, 1 patient had a low, asymptomatic 72-hour MTX blood level exceedance, calcium folinate 15 mg was added at 6-hour intervals, and the blood drug concentration returned to normal after 1 day. In the other case, the 72-hour MTX blood drug concentration exceeded the limit by a large margin, and the symptoms of toxicity were severe, the most serious of which was a degree IV myelosuppression and a degree IV oral mucositis, which prevented the patient from eating for more than a month due to blood oozing from the mucous membrane of the mouth and lips and restricted mouth opening. The patient was treated with intravenous calcium folinate drip until the MTX blood levels dropped to normal and then gradually improved after more than 1 month of symptomatic treatment.

3.4. Analysis of Local Recurrence and Distant Metastasis Rates in 21 Patients with Osteosarcoma during the 3-Year Follow-Up Period. During the 3-year follow-up period, the local recurrence rates of the 21 patients with osteosarcoma were 0.00% (0/21), 4.76% (1/21), and 9.52% (2/21) in years 1, 2, and 3, respectively, and the distant metastasis rates were 4.76% (1/21), 9.52% (2/21), and 28.57% (6/21), as seen in Figure 1.

3.5. Analysis of the Survival Rate of 21 Patients with Osteosarcoma during the 3-Year Follow-Up Period. During the 3-year follow-up period, the overall survival rates of the 21 patients with osteosarcoma were 90.48% (19/21), 85.71% (18/21), and 80.95% (17/21) at year 1, year 2, and year 3, respectively, as seen in Figure 2.

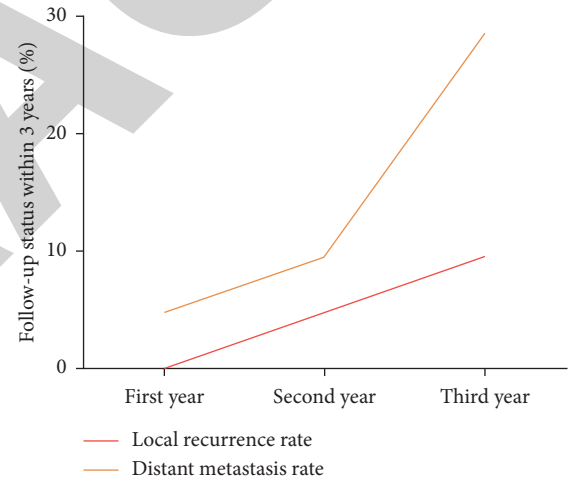

Figure 1: Local recurrence and distant metastasis rates in 21 patients with osteosarcoma during the 3-year follow-up period (%).

4. Discussion

In 2009, the annual meeting of the European Society of Clinical Oncology recommended that the recognised effective and commonly used first-line chemotherapeutic agents be MTX, ADR, PDD, and IFO (Class Ib, Evidence Category A) [12]. The efficiency of the above four agents alone is only close to 30%, but the combination of these agents can have a synergistic effect and may result in 100% tumour necrosis in vivo, in addition to reducing drug resistance development [13].

Currently, the clinical use of MTX, ADR, PDD, and IFO in combination with chemotherapy for osteosarcoma can result in a 5-year survival rate of 44–65%, but some patients still have a poor prognosis [14]. In order to identify treatment strategies to improve osteosarcoma and to determine whether patients have a better or worse risk of local

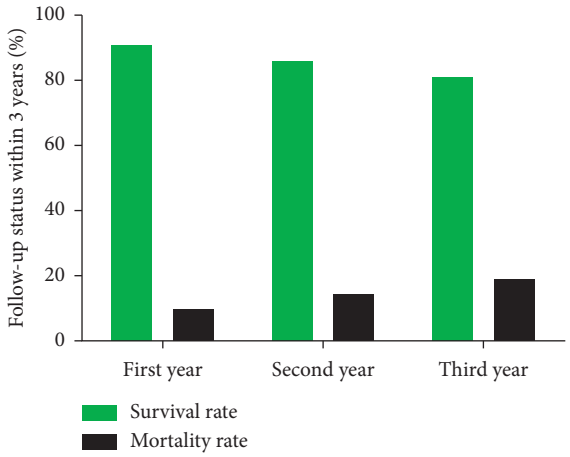

Figure 2: Survival situation of 21 patients with osteosarcoma during the 3-year follow-up period (%).

recurrence, distant metastases and death are significant. In this study, 21 patients with osteosarcoma were treated with HD-MTX combined with ADR and PDD neoadjuvant chemotherapy. After treatment, 85.71% of the 21 patients with osteosarcoma had a tumour necrosis rate ≥90%, and 57.14% had successful limb salvage. The above indicates that the short-term efficacy of patients is obvious. However, due to the small number of patients and the short observation time, it is necessary to accumulate the number of patients in the future to continue to observe the short-term and long-term efficacy of large samples.

HD-MTX has a dramatic effect on bone marrow cells, gastrointestinal tract, skin, oral mucosal cells, and hepatocytes, which have a short cell cycle and rapid proliferation rate, and can lead to a variety of adverse reactions such as bone marrow suppression, gastrointestinal reactions, mucositis, oral ulcers, and liver function damage [15, 16], and the mortality of related adverse reactions is about 6% [17]. Therefore, the status of HD-MTX multidrug combined chemotherapy in the treatment of osteosarcoma is controversial. In this study, 21 patients with osteosarcoma were treated with HD-MTX in combination with ADR and PDD under various control measures. During chemotherapy, all patients experienced various degrees of chemotherapy response. From the incidence of chemotherapy reaction, the main manifestations of patients were bone marrow suppression, gastrointestinal reactions, hair loss, liver function damage, and heart damage. In terms of the grade and degree of chemotherapy reaction, with the exception of haematological toxicity, the majority of patients had mildly reversible side effects, and those with grade III or IV toxicity had mainly haematological, some gastrointestinal reactions, and cardiotoxicity, all of whom improved and completed their treatment after effective management. This shows that the safety of patients with osteosarcoma treated with the MAP regimen is guaranteed under strict protection and relief measures. This study also retrospectively evaluated the survival status of 21 patients with osteosarcoma during the 3-year follow-up period and found that the local recurrence rate was 9.52%, the distant metastasis rate was 28.57%, and the overall survival rate was 80.95% in all patients. The results were generally consistent with previous reports.

Most scholars have concluded that pharmacokinetic parameters such as drug blood peak concentration, area under the drug-time curve, elimination rate, and half-life of HD-MTX used in patients with osteosarcoma are closely related to the degree of adverse effects and prognosis of tumour tissue [18–20]. However, the incidence and severity of adverse effects are more complicated in the case of HD-MTX in combination with multidrug chemotherapy. How to ensure the effective blood peak concentration of MTX without affecting the survival rate of patients and how to reasonably use calcium folinate for detoxification have become an important issue in the multidrug combination chemotherapy regimens containing HD-MTX. In this study, for patients whose MTX blood drug concentration was still >0.1 μmol/L at 72 hours, the blood drug concentration was repeated daily until it was <0.1 μmol/L. At the same time, effective detoxification measures had been taken. For those with low MTX blood levels and mild symptoms of poisoning, oral treatment with calcium folinate was administered and the patient's blood drug concentration returned to normal after 1 day; for those with high MTX blood drug concentration and severe symptoms of poisoning, especially those with severe gastrointestinal reactions, treatment with intravenous calcium folinate injection was used until the blood drug concentration returned to normal. The above monitoring of MTX blood drug concentration and the effective rescue of calcium folinate make the incidence of MTX poisoning affecting the course of chemotherapy in this study only 4.76%, and there are no deaths during chemotherapy. It can be concluded that the use of HD-MTX in combination with ADR and PDD neoadjuvant chemotherapy for the treatment of osteosarcoma patients in this study not only ensures the drug blood peak concentration and efficacy of MTX but also does not lead to an increased incidence of MTX toxicity, which is a multidrug combination chemotherapy regimen with both safety and efficacy.

In summary, the drug toxicities of multidrug combination chemotherapy regimens using HD-MTX-containing chemotherapy are more complex and diverse than those of single-agent HD-MTX chemotherapy, but with stringent protection and relief measures, patients with osteosarcoma treated with the MAP regimen have promising near-term outcomes, with high survival rates over 3 years and tolerable chemotherapy responses.

Data Availability

The data to support this study are available at reasonable request to the corresponding author.

Disclosure

Dawei Tian and Kun Feng are co-first authors.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Retraction

Retracted: Analysis of the Relationship between Nutritional Status and Bone Age and Sexual Development in Children and Adolescents

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] H. Sun, W. Wang, S. Zhang, and C. Lin, "Analysis of the Relationship between Nutritional Status and Bone Age and Sexual Development in Children and Adolescents," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 8325756, 6 pages, 2022.

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Research Article

Analysis of the Relationship between Nutritional Status and Bone Age and Sexual Development in Children and Adolescents

Hong Sun, Weiqun Wang, Shouyuan Zhang, and Chenglei Lin

Department of Pediatrics, Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine, Hangzhou, Zhejiang 310003, China

Correspondence should be addressed to Hong Sun; sunhong09131983@163.com

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Purpose. To observe the correlation between nutritional status, bone age, and sexual development in children and adolescents. *Methods*. 895 children and adolescents who underwent physical examination in the growth and development clinic and height clinic of our hospital from 2019 to 2021 were selected as the research objects. The subjects were divided into emaciation group, normal group, overweight group, and obesity group. The bone age level, bone age assessment, sexual development, and early maturity rate of each group were compared. *Results*. The bone age difference (BAD) of the overweight and obesity groups was higher than that of the normal group, and the BAD of the obesity group was higher than that of the emaciation group ($P < 0.05$). Compared with the normal group, the risk of advancement of bone age in the overweight group increased by 2.674 times (male) and 1.908 times (female), the risk of advancement of bone age in the obesity group increased by 6.376 times (male) and 14.687 times (female), the risk of retardation of bone age in the emaciation group increased by 2.150 times (male) and 3.092 times (female). Whether it was male or female, the sexual development of overweight and obese was higher than that of the normal weight group in the same age group. Among female children, the sexual precocious puberty rate of the overweight + obesity group is higher. *Conclusion*. The nutritional status of children and adolescents is closely related to their bone age and sexual development.

1. Introduction

The nutritional status of children and adolescents is a sensitive index to measure their health level, and improving the nutritional status of children and adolescents is also an important foundation to improve the quality of the population [1]. Lack of nutrition will not only reduce people's immunity but also directly affect their intellectual development, physical development, psychological development, etc. It will also cause children's physical disharmony, lethargy, poor language expression ability, decreased learning ability, and even cause diseases [2]. In recent years, with the improvement of living standards, the detection rates of overweight and obesity among children and adolescents have been increasing year by year worldwide. Obese children and adolescents are often accompanied by lipid metabolism disorders, which are directly related to the occurrence of hypertension, coronary heart disease, and type 2 diabetes [3]. Obesity has become a serious global public health problem. Studies have predicted that by 2030, the prevalence of overweight + obesity among adults, school-aged children, and preschool-aged children will be 65.3%, 31.8%, and 15.6%, respectively, and the number of overweight + obesity patients will reach 789.95 million, 58.92 million, and 18.19 million, respectively [4]. Lack of nutrition and overnutrition have a long-term impact on children and adolescents, which may reduce the level of physical health in adulthood. At the same time, unhealthy nutritional status will also have a certain negative impact on the psychology of children and adolescents, resulting in psychological problems such as inferiority, being unsociable, loneliness, and irritability [5]. Therefore, ensuring proper nutritional intake of the human body is particularly important for the healthy growth of children and adolescents. Body mass index (BMI) is an

important index to measure the body shape that is often used to quickly evaluate the nutritional status. BMI is often used clinically in the field of monitoring and screening children's obesity and thinness [6].

Bone age is an index to evaluate the maturity of skeletal development in children and adolescents. Compared with height, weight, chest circumference and other growth, and development-related indicators, bone age can more accurately reflect the level of individual growth and development [7]. In addition, studies have shown that the initiation of sexual development is related to nutritional metabolism, genetics, environment, and other factors [8]. Precocious puberty is an abnormal growth and development, which is characterized by the early appearance of puberty characteristics. It is generally believed that obesity in children and adolescents is closely related to precocious puberty [9]. At present, the nutritional status, growth and development, and sexual characteristics of children and adolescents have attracted widespread attention. Through physical examination of 895 children and adolescents, this study observed the correlation between their nutritional status, bone age, and sexual development.

2. Materials and Methods

2.1. Research Object. 895 children and adolescents who underwent physical examination in the growth and development clinic and height clinic of our hospital from 2019 to 2021 were selected as the research objects. Inclusion criteria were as follows: 4–17 years old; able to cooperate with physical examination; and clinical data are complete. Exclusion criteria were as follows: severe organic diseases; suffering from genetic syndrome; suffering from congenital malformation; skeletal developmental malformation; severe scoliosis; abnormal sexual differentiation; drugs such as growth hormone and sex development inhibitors that affect the research results are being used; and long-term use of corticosteroids, antihypertensive, and lipid-lowering drugs.

2.2. Research Methods

① The height and weight of the subjects were measured by standardized measuring tools and methods. In the measurement of height and weight, it is necessary to carry out quality control. Height measurement is accurate to 0.1 cm and weight measurement is accurate to 0.1 kg. Measuring instruments are verified and calibrated before use. The measurement needs to be carried out three times. Calculate the BMI of the subjects. BMI (kg/m^2) = weight/height^2.

② The nutritional status of children and adolescents was assessed according to the classification standards recommended by the WHO. Height and weight < M-2SD are defined as emaciation, BMI > P85 as overweight, and BMI > P95 as obesity.

③ Bone age was judged by X-ray film of the left wrist bone. Bone age assessment was performed by Yitu Children bone age assessment software. Bone age difference (BAD) = bone age−age. −1 year old ≤ BAD ≤ +1 year old is defined as normal bone age development, BAD > +1 year old is defined as advancement of bone age, BAD < −1 year old is defined as retardation of bone age.

④ The development level of sexual characteristics is evaluated by uniformly trained clinicians of the same sex as the examinee, including breasts and pubic hair of girls, external genitalia, testicular volume, and pubic hair of boys. The assessment of breast development in girls was performed by visual inspection combined with palpation, the assessment of testicular volume in boys was performed by palpation, and the assessment of pubic hair development was performed by visual inspection. When the size of the testicles on both sides of the boy is inconsistent, the larger side is selected; when the breast development stages of the two sides of the girl are inconsistent, the more mature side is selected. According to the Tanner staging criteria, girls are divided into B1-5 stages according to breast and pubic hair development criteria, and boys are divided into G1-5 stages according to testicular volume and pubic hair development criteria. Reaching the Tanner stage 2 of development marks the start of puberty development. Precocious puberty is defined as the presence of secondary sexual characteristics in boys under the age of 9. Precocious puberty is defined as the presence of secondary sexual characteristics in girls under the age of 8 or menstrual cramps under the age of 10 [10].

2.3. Statistical Methods. SPSS 20.0 software was used for analysis. Measurement data were expressed as mean ± standard deviation, t-test or was F-test was used to analyze the comparison. When the data met the homogeneity of variance normality, the Bonferroni method was further used for multiple comparisons. Count data were expressed as a ratio, χ^2-test was used to analyze the comparison. The odds ratio (OR) value of risk assessment was calculated using $2 * 2$ crosstab data. $P < 0.05$ was statistically significant.

3. Results

3.1. Age Distribution of 895 Children and Adolescents. A total of 895 children and adolescents were included in the study, including 466 males and 429 females. The age distribution is shown in Table 1.

3.2. Nutritional Status and Bone Age Level of Children and Adolescents. The average bone age of emaciation, normal, and overweight groups is consistent with the actual age. There was a significant difference in the BAD of children and adolescents under different nutritional status ($P < 0.05$). The BAD of the overweight and obesity group was higher than that of the normal group, and the BAD of the obesity group was higher than that of the emaciation group ($P < 0.05$). See Table 2.

Table 1: Age distribution of 895 children and adolescents (n, %).

Age	Male ($n = 466$)	Female ($n = 429$)	Total ($n = 895$)
4 years~	61 (13.1%)	28 (6.5%)	89 (9.9%)
6 years~	82 (17.6%)	94 (21.9%)	176 (19.7%)
8 years~	87 (18.7%)	192 (44.8%)	279 (31.2%)
10 years~	150 (32.2%)	98 (22.8%)	248 (27.7%)
12 years~	76 (16.3%)	17 (4.0%)	93 (10.4%)
14 years~	10 (2.1%)	0 (0.0%)	10 (1.1%)

Table 2: Nutritional status and bone age level of children and adolescents (n, $M \pm$ SD).

Male	Age (years)	Bone age (years)	BAD	F_{BAD} value	P_{BAD} value
Emaciation group ($n = 9$)	9.10 ± 2.31	8.61 ± 2.39	-0.48 ± 1.39	20.38	<0.001
Normal group ($n = 316$)	9.25 ± 2.77	9.13 ± 3.15	-0.13 ± 1.08		
Overweight group ($n = 88$)	10.45 ± 2.21	10.88 ± 2.70	$0.43 \pm 1.12^{\#}$		
Obesity group ($n = 53$)	9.52 ± 2.32	10.55 ± 2.83	$1.03 \pm 1.13^{*\#\triangle}$		
Female	Age (years)	Bone age (years)	BAD	F_{BAD} value	P_{BAD} value
Emaciation group ($n = 4$)	9.15 ± 2.22	8.48 ± 1.84	-0.67 ± 1.08	20.33	<0.001
Normal group ($n = 331$)	8.98 ± 1.82	9.00 ± 2.35	0.01 ± 1.12		
Overweight group ($n = 65$)	8.76 ± 1.72	9.56 ± 1.88	$0.80 \pm 0.93^{\#}$		
Obesity group ($n = 29$)	8.14 ± 1.77	9.42 ± 2.28	$1.27 \pm 0.87^{*\#}$		

Note. Compared with the emaciation group, $^{*}P < 0.05$; compared with the normal group, $^{\#}P < 0.05$; compared with the overweight group, $^{\triangle}P < 0.05$.

3.3. Nutritional Status and Bone Age Assessment of Children and Adolescents. There was a significant difference in the bone age assessment of children and adolescents under different nutritional status ($P < 0.05$). Compared with the normal group, the risk of advancement of bone age in the overweight group increased by 2.674 times (male) and 1.908 times (female). Compared with the normal group, the risk of advancement of bone age in the obesity group increased by 6.376 times (male) and 14.687 times (female). Compared with the normal group, the risk of retardation of bone age in the emaciation group increased by 2.150 times (male) and 3.092 times (female). See Table 3.

3.4. Nutritional Status and Sexual Development of Children and Adolescents. Among male children aged 10 to 12 years, the probability of sexual development in the overweight + obesity group was 1.275 times that of the normal group. Among female children aged 6 to 8 years, the probability of sexual development in the overweight + obesity group was 2.156 times that of the normal group. Among female children aged 8 to 10 years, the probability of sexual development in the overweight + obesity group was 1.114 times that of the normal group. Among female children aged 10 to 12 years, the probability of sexual development in the overweight + obesity group was 1.027 times that of the normal group. See Table 4.

3.5. Relationship between Nutritional Status and Early Maturity of Children and Adolescents. No early maturity was found in male children and adolescents. Among female children, the sexual precocious puberty rates of the emaciation, normal, overweight, and obesity groups were 0.00% (0/4), 6.34% (21/331), 15.38% (10/65), and 13.79% (4/29), respectively. See Figure 1.

4. Discussion

The growth and development of the human body is a long-term continuous process with a certain law of change and is comprehensively influenced by environmental factors, genetic factors, nutritional status, and other aspects [11]. Nutritional status is one of the important bases for evaluating the physique and health of children and adolescents. Poor nutrition status not only affects people's physical health and increases the risk of diseases but also has certain adverse effects on their normal psychological development [12, 13].

Studies have shown that bone age is not exactly equal to actual age, and bone age can better reflect the overall development degree of individuals [14]. Advanced bone age can lead to early closure of epiphysis in children, which affects the final height, while backward bone age is associated with short stature, delayed sexual development, and other developmental problems [15]. Nutritional status is very important for the growth and development of children's and adolescents' bones. Artioli et al. believed that the average bone age of overweight children is basically consistent with their age, but the bone age of obese children is earlier [16]. In this study, the BAD of the overweight and obesity groups was higher than that of the normal group, and the BAD of the obesity group was higher than that of the emaciation group. It is suggested that overweight and obesity may have a great influence on the bone age of children and adolescents. At the same time, we found that, compared with the normal group, the risk of advance of bone age in the overweight group increased by 2.674 times (male) and 1.908 times (female); the risk of advance of bone age in the obesity group increased by 6.376 times (male) and 14.687 times (female);

Table 3: Nutritional status and bone age assessment of children and adolescents (n, %).

Male	Retardation of bone age	Normal bone age	Advancement of bone age	χ^2 value	P value	OR (95% CI)*	OR (95% CI)#
Emaciation group ($n = 9$)	4 (44.44%)	4 (44.44%)	1 (11.11%)	63.55	<0.001	0.888 (0.108–7.292)	3.150 (0.822–12.067)
Normal group ($n = 316$)	64 (20.25%)	213 (67.41%)	39 (12.34%)			1.000	1.000
Overweight group ($n = 88$)	6 (6.82%)	52 (59.09%)	30 (34.09%)			3.674 (2.112–6.391)	0.288 (0.120–0.690)
Obesity group ($n = 53$)	2 (3.77%)	24 (45.28%)	27 (50.94%)			7.376 (3.911–13.909)	0.154 (0.037–0.651)
Female	Retardation of bone age	Normal bone age	Advancement of bone age	χ^2 value	P value	OR (95% CI)*	OR (95% CI)#
Emaciation group ($n = 4$)	2 (50.00%)	2 (50.00%)	0 (0.00%)	71.11	<0.001	—	4.092 (0.566–29.599)
Normal group ($n = 331$)	65 (19.64%)	201 (60.72%)	65 (19.64%)			1.000	1.000
Overweight group ($n = 65$)	0 (0.00%)	38 (58.46%)	27 (41.54%)			2.908 (1.656–5.105)	—
Obesity group ($n = 29$)	0 (0.00%)	6 (20.69%)	23 (79.31%)			15.687 (6.137–40.099)	—

Note. *Compared with the normal group, the risk of advancement of bone age; #compared with the normal group, the risk of retardation of bone age.

Table 4: Nutritional status and sexual development of children and adolescents (n, %).

Gender	Age	Normal group (developed/undeveloped, development rate)	Overweight + obesity group (developed/undeveloped, development rate)	OR (95% CI)
Male	6 years~8 years	0/54 (0.00%)	0/24 (0.00%)	—
	8 years~10 years	0/60 (0.00%)	3/26 (11.54%)	—
	10 years~12 years	43/95 (45.26%)	30/52 (57.69%)	1.275 (0.717–2.267)
Female	6 years~8 years	12/69 (17.39%)	9/24 (37.5%)	2.156 (0.808–5.752)
	8 years~10 years	108/147 (73.47%)	36/44 (81.82%)	1.114 (0.672–1.847)
	10 years~12 years	73/80 (91.25%)	15/16 (93.75%)	1.027 (0.474–2.225)

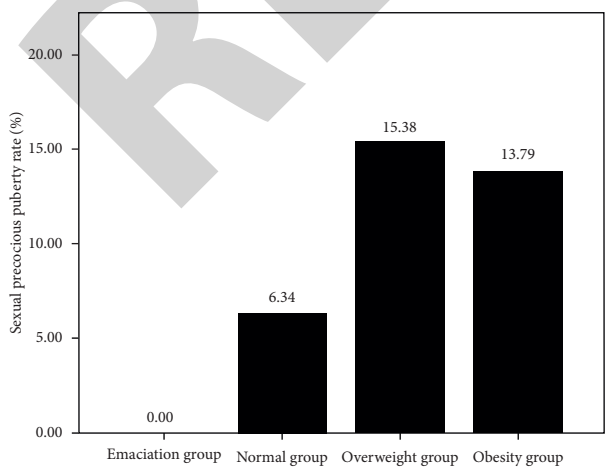

Figure 1: Relationship between nutritional status and early maturity of female children.

and the risk of retardation of bone age in the emaciation group increased by 2.150 times (male) and 3.092 times (female). This shows that the rate of bone age retardation in emaciated children is greater than the rate of bone age advancement, and the rate of bone age advancement in overweight and obese children is greater than the rate of bone age retardation. The possible reasons are as follows: ① studies have found that obese children have high levels of leptin. Leptin is a peptide hormone secreted by adipocytes, which has an interaction relationship with other hormones in the body, such as insulin, thyroid hormone, sex hormone, and insulin-like growth factor-1. Leptin can promote the initiation of sexual development and increase the secretion of sex hormones. There is a positive correlation between E_2 and leptin, and there is also a positive correlation between leptin and FT3. Both E_2 and FT3 can act on the ossification center of cartilage, which can increase the number of cells. Increased volume increases, accelerates the differentiation of

cell morphology, advances bone maturation, and ultimately leads to accelerated bone age [17–19]. ② Excessive adipose tissue will produce more aromatase, which can induce androgen to be converted into estrogen. A high concentration of estrogen can promote the maturation and apoptosis of growth plate chondrocytes, and chondrocytes in the depleted hyperplasia layer can induce the fusion of the growth plate, which will accelerate the development of children's bone age. The secretion disorders of estrogen, testosterone, and insulin in overweight and obese children are all related to bone maturation, which adversely affects the speed of bone development [20, 21]. ③ Children and adolescents with excessive BMI usually have higher levels of adrenal androgen, thus increasing the secretion of leptin and increasing the risk of premature bone age [22].

Sexual development may be related to genetic susceptibility, diet, exercise, nutritional status, social economy, etc. Research by Liu et al. showed that the prevalence of precocious puberty after Tanner stage adjustment is 11.47% for girls and 3.26% for boys, and the incidence of precocious puberty in the obesity group is higher than that in the normal weight group [23]. Reinehr et al. investigated 160 overweight children and found that obese girls had earlier puberty, while obese boys showed delayed puberty [24]. In this study, there was a significant difference in the sexual development of children and adolescents under different nutritional status. Whether it was male or female, the sexual development of overweight and obesity was higher than that of the normal weight group in the same age group. Meanwhile, among female children, the sexual precocious puberty rate of the overweight + obesity group is higher. It is suggested that the sexual development of children and adolescents is closely related to their nutritional status. Some scholars believe that body fat can be transformed into estrogen. Compared with the normal population, obese girls are more likely to develop precocious puberty [25]. In addition, clinically, it is generally believed that overweight and obese people have high leptin levels, and leptin acts on the hypothalamus-pituitary-gonad axis, which can provide fat storage, promote the secretion of hypothalamic gonadotropin-releasing hormone, and increase the pulse frequency of luteinizing hormone, thus causing precocious puberty [26].

5. Conclusion

To sum up, the nutritional status of children and adolescents is closely related to their bone age and sexual development. People should pay more attention to the nutritional intake of children and adolescents, correct their partial and picky eating behaviors as early as possible, adjust the dietary structure, and increase food diversity. Parents also need to take reasonable measures to control the weight of children and adolescents, for example, ensuring regular meals, not overeating, choosing snacks reasonably, and actively carrying out physical activities. In addition, schools, communities, and medical and health institutions should work together to popularize nutrition and health knowledge among children, adolescents, and their parents, so as to ensure the balanced nutrition and physical health of children and adolescents. This study cannot dynamically observe the longitudinal development of bone age and sexual characteristics in children and adolescents, and it still needs to be further improved in future research.

Data Availability

All data included in this study are available upon request by contact with the corresponding author.

Ethical Approval

This study was approved by the ethics committee of our hospital (EA2019056).

Conflicts of Interest

The authors state that they have no conflicts of interest.

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Research Article

Effects of Different Concentrations of Ropivacaine Lumbar Plexus-Sciatic Nerve Block on Recovery from Anesthesia, Postoperative Pain and Cognitive Function in Elderly Patients with Femoral Neck Fracture

Pingping Cheng, Feng Ying, and Yafeng Li

Department of Anesthesiology, Nanchang Hongdu Hospital of Traditional Chinese Medicine, Nanchang, Jiangxi 330000, China

Correspondence should be addressed to Yafeng Li; liyafeng1008@126.com

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Objective. To investigate the effects of lumbar plexus-sciatic nerve block with different concentrations of ropivacaine on recovery from anesthesia, postoperative pain, and cognitive function in elderly patients with femoral neck fracture. *Method*. A total of 110 elderly patients with femoral neck fractures who were treated in our hospital from January 2020 to January 2022 were selected as the research objects. According to the concentration of ropivacaine, they were divided into low-, medium-, and high-concentration groups (concentrations of ropivacaine were 0.15%, 0.25%, and 0.40%, respectively), with 36, 37, and 37 cases, respectively. Extubation time, anesthesia recovery time, and hospitalization time were recorded. Cognitive symptoms were assessed by the spatial cognitive ability, working memory ability, simple computing ability, and picture recognition ability test. The pain degree of patients was assessed by visual analogue scale (VAS). The occurrence of adverse reactions in patients was recorded. *Result*. There was no significant difference in extubation time, anesthesia recovery time, and hospitalization time among the three groups ($P > 0.05$). The PCA time of the patients in the high-concentration group was significantly longer than that in the low- and medium-concentration groups. The dosage of sufentanil within 24 hours and total sufentanil in the high-concentration group were significantly lower than those in the low- and medium-concentration groups, and the dosage of sufentanil within 24 hours and total sufentanil in the medium-concentration group was significantly less than that in the low-concentration group ($P < 0.05$). The cognitive function score for each entry of the three groups 1 d after surgery was lower than that before surgery ($P < 0.05$); On the 1 day after operation, the cognitive function score for each entry of the patients in the low-concentration group was significantly higher than that in the middle- and high-concentration groups, and the cognitive function score for each entry in the middle-concentration group was significantly higher than that in the high-concentration group ($P < 0.05$). There was no significant difference in VAS scores between the three groups at 2 h and 8 h after surgery ($P > 0.05$); 16 h and 24 h after operation, the VAS score of patients in the high-concentration group was significantly lower than that in the low- and medium-concentration groups, and the VAS score in the medium-concentration group was significantly lower than that in the low-concentration ropivacaine group ($P < 0.05$). The incidence of adverse reactions in the high-concentration ropivacaine group was significantly higher than that in the low- and medium-concentration groups ($P < 0.05$). *Conclusion*. The middle concentration of ropivacaine has good analgesic and nerve block effects and has less influence on cognitive function and less adverse reactions in elderly patients.

1. Introduction

Femoral neck fracture is a common type of fracture in the elderly. Conventional conservative treatment of femoral neck fractures has limited therapeutic effect. The anatomical structure of the femoral neck is special, and patients often have difficulty in fracture healing and necrosis of the femoral head due to poor treatment results, resulting in poor

prognosis [1, 2]. In addition, due to the weakened immunity of elderly patients, combined with other underlying diseases, low organ function, and cognitive dysfunction and abnormal circulatory and respiratory system caused by the trauma of the operation itself, the tolerance of elderly patients to anesthesia surgery is reduced. Therefore, the choice of methods and drugs is particularly important [3]. With the rapid development of regional nerve block technology, peripheral nerve block has been gradually applied to various fracture operations. Lumbar plexus-sciatic nerve block can inhibit the sensation around the hip joint, and has little effect on the functions of breathing, circulation, and urinary system, so it is widely used in clinical practice. Many studies have shown that ropivacaine is a long-acting, novel, and low-toxic amide local anesthetic, with the characteristics of separation of sensory tissue and motor tissue [4, 5]. It has been proved in clinical practice that it can achieve good analgesic effect when applied to lumbar plexus-sciatic nerve block. It is widely used in China, but its concentration has not been unified [6]. In this study, in order to reveal the optimal concentration of ropivacaine in combined lumbar plexus-sciatic nerve block provides a theoretical basis, different concentrations of ropivacaine combined lumbar plexus-sciatic nerve block anesthesia were used in elderly patients with femoral neck fractures to evaluate the efficacy and safety of different concentrations of ropivacaine in elderly patients with femoral neck fracture surgery.

2. Materials and Methods

2.1. General Information. A total of 110 elderly patients with femoral neck fracture who were treated in our hospital from January 2020 to January 2022 were selected as the research objects. According to the concentration of ropivacaine, they were divided into low-, medium-, and high-concentration groups of ropivacaine, with 36, 37, and 37 cases, respectively. The concentrations of ropivacaine in the high-, medium-, and low-concentration groups were 0.40%, 0.25%, and 0.15%, respectively. There were 15 males and 21 females in the low-concentration group, aged 68–85 years, with an average age of (73.68 ± 3.54) years; there were 13 males and 24 females in the medium-concentration group, aged 65–81 years, with an average age of (72.92 ± 3.28) years; there were 15 males and 22 females in the high-concentration group, aged 66–80 years, with an average age of (73.01 ± 3.14) years. There were no significant differences in age and gender among the three groups ($P > 0.05$). Inclusion criteria were defined as follows: ① femoral neck fracture confirmed by X-ray examination; ② age ≥ 65 years; ③ no multiple injuries and mixed injuries; ④ American Society of Anesthesiologists (ASA) III or below(ASA III: the patients also suffered from severe illness and limited physical activity, but they were able to cope with daily activities). Exclusion criteria were defined as follows: ① combined abnormal coagulation function; ② mental dysfunction, cognitive insufficiency, emotional instability; ③ no recent use of psychotropic drugs and anesthetics; ④ abnormal liver and kidney function; ⑤ allergic to local anesthetics. This study was approved by the hospital ethics committee, and the patients knew and gave informed consent.

2.2. Methods. All patients were made to fast and were deprived of water before surgery, and routine electrocardiogram and physical signs were monitored. Sodium lactated Ringer's solution (manufacturer: Shandong Qidu Pharmaceutical Co., Ltd., approved by H20023278, specification: 500 ml) was intravenously injected to establish venous access, and tracheal intubation was given. Anesthesia: all three groups received ropivacaine lumbar plexus-sciatic nerve block anesthesia combined with general anesthesia. A 3-4 cm port was opened in the L3-L4 space as a puncture point for lumbar plexus block, 30 ml of ropivacaine was injected (manufacturer: Hebei Yipin Pharmaceutical Co., Ltd.; National Medicine Zhunzi H20113463; Specifications: 10 ml: 75 mg), and the concentration of ropivacaine in the high-, medium-, and low-concentration groups were 0.40%, 0.25%, and 0.15%, respectively. Parasacral sciatic nerve block was performed at the puncture point 3 cm down from the middle of the line connecting the posterior superior iliac spine and the greater trochanter, and 15 mL of ropivacaine was injected. The concentration of ropivacaine in the high-, medium-, and low-concentration groups was 0.40%, 0.25%, and 0.15%, respectively. After the operation, the intravenous analgesia pump was connected, and the parameters were set as: no background dose, patient-controlled analgesia (PCA) dose was 0.05 μg/kg of sufentanil citrate once, with a lock-in time of 15 min. 100 mg of intravenous flurbiprofen axetil was given as background analgesia twice a day. If the numerical rating scale (NRS) ≥ 4 points, 5 mg of paracetamol and oxycodone tablets were given orally, and if still invalid after 60 minutes, 50 mg of intramuscular injection of pethidine hydrochloride was given.

2.3. Observation Indicators

2.3.1. Surgical Indicators. The extubation time, anesthesia recovery time, and hospitalization time of the three groups of patients were recorded.

2.3.2. Cognitive Function. The tests were performed once preoperatively and once 1 day postoperatively, the whole test took 10 min and all tests were performed by the same physician. ① The method was to rotate the Chinese characters by 0, 90, 180, and 270, with 1 positive and 1 negative for each direction, to limit the patient to recognize within 10 seconds, with 4 points for each time and a total of 20 points. The higher score represented the better spatial cognitive ability of the patient. ② A word recall test was used to test working memory ability by asking the patient to recite 5 words (all words chosen were real words and not easily ambiguous) and after 2 min to recall the 5 words, 2 points were awarded for those words that could be recalled correctly [7]. ③ Simple computing skills were used to test thinking skills by doing several simple mathematical problems to test the subject's intellectual status, including

adding and subtracting two single-digit numbers, subtracting two two-digit numbers, and adding and subtracting three two-digit numbers. ④The method that had pictures with bright colors and clear details needed to be described clearly within 30 s which was used to test picture recognition ability. Patients were shown 5 pictures, then 5 unseen pictures were mixed in, and patients were asked to select the pictures they had seen from 10 pictures, and 2 points were awarded for each correctly remembered picture.

2.3.3. Pain Assessment. The first PCA compression time, the sufentanil dosage within 24 hours after surgery and the total sufentanil dosage during hospitalization were recorded and compared among the three groups.

Visual analogue scale (VAS) [8] was used to evaluate the pain degree of patients at 2 h, 8 h, 16 h, and 24 h after surgery. A walking scale was used, about 10 cm long, with 10 scales on one side, and the two ends are the "0" end and the "10" end, where 0 means no pain, and 10 means the most unbearable pain.

2.4. Statistical Processing. SPSS 21.0 statistical software was used for data analysis, and the measurement data with normal distribution and homogeneous variance were expressed in the form of $(\overline{x} \pm s)$. The differences among multiple groups were compared using the F-test. The count data are expressed as rate (%). Differences between groups were tested by χ^2, and $P < 0.05$ indicated statistical significance.

3. Results

3.1. Comparison of Surgical Indicators among the Three Groups of Patients. There was no significant difference in extubation time, anesthesia recovery time, and hospitalization time between the low, medium, and high-concentration groups of ropivacaine ($P > 0.05$), as shown in Table 1.

3.2. Comparison of Analgesic Effects among the Three Groups of Patients. The PCA time of the patients in the high-concentration group was significantly longer than that in the low- and medium-concentration groups. The dosage of sufentanil within 24 hours and total sufentanil in the high-concentration group were significantly lower than those in the low- and medium-concentration groups, and the dosage of sufentanil within 24 hours and total sufentanil in the medium-concentration group were significantly less than those in the low-concentration group ($P < 0.05$), as shown in Table 2.

3.3. Comparison of Postoperative Cognitive Function of the Three Groups of Patients. The cognitive function scores for each entry of patients in the low, medium, and high-concentration groups of ropivacaine 1 d after surgery were all lower than those before surgery ($P < 0.05$); on the 1 day after operation, the cognitive function scores for each entry of the patients in the low-concentration group were significantly higher than those in the medium- and high-concentration groups ($P < 0.05$); The cognitive function score for each entry in the medium-concentration group was significantly higher than that in the ropivacaine high-concentration group ($P < 0.05$), as shown in Table 3.

3.4. Comparison of Postoperative Pain in the Three Groups of Patients. There was no significant difference in the VAS scores between the low, medium, and high-concentration groups at 2 h and 8 h after surgery ($P > 0.05$); 16 h and 24 h after operation, the VAS score of patients in the high-concentration group was significantly lower than that in the low- and medium-concentration groups, and the VAS score in the medium-concentration group was significantly lower than that in the low-concentration group ($P < 0.05$), as shown in Table 4.

3.5. Comparison of Adverse Reactions in the Three Groups of Patients. The incidence of adverse reactions in the high-concentration group was significantly higher than that in the low- and medium-concentration groups ($P < 0.05$), as shown in Table 5.

4. Discussions

Elderly patients are often associated with medical diseases, and their physiological functions and immunity are low, which makes their tolerance to anesthesia and surgery significantly reduced. The operation itself may also lead to cognitive dysfunction and circulatory and respiratory system abnormalities in elderly patients. In order to improve the safety of surgery in elderly patients, reduce postoperative complications, and improve postoperative pain, it is necessary to strictly control the concentration of local anesthetics for nerve block [8, 9]. This study provides ideas for exploring the optimal concentration of ropivacaine in clinical practice by comparing the anesthesia effect, analgesic effect, and effect on postoperative cognition and postoperative pain of lumbar plexus-sciatic nerve block with different concentrations of ropivacaine.

The transmission of perioperative stimulation to the central system can easily lead to unstable hemodynamic fluctuations, delayed catheter removal caused by slow postoperative respiratory recovery which increases the risk of perioperative complications, and the stress response during catheter insertion and removal can also lead to hemodynamic changes, which are all important factors leading to postoperative death [10]. Therefore, the use of an appropriate amount of local anesthetic, which does not cause the patient to wake up from anesthesia and prolong the extubation time, is the key to ensuring the patient's prognosis [11]. The results of this study showed that there was no significant difference in extubation time, anesthesia recovery time, and hospitalization time between the low, medium, and high-concentration groups, indicating that the anesthesia effect of different concentrations of ropivacaine was equivalent, and there was no significant difference in the

Table 1: Comparison of surgical indicators among the three groups of patients (n, $\pm s$).

Group	Extubation time (min)	Anesthesia recovery time (min)	Hospitalization time (d)
Ropivacaine low-concentration group ($n = 36$)	18.06 ± 0.78	10.75 ± 0.67	6.99 ± 0.75
Ropivacaine mid-concentration group ($n = 37$)	17.95 ± 1.23	10.96 ± 0.64	7.05 ± 0.62
Ropivacaine high-concentration group ($n = 37$)	18.22 ± 0.97	11.08 ± 0.73	7.11 ± 0.83
F	0.666	2.190	0.241
P	0.516	0.117	0.786

Table 2: Comparison of analgesic effects among the three groups of patients (n, $\pm s$).

Group	First compression PCA time (h)	Sufentanil dosage within 24 hours (μg)	Total sufentanil dosage (μg)
Low-concentration group ($n = 36$)	9.72 ± 3.21	17.59 ± 3.52	41.36 ± 6.27
Mid-concentration group ($n = 37$)	12.35 ± 4.48	15.46 ± 3.36	35.49 ± 5.74
High-concentration group ($n = 37$)	15.25 ± 4.56	11.23 ± 3.01	22.67 ± 5.35
F	16.320	35.200	99.670
P	<0.001	<0.001	<0.001

Table 3: Comparison of postoperative cognitive function among the three groups of patients (n, $\pm s$).

Group	Spatial cognitive ability (score)		Working memory ability (score)		Simple computing ability (score)		Picture recognition ability (score)	
	Preoperative	1 d after surgery	Preoperative	1 d after surgery	Preoperative	1 d after surgery	Preoperative	1 d after surgery
Low-concentration group ($n = 36$)	15.86 ± 1.22	14.52 ± 0.92	8.44 ± 1.06	7.23 ± 1.10	4.06 ± 0.63	3.56 ± 0.56	9.06 ± 0.33	8.50 ± 0.51
Mid-concentration group($n = 37$)	15.74 ± 1.31	14.10 ± 0.84	8.37 ± 1.10	6.72 ± 0.88	4.11 ± 0.70	3.19 ± 0.88	9.05 ± 0.40	8.19 ± 0.70
High-concentration group ($n = 37$)	15.79 ± 1.34	13.65 ± 0.90	8.40 ± 1.09	6.15 ± 0.74	4.11 ± 0.77	2.76 ± 0.93	9.05 ± 0.52	7.84 ± 0.76
F	0.079	8.784	0.038	12.680	0.061	8.950	0.007	8.962
P	0.924	<0.001	0.963	<0.001	0.941	<0.001	0.993	<0.001

Table 4: Comparison of postoperative pain levels among the three groups of patients (n, $\pm s$).

Group	VAS scale (score)			
	2 h after surgery	8 h after surgery	16 h after surgery	24 h after surgery
Low-concentration group ($n = 36$)	1.83 ± 0.41	1.52 ± 0.39	1.48 ± 0.36	1.34 ± 0.25
Mid-concentration group ($n = 37$)	1.82 ± 0.39	1.53 ± 0.22	1.29 ± 0.20	1.18 ± 0.28
High-concentration group ($n = 37$)	1.79 ± 0.44	1.42 ± 0.25	1.19 ± 0.15	1.02 ± 0.16
F	0.093	1.567	12.460	16.850
P	0.912	0.213	<0.001	<0.001

Table 5: Comparison of adverse reactions among the three groups of patients (n, (%)).

Group	Feverr	Feel sick and vomit	Itching	Poor sight	Dizziness	Total adverse reaction rate (%)
Low-concentration group ($n = 36$)	1	2	1	0	0	5 (13.89)
Mid-concentration group ($n = 37$)	1	3	0	1	1	6 (16.22)
High-concentration group ($n = 37$)	3	4	2	1	3	14 (37.84)
χ^2						7.305
P						0.026

anesthetic effect of ropivacaine. Extubation time and hospitalization time were prolonged due to concentration differences, but there was no statistical difference among the three groups.

The results of this study showed that the PCA time of the patients in the high-concentration group was significantly longer than that in the low- and medium-concentration groups, and the PCA time in the medium-concentration group was significantly longer than that in the low-concentration group. It shows that the nerve block of high-concentration ropivacaine lasts longer, and the dosage of sufentanil and sufentanil within 24 hours in the high-concentration group is significantly less than that of the low- and medium-concentration groups. The dosage of sufentanil in

the medium-concentration group was significantly lower than that in the ropivacaine low-concentration group because the nerve block duration of the patients in the high ropivacaine concentration group lasted longer, thus reducing the postoperative dose of opioids, suggesting that high-concentration ropivacaine has a stronger analgesic effect. In addition, the results of this study showed that there was no significant difference in the VAS scores between the three groups of patients at 2 h and 8 h after surgery, but at 16 h and 24 h after surgery, the higher the concentration of ropivacaine, the lower the VAS score of the patients, further indicating that high concentrations of ropivacaine have better analgesic effect and can effectively relieve postoperative pain. Previous studies have shown [12, 13] that low concentrations of ropivacaine have the property of blocking the separation of motor and sensory nerves, and its blocking effect also increases with the concentration of ropivacaine, which is consistent with the results of this study.

The results of this study showed that after the use of ropivacaine for nerve block, the cognitive function score for each entry of the patients was decreased, and the cognitive function score for each entry of the patients in the low-concentration group was significantly higher than that in the medium- and high-concentration groups on the 1 postoperative day, and the cognitive function score for each entry in the medium-concentration group was significantly higher than that in the high-concentration group. This indicates that the lower the concentration of ropivacaine, the smaller the impact on neurocognitive function of patients and the stimulation of surgical trauma itself on patients, especially for elderly patients with underlying diseases. High concentration of ropivacaine is more likely to cause postoperative cerebral hemodynamic changes, leading to cognitive dysfunction, and low-concentration ropivacaine reduces nerve stimulation, which may be the reason for the better recovery of cognitive function scores in patients with low-concentration ropivacaine [14]. In this study, the incidence of adverse reactions in the high-concentration ropivacaine group was significantly higher than that in the low- and medium-concentration ropivacaine groups. It may be because the low concentration of ropivacaine has little effect on the physiological and hemodynamic stability of the body, and will not affect the auxiliary muscle group and nerve function of the patient's respiratory muscles. Some studies have pointed out that low-concentration ropivacaine will not cause complete blockade of nerves because it will not significantly affect the patient's respiratory function, which improves the safety of treatment [15]. Tian et al. [16] used 0.4%, 0.5%, and 0.6% of ropivacaine for anesthesia, and found that the total adverse reaction rate of 0.6% ropivacaine was significantly higher than that of the low-concentration group. The results are consistent with this study.

In conclusion, low-concentration ropivacaine has limited nerve block effect, analgesic effect, and anesthesia maintenance time, but it has less influence on patients' neurocognitive function, fewer adverse reactions, and higher safety. Although high-concentration ropivacaine has better nerve block function and is more effective in relieving postoperative pain, high-concentration ropivacaine is accompanied by high side effects. Medium-concentration ropivacaine has good analgesic effect, can exert effective nerve block function, relieve postoperative pain, and has less impact on cognitive function and less adverse reactions in elderly patients. At the same time, it has efficacy and safety, and it is a concentration worthy of clinical promotion.

Data Availability

The raw data supporting the conclusion of this article will be available from the authors without undue reservation.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Retraction

Retracted: Levels of Serum IGF-1, HCY, and Plasma BNP in Patients with Chronic Congestive Heart Failure and Their Relationship with Cardiac Function and Short-Term Prognosis

Evidence-Based Complementary and Alternative Medicine

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(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

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The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] Z. Hu, L. Mao, and L. Wang, "Levels of Serum IGF-1, HCY, and Plasma BNP in Patients with Chronic Congestive Heart Failure and Their Relationship with Cardiac Function and Short-Term Prognosis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4118976, 5 pages, 2022.

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Research Article

Levels of Serum IGF-1, HCY, and Plasma BNP in Patients with Chronic Congestive Heart Failure and Their Relationship with Cardiac Function and Short-Term Prognosis

Zhengyi Hu,[1] Leifang Mao,[2] and Ling Wang[3]

[1]*Ethics Office, Henan Provincial Chest Hospital, Zhengzhou 450003, Henan, China*
[2]*Department of Rehabilitation, Henan Provincial Chest Hospital, Zhengzhou 450003, Henan, China*
[3]*Department of Clinical Laboratory, Henan Provincial Chest Hospital, Zhengzhou 450003, Henan, China*

Correspondence should be addressed to Ling Wang; kingling2000@126.com

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Objective. To investigate the levels of serum insulin like growth factor-1 (IGF-1), homocysteine (HCY), and plasma brain natriuretic peptide (BNP) in patients with chronic congestive heart failure (CCHF) and their relationship with cardiac function and short-term prognosis. *Methods*. A total of 95 patients with CCHF admitted to our hospital from October 2017 to December 2018 were selected as the observation group. Patients conform to grade II~IV of the New York Heart Association (NYHA) heart function class. At the same time, the people with normal physical examination results were selected as a control group. Serum IGF-1, HCY, and plasma BNP levels were detected in the two groups, and left ventricular end-diastolic diameter (LVDd) and left ventricular ejection fraction (LVEF) were detected in the observation group. According to the follow-up results, the observation group was divided into the subgroup with good prognosis and the subgroup with poor prognosis. The relationship between the levels of serum IGF-1, HCY, and plasma BNP among cardiac function and short-term prognosis were analyzed. *Results*. The serum IGF-1 level of the observation group was lower than that of the control group, and the serum HCY and plasma BNP levels were higher than those of the control group ($P < 0.05$). Serum IGF-1 level in grade III of NYHA was lower than that in grade II, and serum HCY and plasma BNP levels were higher than those in grade II. Serum IGF-1 level in grade IV was lower than that in grade II and grade III, and serum HCY and plasma BNP levels were higher than those in grade II and grade III ($P < 0.05$). Serum IGF-1 level was negatively correlated with LVDd and positively correlated with LVEF. Serum HCY and plasma BNP levels were positively correlated with LVDd and negatively correlated with LVEF ($P < 0.05$). There were 42 patients with poor prognoses (44.21%). Serum IGF-1 levels of patients with poor prognosis were lower than those with good prognosis, and serum HCY and plasma BNP levels were higher than those with good prognosis ($P < 0.05$). *Conclusion*. The serum IGF-1 level in patients with CCHF decreased, and serum HCY and plasma BNP levels increased. Serum IGF-1, HCY, and plasma BNP were correlated with cardiac function and have some clinical value for short-term prognosis.

1. Introduction

Chronic congestive heart failure (CCHF) is a series of clinical syndromes resulting from insufficient perfusion of various tissues and organs due to pathological changes in cardiac structure and insufficient cardiac function after the development of cardiovascular disease to the end stage [1, 2]. At present, the specific pathogenesis of CCHF is still unclear, and inflammation, vascular injury, and neuroendocrine activation are closely related to it [3]. Insulin like growth factor-1 (IGF-1) is a cardiogenic hormone involved in regulating the physiological and pathological activities of the heart [4]. Homocysteine (HCY) can reflect vascular damage and is an independent risk factor for cardiovascular disease [5]. BNP is a cardiac neurohormone, which is mainly synthesized by ventricular myocytes and is closely related to the cardiac function state. It can reflect the functional changes caused by the overall and even local structural

changes of the heart at an early stage. It is less affected by external factors and can be more accurate and objectively reflect the severity of elderly chronic CHF patients, the increase of BNP level can reflect the increase of ventricular diastolic blood pressure to a certain extent, whether it is cardiac systolic dysfunction or heart failure caused by diastolic dysfunction, it can cause the increase of BNP level. It can increase with the aggravation of heart failure, and it can also decrease with the correction of heart failure. It has a good correlation with NYHA cardiac function class, LVEF and CO, and LVD and LVS. It is one of the most sensitive indicators to detect. Brain natriuretic peptide (BNP) is a neuropeptide hormone synthesized in cardiomyocytes, which has cardiovascular effects such as vasodilation and inhibition of vascular smooth muscle [6]. This study detected the levels of serum IGF-1, HCY, and plasma BNP in CCHF patients, aiming to explore their clinical significance in CCHF and their impact on prognosis by exploring their relationship with cardiac function. The specific report is as follows.

2. Materials and Methods

2.1. General Information. A total of 95 patients with CCHF admitted to our hospital from October 2017 to December 2018 were selected as the observation group, including 51 males and 44 females, aged 36–75 years, with an average age of (61.49 ± 12.85) years. Etiology: 35 cases of hypertensive heart disease, 26 cases of coronary heart disease, 15 cases of rheumatic heart disease, 12 cases of dilated heart disease, and 7 other cases. Cardiac Association (NYHA) classification: 38 cases were grade II, 35 cases were grade III, and 22 cases were grade IV. Inclusion criteria: in line with the diagnostic criteria of "China Heart Failure Diagnosis and Treatment Guidelines (2014)" [7]; left ventricular ejection fraction <40%; cognitive function normal. Exclusion criteria: abnormal thyroid function; combined with malignant tumors; combined with endocrine system or blood system diseases; severe liver and kidney insufficiency; mental disorders. NYHA class II patients included 20 males and 18 females, with an average age of (60.92 ± 9.11) years old, etiology: 14 hypertensive heart disease, 10 coronary heart disease, 5 rheumatic heart disease, 5 dilated heart disease, and others 4 cases. There were 16 males and 19 females with NYHA grade III, with an average age of (61.57 ± 8.52) years old. The etiology: 12 cases of hypertensive heart disease, 11 cases of coronary heart disease, 6 cases of rheumatic heart disease, 4 cases of dilated heart disease, and others 2 cases. NYHA grade IV patients included 15 males and 7 females, with an average age of (62.34 ± 7.05) years, etiology: 9 cases of hypertensive heart disease, 5 cases of coronary heart disease, 4 cases of rheumatic heart disease, 3 cases of dilated heart disease, and 1 other case. A total of 95 healthy patients with normal physical examination results during the same period were selected as the control group, including 53 males and 42 females, aged 35–75 years, with an average age of (60.74 ± 11.56) years. There was no statistical difference in the general data of patients in each group ($P > 0.05$), which was comparable. This study was approved by the ethics committee of our hospital, and all patients and their families gave informed consent and signed the informed consent.

2.2. Research Methods. After admission, CCHF patients were treated with symptomatic and supportive treatment, including bed rest, oxygen inhalation, diuresis, vasodilator, and other cardiac function improvement measures to improve myocardial remodeling, etiology, and control of inducing factors. Venous blood was drawn on an empty stomach in the morning on the 2nd day of admission of the patient 2 ml was placed in a disodium edetate (EDTA) anticoagulant tube, and aprotinin was added at the same time. The plasma was separated by centrifugation (3000 r/min, 10 min at room temperature) after the enzyme.

Determination of plasma BNP and HCY levels in patients was performed by fluorescence immunoassay and the level of serum IGF-1 was detected by radioimmunoassay. The kit was purchased from DRG Company in Germany; the serum HCY level was detected by enzyme colorimetric method, and the kit was purchased from Roche, Germany. Plasma BNP levels were detected by using the American Biosite Triage MeterPro analyzer. After admission in CCHF patients, the American general LOGIQ E9 color Doppler ultrasound system was used to detect the cardiac structure, and the left ventricular end-diastolic diameter (LVDd) and left ventricular entry fraction (LVEF) were recorded. Patients were followed up on the 1st day after discharge. Adverse cardiac events were used as the observation endpoint, which was recorded as poor prognosis, and no cardiac events were recorded as good prognosis. Adverse cardiac events included recurrent heart failure, myocardial infarction, admission to hospital for malignant arrhythmia, or death, and follow-up time was until November 30, 2019.

2.3. Statistical Methods. Using SPSS22.0 software for data processing, measurement data were expressed as mean ± standard deviation ($\overline{x} \pm s$), and a t-test or analysis of variance was used for comparison. Correlation analysis was performed using Spearman's method. The test level was $\alpha = 0.05$ and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of Serum IGF-1, HCY, and Plasma BNP Levels between the Two Groups. The serum IGF-1 level in the observation group was lower than that in the control group, and the serum HCY and plasma BNP levels were higher than those in the control group, with statistical significance ($P < 0.05$), as shown in Table 1.

3.2. Comparison of Serum IGF-1, HCY, and Plasma BNP Levels in Patients with Different NYHA Grades. The serum IGF-1 level of NYHA class III patients was lower than that of class II patients, and the serum HCY and plasma BNP levels were higher than those of class II patients; the serum IGF-1 level of class IV patients was lower than that of class II and class III patients, and the level of serum HCY and the level of

Table 1: Comparison of serum IGF-1, HCY, and plasma BNP levels between the two groups (n, $\overline{x} \pm s$).

Group	Number of cases	IGF-1 in serum (μg/L)	HCY in serum (μmol/L)	BNP in serum (ng/L)
Observation group	95	165.85 ± 20.47	8.54 ± 3.07	58.63 ± 17.82
Control group	95	118.25 ± 18.76	23.68 ± 8.96	635.28 ± 142.19
t value		16.709	15.580	39.221
P value		<0.001	<0.001	<0.001

plasma BNP was higher than that of patients with grades II and III, and the difference were statistically significant ($P < 0.05$), as shown in Table 2.

3.3. Correlation between Serum IGF-1, HCY, Plasma BNP Levels, and Parameters Related to Cardiac Function. Correlation analysis showed that serum IGF-1 level was negatively correlated with LVDd ($r = -0.527$, $P < 0.05$), and positively correlated with LVEF ($r = 0.702$, $P < 0.05$), serum HCY and plasma BNP levels were positively correlated with LVDd ($r = 0.596$, $P < 0.05$; $r = 0.640$, $P < 0.05$), and negatively correlated with LVEF ($r = -0.436$, $P < 0.05$; $r = -0.668$, $P < 0.05$), as shown in Table 3.

3.4. The Relationship between Serum IGF-1, HCY, Plasma BNP Levels, and Short-Term Prognosis. During the follow-up period, 42 patients (44.21%) had a poor prognosis. The level of serum IGF-1 in patients with poor prognosis was lower than that in patients with good prognosis, and the levels of serum HCY and plasma BNP were higher than those in patients with good prognosis, with statistical significance ($P < 0.05$), as shown in Table 4.

4. Discussions

At present, the problem of population aging in my country has become increasingly prominent, and the incidence of coronary heart disease, hypertension, and other cardiovascular diseases has continued to rise, making CCHF a common clinical complex syndrome [8]. CCHF is the result of decompensation due to abnormal heart structure and function after disease-induced myocardial damage, so it usually involves the whole body, and the endocrine system, circulatory system, and digestive system are all affected. It manifests as water and sodium retention, dyspnea, malnutrition, and other symptoms, and many biochemical markers change significantly with the development of the disease [9, 10]. By inhibiting ventricular remodeling and reducing cardiac damage, the recovery of cardiac function can be promoted. Therefore, it is of great significance to seek simple and effective cardiac function diagnosis and treatment indicators to guide the diagnosis and prognosis [11].

IGF-1 is an important link in the activity of growth hormone, which directly participates in the growth and development, proliferation and differentiation, lipid metabolism, and other physiological activities of tissue cells. By binding to specific receptors on the myocardial cell membrane, it promotes the production of new blood vessels and the proliferation of myocardial cells, inhibits the apoptosis of myocardial cells, and plays a pathophysiological effect on the heart [12–14]. HCY is an intermediate product of protein transformation and metabolism, which can act on vascular endothelial cells to cause abnormal vascular function, initiate an inflammatory response, enhance oxidative stress, cause myocardial hypertrophy, and interstitial fibrosis, and induce ventricular remodeling [15, 16]. BNP is a relatively mature indicator of cardiovascular disease and is widely used in disease diagnosis and evaluation. It can promote natriuretic urination and increase secretion when the ventricular is overloaded and is not interfered by other factors [17, 18]. Therefore, IGF-1, HCY, and BNP may become serum markers for the differential diagnosis of heart failure.

The results of this study showed that compared with the normal population, the serum IGF-1 level in CCHF patients was significantly lower, and the serum HCY and plasma BNP levels were significantly increased. Among patients with different NYHA grades, all three indicators were statistically different. The higher the NYHA grade, the more severe the patient's condition, the lower the serum IGF-1 level, and the higher the serum HCY and plasma BNP levels. This may be related to the pathological changes in CCHF patients, the systemic circulation congestion reduces the synthesis of IGF-1 in the liver, and the level of serum IGF-1 decreases. Changes in nutritional structure lead to abnormal metabolism of the body, resulting in insufficient HCY catabolism and increased serum HCY levels. Cardiac volume overload leads to the activation of the natriuretic peptide system, the myocardial cells secrete a large amount of BNP, and the plasma BNP level increases [19–21]. From the correlation analysis, serum IGF-1 levels were positively correlated with cardiac function, and serum HCY and plasma BNP levels were negatively correlated with cardiac function. In terms of short-term prognosis, patients with high serum IGF-1 levels and low serum HCY and plasma BNP levels have a better prognosis, which further shows that the three are related to CCHF, and also indicates that when the three indicators of patients have significant changes. They regulate extracellular cathepsin activity, and are involved in atherosclerosis, inflammatory response, and myocardial cell remodeling process in a variety of cardiovascular diseases such as coronary heart disease, hypertension, and heart failure risk factors such as exhaustion can predict the occurrence and progression of cardiovascular disease.

In conclusion, the serum IGF-1 level was decreased, and the serum HCY and plasma BNP levels were increased in CCHF patients. Plasma BNP and HCY and serum IGF-1 levels can well predict the changes and severity of cardiac function in elderly patients with chronic CHF, dynamic monitoring of plasma BNP and HCY and serum IGF-1 levels, and early clinical development of corresponding anti-heart failure treatment measures and rescue plans.

Table 2: Comparison of serum IGF-1, HCY, and plasma BNP levels in patients with different NYHA grades (n, $\overline{x} \pm s$).

Group		Number of cases	IGF-1 in serum (μg/L)	HCY in serum (μmol/L)	BNP in serum (ng/L)
Phase of NYHA	Phase II	38	124.60 ± 13.52	17.94 ± 7.02	414.44 ± 115.49
	Phase III	35	$118.69 \pm 11.49^{*}$	$24.67 \pm 6.86^{*}$	$661.92 \pm 137.62^{*}$
	Phase IV	22	$106.58 \pm 10.26^{*\#}$	$32.02 \pm 5.28^{*\#}$	$974.35 \pm 150.68^{*\#}$
F value		2.247	3.286	6.346	
P value		0.025	0.011	<0.001	

Compared with grade II, $^{*}P < 0.05$; compared with grade III, $^{\#}P < 0.05$.

Table 3: Correlations between serum IGF-1, HCY, plasma BNP levels, and parameters related to cardiac function.

Indexes	LVDd		LVEF	
	r value	P value	r value	P value
IGF-1	−0.527	0.019	0.702	0.002
HCY	0.596	0.002	−0.436	0.010
BNP	0.640	0.014	−0.668	<0.001

Table 4: Relationship between serum IGF-1, HCY, plasma BNP levels, and short-term prognosis (n, $\overline{x} \pm s$).

Group	Number of cases	IGF-1 in serum (μg/L)	HCY in serum (μmol/L)	BNP in serum (ng/L)
Patients with a good prognosis	53	127.80 ± 31.63	19.65 ± 8.72	510.85 ± 96.24
Patients with a poor prognosis	42	110.68 ± 36.78	28.77 ± 7.38	792.30 ± 122.39
t value		2.438	5.412	12.551
P value		0.017	<0.001	<0.001

Data Availability

The raw data supporting the conclusion of this article will be available by the authors without undue reservation.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Retraction

Retracted: Effects of Continuous Infusion of Lidocaine under Ultrasound-Guided Cervical Sympathetic Ganglion Catheterization on Cerebral Hemodynamics and Thermal Imaging Characteristics of Head and Neck in Patients with Angioneurotic Headache

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Research Article

Effects of Continuous Infusion of Lidocaine under Ultrasound-Guided Cervical Sympathetic Ganglion Catheterization on Cerebral Hemodynamics and Thermal Imaging Characteristics of Head and Neck in Patients with Angioneurotic Headache

Yeming Wang,[1] **Tengchen Feng**,[1] **Shutie Li**,[2] **Ning Li**,[3] **Zhanlong Yang**,[3] **Xiaojia Sun**,[1] **and Fulong Li**[1]

[1]*Department of Anesthesiology, The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei 075000, China*
[2]*Department of Geriatrics, The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei 075000, China*
[3]*Operating Room, The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei 075000, China*

Correspondence should be addressed to Yeming Wang; 18131358011@163.com

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Angioneurotic headache is a common headache type in clinical treatment. At present, patients with nervous headache are mainly treated with oral western medicine in clinic, but it is usually difficult to obtain the ideal effect. In this study, we analyzed the effects of continuous lidocaine infusion through an ultrasound-guided cervical sympathetic ganglia (SG) catheter on cerebral hemodynamics and thermal imaging characteristics of head and neck in patients with angioneurotic headache and explored the clinical feasibility of this scheme. The results show that continuous infusion of lidocaine under ultrasound-guided SG catheterization can alleviate headache in patients with angioneurotic headache, which may be related to improving cerebral hemodynamics.

1. Introduction

Angioneurotic headache is one of the clinical chronic headache diseases, which can occur at all ages, especially in young and middle ages. It may be related to neurological disorders caused by great mental stress. Spasmodic constriction of the blood vessels in the head induces headache [1, 2]. The types of drugs clinically used for angioneurotic headaches include calcium ion antagonists, beta-blockers, antihistamines, antidepressants, and so on. Although the clinical treatment of headache symptoms is more effective, it cannot be cured and can only relieve headache symptoms. After stopping the drug, the headache symptoms will recur again, aggravating the pain of the patient's headache, inducing the negative emotions, and aggravating the psychological pressure of the patient. Repeated headache will form a vicious circle, affecting the patient's work and life [3–5]. The cervical sympathetic ganglion (SG) is the cervical ganglion composed of the sixth and seventh cervical nerves fused with the first thoracic ganglion to form the inferior cervical ganglion [6]. With the deepening of research on angioneurotic headache, medical workers have found that cervical sympathetic ganglia block (SGB) can inject local anesthetics into the loose connective tissue containing SG, so that the SGB nerves are innervated, thus effectively treating headache [7]. However, complications such as nerve injury and pneumothorax in conventional SGB are high in risk and are easily affected by insufficient puncture experience. However, the cervical sympathetic nerve block technique under the guidance of ultrasound can significantly improve

the success rate and reduce the adverse reactions during the puncture. However, there are few reports regarding the treatment of angioneurotic headache with ultrasound-guided cervical sympathetic nerve block. This study explored the effects of continuous infusion of lidocaine through SG catheter under the guidance of ultrasound on cerebral hemodynamics and thermal imaging characteristics of head and neck in patients with angioneurotic headache.

2. Materials and Methods

2.1. General Information. 80 patients with angioneurotic headache admitted to the hospital from May 2021 to May 2022 were selected and divided into the control group and the observation group by random number table, with 40 cases in each group. The subjects included in this study were informed about the study, voluntarily participated in the study, and signed the informed consent form, which was approved by the hospital ethics committee.

2.2. Inclusion Criteria. Inclusion criteria were as follows: meet the diagnostic criteria for angioneurotic headache [8]; patients who meet SGB indications [9]; and patients with good compliance during treatment.

2.3. Exclusion Criteria. Exclusion criteria were as follows: craniocerebral injury, traumatic brain injury, intracranial space-occupying lesions, cerebral infarction, and cerebral hemorrhage; nasal or drug-induced trigeminal headache; abnormal liver and kidney function, cardiac insufficiency, and coagulation dysfunction; headache due to liver and lung diseases; allergic to the drug used in the study; pregnancy and lactation; and hypertension and diabetes.

2.4. Methods

2.4.1. Collection of Basic Patient Data. Through the hospital electronic case management system, the basic information of the patient is retrieved and entered in double copies. Basic information includes age, gender, course of disease, place of residence, drinking history, smoking history, headache location, and so on.

2.4.2. Treatment Methods. The control group received traditional SGB treatment. The root of the anterior nodule of C6 transverse process, 1.5 cm away from the midline, and 2.5-3 cm cephalad of the sternoclavicular joint were used as the needle insertion points, and a 10 mL syringe was inserted perpendicular to the coronal plane to the root of the C6 transverse process. The depth of needle insertion is 1.5–3.5 cm. After no blood, spinal fluid, or gas is recovered, a mixed solution of 1% lidocaine [National Medicine Zhunzi H13022313, Hebei Tiancheng Pharmaceutical Co., Ltd.] and normal saline (5 mL 1% lidocaine + 5 mL of normal saline) was injected once a day, alternately on both sides, for 10 days of continuous treatment. The observation group was treated with continuous pumping of lidocaine with SG catheter under the guidance of ultrasound. The patient was placed in a supine position with the occiput removed, and the head was slightly tilted back. The ultrasound showed the transverse processes of C6 and C7, and the posterior edge of the sternocleidomastoid muscle was selected. Lateral approach, pay attention to avoid the thyroid, esophagus, blood vessels and nerves, and place a tube on the surface of the longus neck muscle at the level of the C7 transverse process. The lidocaine solution was 1 mL/h, the volume of each self-controlled pump was 1 mL, the locking time was 0.5 h, and the limit volume was 3 mL/h. The two operating physicians were the same person.

2.5. Observation Indicators and Detection Methods

2.5.1. Record Indicators. The postoperative adverse reactions of the patients were recorded, including the number of headaches, the degree of headache, and the duration of each headache at 1 month (T1), 3 months (T3), and 6 months (T6) after surgery. Cerebral hemodynamics and head and neck thermal imaging changes were recorded.

2.5.2. Numerical Rating Scale (NRS). The scoring method can finely divide pain into 10 grades. The more severe the pain, the higher the score, which is no pain (0 points), mild pain (1–3 points), moderate pain (4–6 points), and severe pain (7–10 points).

2.5.3. Detection of Cerebral Hemodynamic Indexes. Transcranial Doppler (TCD) was used to detect the changes of cerebral hemodynamics in patients. The parameters recorded were middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior inferior cerebellar artery (PICA), vertebral artery (VA), and basilar artery (BA) blood flow.

2.5.4. Infrared Thermal Imaging (IR-TI) Technology. To observe the thermal imaging changes of the patient's head and neck, the patient exposed the head and neck and waited for 20 minutes in a quiet state in the room. The DW-910 medical far-infrared thermal imager was used, and the focal length was set to 1.5~2.0 m; the thermal image of the patient was collected, and IIRA special software was used to locate and quantitatively analyze the change of color code temperature value.

2.6. Statistical Method. SPSS 19.0 software was used for statistical analysis in this study, measurement data were expressed as mean ± standard deviation, t-test was used between groups, and repeated-measures analysis of variance was used for analysis of different time periods in the same group. The enumeration data were expressed as the number of cases (percentage), and the χ^2 test was used for the analysis between groups ($a = 0.05$).

Table 1: Comparison of the basic data of the two groups of patients.

Indexes	Control group ($n = 40$)	Observation group ($n = 40$)	t/χ^2 value	P value
Age (year)	47.52 ± 5.26	47.85 ± 4.63	0.293	0.770
Gender			0.450	0.502
Male	21 (52.50)	18 (45.00)		
Female	19 (47.50)	22 (55.00)		
Course of disease (year)	3.20 ± 0.56	3.18 ± 0.59	0.193	0.847
Place of residence			0.238	0.626
Urban	29 (72.50)	27 (67.50)		
Rural	11 (27.50)	13 (32.50)		
Drinking history			0.051	0.822
Yes	23 (57.50)	22 (55.00)		
No	17 (42.50)	18 (45.00)		
Smoking history			0.220	0.639
Yes	27 (67.50)	25 (62.50)		
No	13 (32.50)	15 (37.50)		
Headache area			0.374	0.829
Left	14 (35.00)	12 (30.00)		
Right	24 (60.00)	25 (62.50)		
Bilateral	2 (5.00)	3 (7.50)		

Table 2: Comparison of postoperative complications and headache in two groups of patients.

Group	Control group ($n = 40$)	Observation group ($n = 40$)	χ^2 value	P value
Blurred vision	1 (2.50)	0 (0)	1.013	1.000
Decreased appetite	2 (5.00)	1 (2.50)	0.346	1.000
Feeling sick and vomiting	1 (2.50)	2 (5.00)	0.346	1.000
Rash	2 (5.00)	1 (2.50)	0.346	1.000
Stomach ache	2 (5.00)	1 (2.50)	0.346	1.000
Overall incidence	8 (20.00)	5 (12.50)	0.827	0.363

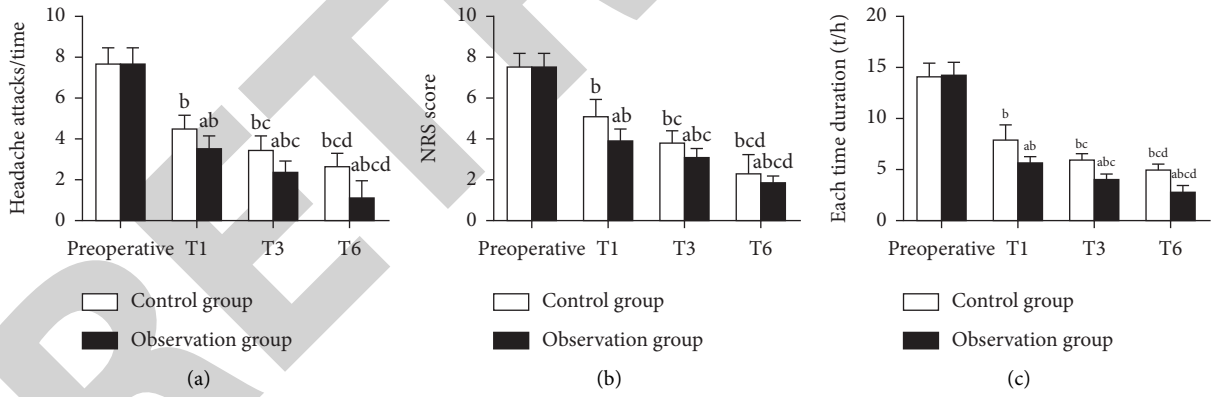

Figure 1: Comparison of postoperative headache in two groups of patients. (a) The number of headaches. (b) NRS score. (c) The duration of each headache. Compared with the control group, $^aP < 0.05$; compared with preoperative, $^bP < 0.05$; compared with T1, $^cP < 0.05$; compared with T3, $^dP < 0.05$.

3. Results

3.1. Comparison of the Basic Data of the Two Groups of Patients. There was no statistical difference in the basic data of the two groups of patients ($P > 0.05$, Table 1).

3.2. Comparison of Postoperative Adverse Reactions and Headaches in the Two Groups of Patients. There was no statistical difference in postoperative blurred vision, decreased appetite, nausea and vomiting, rash, stomach pain, and postoperative adverse reactions between the two groups ($P > 0.05$, Table 2).

3.3. Comparison of Postoperative Headache in Two Groups of Patients. Compared with before operation, the number of headaches, NRS, and duration of each headache at time points T1, T3, and T6 in the two groups were decreased after operation ($P < 0.05$). At T1, T3, and T6 time points, the

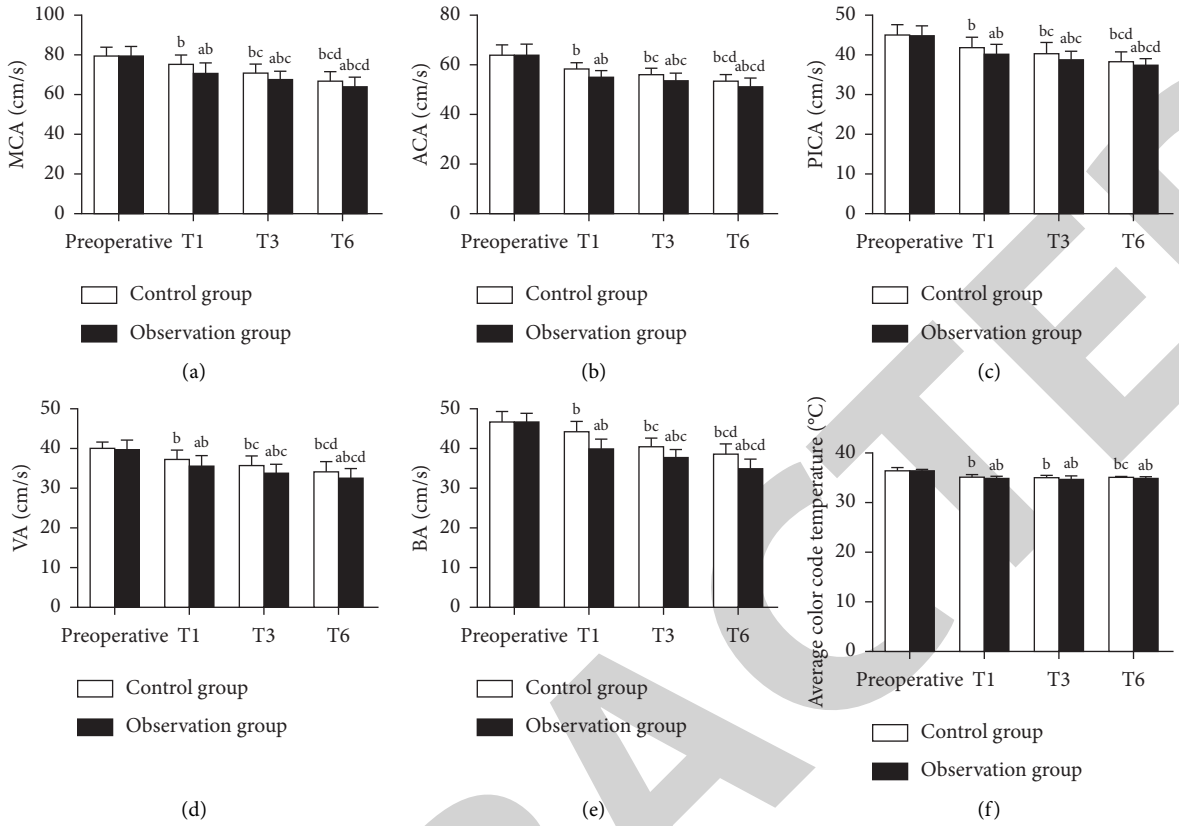

Figure 2: Comparison of postoperative cerebral hemodynamics and thermal imaging changes of head and neck between two groups of patients. (a) The number of headaches. (b) NRS score. (c) The duration of each headache. Compared with the control group, $^{a}P < 0.05$; compared with preoperative, $^{b}P < 0.05$; compared with T1, $^{c}P < 0.05$; compared with T3, $^{d}P < 0.05$.

number of headaches, NRS, and duration of each headache in the observation group were lower than those in the control group ($P < 0.05$, Figure 1).

3.4. Comparison of Postoperative Cerebral Hemodynamics and Thermal Imaging Changes of Head and Neck between Two Groups of Patients. Compared with preoperative, MCA, ACA, PICA, VA, and BA at T1, T3, and T6 time points in the two groups were decreased ($P < 0.05$). At T1, T3, and T6 time points, the MCA, ACA, PICA, VA, and BA of the observation group were lower than those of the control group ($P < 0.05$). Compared with preoperative, the average color code temperature values of head and neck at T1, T3, and T6 time points in both groups were decreased ($P < 0.05$, Figure 2).

4. Discussion

The pathological mechanism of angioneurotic headache has not been clearly elucidated. There are currently vasoconstriction theory and self-limited neuritis theory on the pathogenesis of this disease. Emotional stress, mental stimulation, endocrine disorders, metabolic disorders, neuromodulation disorders, and sleep disorders are also the main causes of the disease. During the onset of the disease, one or both sides of the head may have recurring fluctuating pain. Some patients may also experience symptoms such as vomiting and nausea, which seriously affect the patients' daily life and works [10]. SG belongs to the cervical sympathetic ganglion, and the sympathetic nerve fibers from the SG can participate in the activities of the heart and blood vessels [11]. Studies have shown that SGB treatment can effectively reduce the severity of posttraumatic stress disorder and can be used as adjunctive treatments for posttraumatic stress disorder [12]. At the same time, SGB can also be used for the treatment of vascular neuropathic headache. It can relieve the excessive tension and hyperfunction of the ganglion and is conducive to the expansion of blood vessels in the head, neck, upper limbs, and heart. Thereby, it can improve blood flow, regulate the function of the endocrine system, and achieve the function of stabilizing the autonomic nerve function of the whole body [13, 14].

Although traditional SGB has achieved good results in the treatment of pain, it also has some drawbacks, for example, the operation is obviously empirical and the treatment effect is greatly affected by the operator himself [15]. In order to improve the safety of treatment, the process of using SG intubation and pumping anesthetic drugs under the real-time guidance of ultrasound not only accurately guides and locates the patient's drug delivery site but also avoids vascular damage and nerve damage during the puncture process and avoids the occurrence of intravascular drug injection accidents [16]. In addition, the continuous administration of

analgesia pump can continuously deliver drugs around the nerves, and at the same time, it can control the dosage of drugs and realize personalized medicine. The results of this study showed that the number of headaches, NRS, and duration of each headache in the two groups at different times after treatment were significantly lower than those before surgery, and the decrease trend of the above indicators in the observation group was more obvious at the same time point after surgery [17]. This indicates that SGB treatment can improve the severity of headache in patients with angioneurotic headache, and the treatment effect of ultrasound-guided SG catheter with continuous infusion of lidocaine is more significant. Secondary vasoconstriction of intracranial arteries during headache attacks affects cerebral hemodynamics [18]. Thermal imaging is the result of infrared radiation through the thermal motion of molecules inside an object. It converts infrared energy into electrical signals and displays images and temperature values on the display. Local hyperthermia on thermal imaging suggests possible vascular disease [19, 20]. Observing the thermal imaging characteristics of head and neck in patients with angioneurotic headache before and after treatment is helpful to judge the changes of local cerebral blood perfusion and objectively and quantitatively analyze the treatment effect. This study also found that the cerebral hemodynamic indexes and the average color code temperature value of thermal imaging in the two groups of patients after treatment showed a significant decrease trend, indicating that SGB technology can significantly improve the cerebral blood flow in patients with angioneurotic headache.

Lidocaine is a class IB antiarrhythmic drug, which can block sodium ion channels and play a role in stabilizing the membrane. It is also an amide local anesthetic, and its anesthetic effect is twice that of procaine. Excessive drug doses can induce adverse reactions such as respiratory depression [21]. Lidocaine has been included in our country's Essential Drug List and can also be provided in primary hospitals. Therefore, in this study, the concentration of lidocaine continuously pumped by ultrasound-guided SG catheter was chosen to be 0.2% [22]. The results of this study showed that there was no statistical difference in the incidence of adverse events in patients with continuous pumping of lidocaine under ultrasound-guided SG catheterization compared with the incidence of adverse events in patients treated with conventional SGB. The concentration of the drug is lower than that used in conventional treatment, and the incidence of adverse reactions should be significantly reduced. However, the results of this study did not show such a trend, which may be related to the small number of cases included in this study, resulting in statistical analysis that cannot be presented. It is also possible that the conventional SGB treatment concentration is already an appropriate concentration with a therapeutic effect, so this study cannot observe significant differences by reducing the drug concentration again.

In conclusion, continuous pumping of lidocaine with SG catheter under ultrasound guidance can significantly reduce the severity and duration of headache in patients with angioneurotic headache and can also improve cerebral hemodynamics in patients with angioneurotic headache. However, this study still has a small number of cases and lacks multi-center exploration.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Retraction

Retracted: Prognostic Value of MUC16 Mutation and Its Correlation with Immunity in Hepatocellular Carcinoma Patients

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] B. Liu, Z. Dong, Y. Lu, J. Ma, Z. Ma, and H. Wang, "Prognostic Value of MUC16 Mutation and Its Correlation with Immunity in Hepatocellular Carcinoma Patients," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 3478861, 9 pages, 2022.

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Research Article

Prognostic Value of MUC16 Mutation and Its Correlation with Immunity in Hepatocellular Carcinoma Patients

Bing Liu,[1] Zhicheng Dong,[2] Yingzhi Lu,[2] Jianhua Ma,[1] Zhaoming Ma,[1] and Hongwei Wang[1]

[1]*Department of Radiotherapy, The Second People's Hospital of Lianyungang (Lianyungang Cancer Hospital), Lianyungang, China*
[2]*Oncology Department, The Second People's Hospital of Lianyungang (Lianyungang Cancer Hospital), Lianyungang, China*

Correspondence should be addressed to Hongwei Wang; ww128318@163.com

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Objective. Identifying gene mutation signatures will enable a better understanding for the occurrence, development, and prognosis of hepatocellular carcinoma (HCC) and provide some potential biomarkers for clinical practice. This study investigated the mutated genes in HCC patients and assessed their relationship with tumor mutation burden (TMB) and prognosis. *Methods*. The somatic mutation annotation format (MAF) document, mRNA expression matrix, and clinical information of HCC patients were obtained from the International Cancer Genome Consortium (ICGC) and the Cancer Genome Atlas (TCGA) database. The differences of TMB between the mutant type and the wild-type genes were detected using the Mann–Whitney *U* test. The link of gene mutations with prognosis was explored by the Kaplan–Meier analysis. The proportion of 22 immune cells' composition was measured using CIBERSORT algorithm. *Results.* The two databases screened 16 common mutated genes, which included TP53, TTN, LRP1B, ZFHX4, MUC16, OBSCN, CSMD3, FLG, CSMD1, SYNE1, SPTA1, USH2A, KMT2C, PCLO, HMCN1, and FAT3. After a series of analysis, MUC16 mutation was found to be highly correlated with TMB and was regarded as an independent factor predicting HCC. Furthermore, gene set enrichment analysis (GSEA) indicated that the MUC16 mutation was significantly involved in HCC cell metabolism. *Conclusions*. MUC16 mutation seems to be a valuable potential biomarker for HCC development and its overall survival.

1. Introduction

According to estimated number in 2020 (worldwide, both sexes, all ages), liver cancer has become the third leading cause of cancer-related death with a higher incidence of 905, 677 patients [1, 2]. As the main subtype of liver cancer, hepatocellular carcinoma (HCC) accounts for 85–90% of all liver cancer subjects [3, 4]. HCC is usually diagnosed at an advanced stage with a 5-year overall survival rate of only 12% [5]. Traditional treatments for HCC, including hepatectomy, surgical resection, liver transplantation, chemotherapy, radiotherapy, and molecular targeted therapy [6], also lead to poor therapeutic outcomes [7]. Therefore, some effective and novel biomarkers are required to improve the prognosis of patients with HCC.

There are about 30,000 genes in human cells, and these genes act as the targets of numerous genetic mutation events that happen over the course of a human life [8]. Many gene mutations are served as prognostic biomarkers for cancers, such as tumor protein P53 (TP53), phosphatase and tensin homolog (PTEN), and RB transcriptional corepressor 1 (RB1) mutations in prostate cancer, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2), and KRAS proto-oncogene and GTPase (KRAS) mutations in gastric cancer, as well as E1A binding protein P300 (EP300) in bladder cancer [9–11]. The progression of HCC involves many factors, including environmental exposure, somatic mutations, and transcriptional or epigenetic variations [12], among which, genetic mutations of several key genes (e.g.,

TP53, catenin beta 1 (CTNNB1), and telomerase reverse transcriptase (TERT)) have considerable relevance to the carcinogenesis and prognosis of HCC [13–15].

In this study, we collected somatic mutation data and transcriptome data in HCC patients from International Cancer Genome Consortium (ICGC) and the Cancer Genome Atlas (TCGA) cohorts. The shared mutant genes in two databases were screened, and the association of these gene mutations with TMB and prognosis was further investigated. The study indicated that MUC16 mutation was related to TMB and promoted anti-tumor immunity in HCC.

2. Materials and Methods

2.1. Data Resource. All the data used in this study were obtained from the publicly TCGA database (https://portal.gdc.cancer.gov/) and the International Cancer Genome Consortium (ICGC) (https://dcc.icgc.org/). The approval from a local ethics committee is not required since the TCGA and ICGC data are open to the public. Patients with complete clinical information, survival data, and complete gene mutation data were included. Somatic gene mutations for TCGA samples ($n = 389$) and ICGC ($n = 105$) were, respectively, analyzed.

2.2. Identification of Key Mutational Genes. The mutation annotation data of HCC were detected by VarScan software (v.2.3.7) and then visualized by the GenVisR package. The characteristics of mutation from the two cohorts were visualized using waterfall plot. The shared mutation genes between the two cohorts were identified using a Venn plot. To explore the prognostic significance of identified mutation genes, the survival analysis was conducted using the "survival" package. The overall survival analysis of genes in wild-type group and mutant group was implemented using the survival package. The mutational genes were eligible if they were significant in the survival analysis with P value < 0.05. Furthermore, we explored the association between the mutation genes and TMB. To calculate the TMB value of individual, the total number of mutations counted was divided by the exome size (38 Mb was treated as the estimate of the exome size) [16].

2.3. Gene Set Enrichment Analysis. Gene set enrichment analysis (GSEA) as a computational algorithm was used to determine whether a prior defined set of genes presents statistically significant differences between two different biological states [17]. GSEA was performed to seek signaling pathways involved in HCC patients between the mutant group and the wild group of identified genes and exhibited significant differences (P value<0.05) in the enrichment of MSigDB Collection (c2.cp.kegg.v7.1.symbols.gmt). The top 10 significant pathways in mutant group were visualized using the gg-plot R package. Gene sets with a nominal P value < 0.05 were considered statistically significant.

2.4. Immune Cell Infiltration. The CIBERSORT tool is widely employed in investigating the proportions of 22 subtypes, which are human immune cell types in the microenvironment. By using CIBERSORT algorithm, this study calculated the HCC individuals' data and obtained the relative proportion of 22 infiltrating immune cells. We uploaded the gene expression matrix data to CIBERSORT (https://cibersort.stanford.edu/index.php) and acquired the immune cell infiltration matrix. A correlation heatmap was plotted to view the correlation of 22 types of infiltrating immune cells. The difference in immune infiltration between mutant group and the wild group of identified genes in 22 types of immune cells was visualized using violin plots.

2.5. Statistical Analysis. All statistical analyses in this study were done using R (version 3.6.3; https://www.r-project.org/). Group comparisons were implemented for continuous variables between mutant genes and TMB using the Mann–Whitney U test. Kaplan–Meier survival analysis was used to estimate survival differences between mutant group and the wild group of identified genes. Univariate and multivariate Cox regression analyses were adapted for survival analysis of clinical variables of patients, including age, sex, grade, stage, TMB, and MUC16. A P value <0.05 was considered statistically significant.

3. Results

3.1. Mutated Genes in HCC. The identification of mutation characteristics is necessary for the exploration of HCC pathogenesis. As demonstrated in Figures 1(a) and 1(b), the details of the top 30 genes with frequent mutation in HCC patients from the TCGA and ICGC databases were displayed in waterfall plots. The Venn plot presented that the following 16 genes were overlapped in these two datasets, including TP53, TTN, LRP1B, ZFHX4, MUC16, OBSCN, CSMD3, FLG, CSMD1, SYNE1, SPTA1, USH2A, KMT2C, PCLO, HMCN1, and FAT3, which were analyzed subsequently (Figure 1(c), Table 1).

3.2. Identification of Prognosis-Related Mutated Genes. It was observed that all 16 genes (TP53, TTN, LRP1B, ZFHX4, MUC16, OBSCN, CSMD3, FLG, CSMD1, SYNE1, SPTA1, USH2A, KMT2C, PCLO, HMCN1, and FAT3) were significantly associated with higher TMB in patients with HCC (Figure 2). Further Kaplan–Meier analysis was carried out to investigate the relationship between mutant group and the wild group of identified genes associated with prognosis in HCC via TCGA cohort. It was revealed that a significant difference was detected only in the two genes ($P = 0.014$for MUC16; $P = 0.033$for FLG, Figure 3) between the two groups. Since MUC16 (the cancer antigen CA125) is the most commonly used serum biomarker in cancers [18,19], MUC16 was selected for the following analysis. The demographic characteristics of the HCC patients from TCGA cohort are presented in Table 2. We then performed the multivariate survival analysis of all variables (stage, age, and

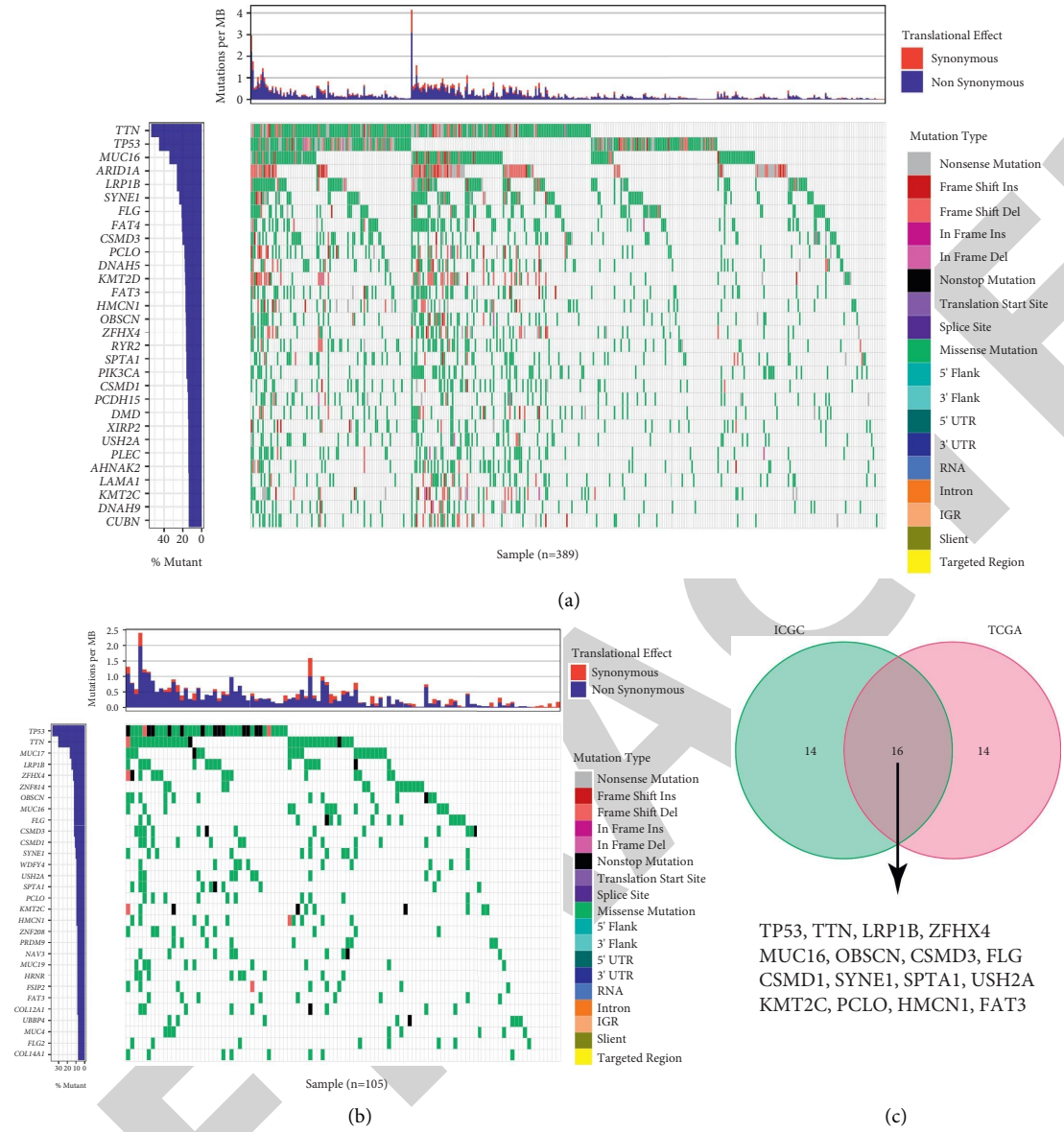

Figure 1: Overview of frequently mutated genes in HCC. Mutational landscape of the top 30 frequently mutated genes in HCC in TCGA cohort (a) and ICGC cohort (b). (c) Venn diagram presents 16 frequently mutated genes shared by both databases.

MUC16 mutation status) with $P < 0.05$ in univariate analysis by Cox proportional hazards analysis, and the result showed that age (HR = 1.65, 95%CI = 1.18–2.31; $P = 0.003$), stage (HR = 2.18, 95%CI = 1.54–3.08; $P < 0.001$), and MUC16 mutation (HR = 0.64, 95%CI = 0.44–0.93; $P = 0.018$) were independent prognostic factors in individuals with HCC (Table 3).

3.3. MUC16 Mutation GSEA. By separating the transcriptome data of HCC into MUC16 wild type and mutation groups, the abnormally expressed genes in HCC may be identified. The application of GSEA in TCGA cohort demonstrated that MUC16 mutation was involved in in cell cycle, metabolic process, and immune process, such as aminoacyl tRNA biosynthesis, base excision repair, cell cycle, cysteine and methionine metabolism, DNA replication, fructose and mannose metabolism, glycosylate and dicarboxylate metabolism, one carbon pool by folate, oocyte meiosis, pyrimidine metabolism, RNA degradation, spliceosome, steroid biosynthesis, terpenoid backbone biosynthesis, valine leucine, and isoleucine degradation (Figure 4).

3.4. The Relationship between Tumor Immune Cell Infiltration and MUC16 Mutation in HCC. With the help of CIBERSORT algorithm, the immune infiltration compositions of 22 types of immune cells in HCC were calculated. The relative percent of 22 immune cell infiltrations in HCC samples was visualized based on the TCGA cohort and is presented in

Table 1: The information of 16 frequently mutated genes.

Gene	Full name	Chromosome position	Gene ID	Ensembl
TP53	Tumor protein P53	17p13.1	7515	ENSG00000141510
TTN	Titin	2q31.2	7273	ENSG00000155657
LRP1B	LDL receptor related protein 1B	2q22.2	53353	ENSG00000168702
ZFHX4	Zinc finger homeobox 4	8q21.13	79776	ENSG00000091656
MUC16	Mucin 16, cell surface associated	19p13.2	94025	ENSG00000181143
OBSCN	Obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF	1q42.13	84033	ENSG00000154358
CSMD3	CUB and Sushi multiple domains 3	8q23.3	114788	ENSG00000164796
FLG	Filaggrin	1q21.3	2312	ENSG00000143631
CSMD1	CUB and Sushi multiple domains 1	8p23.2	64478	ENSG00000183117
SYNE1	Spectrin repeat containing nuclear envelope protein 1	6q25.2	23345	ENSG00000131018
SPTA1	Spectrin alpha, erythrocytic 1	1q23.1	6708	ENSG00000163554
USH2A	Usherin	1q41	7399	ENSG00000042781
KMT2C	Lysine methyltransferase 2C	7q36.1	58508	ENSG00000055609
PCLO	Piccolo presynaptic cytomatrix protein	7q21.11	27445	ENSG00000186472
HMCN1	Hemicentin 1	1q25.3	83872	ENSG00000143341
FAT3	FAT atypical cadherin 3	11q14.3	120114	ENSG00000165323

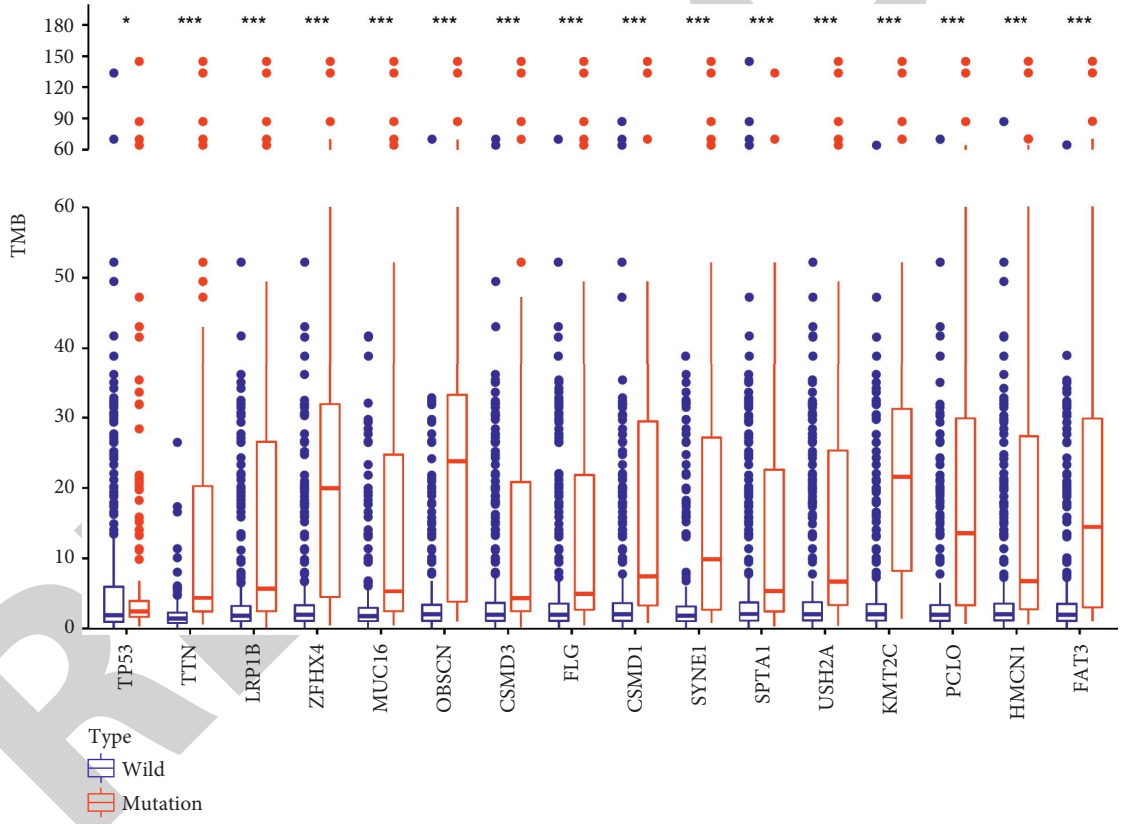

Figure 2: Sixteen gene mutations are associated with TMB. Note: $^{*}P < 0.05$; $^{***}P < 0.005$.

Figure 5(a). Correlation heatmap of the 22 types of immune cells is displayed in Figure 5(b). A majority of immune cells were negatively correlated with each other. For example, M0 macrophages were negatively associated with CD8 T cell ($r = -0.44$); resting NK cells were negatively associated with activated NK cells ($r = -0.39$); resting mast cells were negatively associated with activated mast cells ($r = -0.35$); resting memory CD4T cells were adversely associated with CD8 T cells ($r = -0.38$). The differential expressional proportion of immune infiltration cells in the HCC tissues between wild and mutation types of MUC16 is displayed in Figure 5(c). It was revealed that regulatory T cells ($P < 0.001$), activated NK cells ($P = 0.015$), monocytes ($P = 0.025$), and resting mast cells ($P = 0.013$) in wild type of

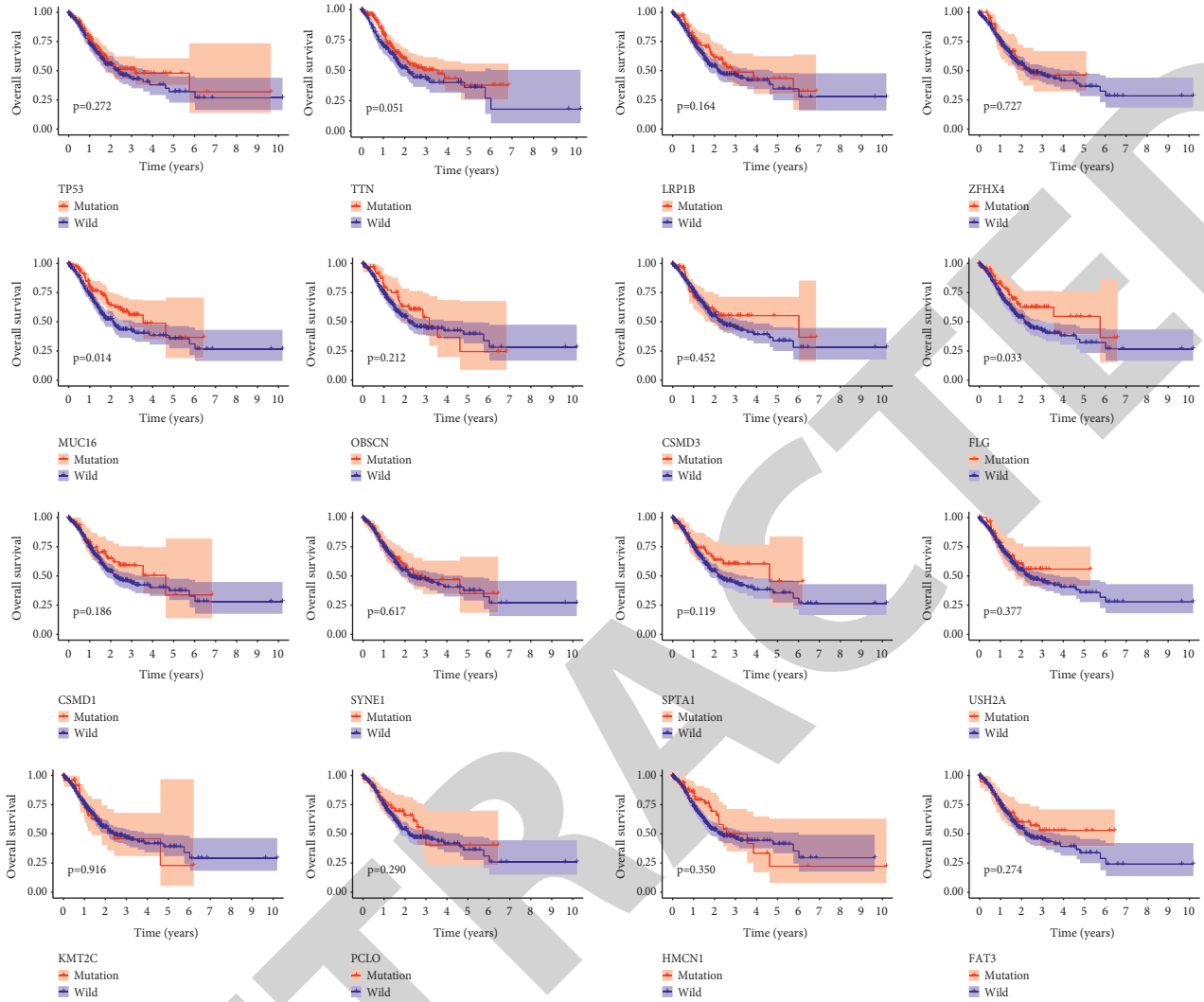

Figure 3: Overall survival of individuals with HCC in wild type and mutation type of 16 gene mutations.

MUC16 were significantly higher than those in mutation type of MUC16 (all $P < 0.05$). In contrast, the infiltration rates of resting NK cells were clearly upregulated in mutation type of MUC16 compared to that in wild type of MUC16 ($P = 0.004$).

4. Discussion

HCC is a serious health concern worldwide with high morbidity and mortality. HCC presents clear molecular heterogeneity, including numerous somatic genome mutations [20]. However, to date, gene mutations associated with TMB and immune response in HCC are not entirely clear.

In this study, somatic mutation landscapes of HCC were described in 389 samples from the TCGA cohort and 105 Japanese samples from the ICGC cohort. Subsequently, 16 genes were frequently mutated in two databases. MUC16 ranked the third-highest mutation frequency, after TTN and TP53. Then, all of the 16 genes were associated with higher TMB, and survival analysis demonstrated that only MUC16 mutation group presented a better OS than the wild-type group. TMB indicates the accumulation of somatic mutations in cancers, and a high TMB promotes the exposure of more neoantigens, which is likely to induce a T-cell-dependent immune response [21]. Therefore, we considered that MUC16 mutation may strengthen immune response. Furthermore, cell cycle and metabolic signaling pathways were significantly enriched in patients with MUC16 mutation. Tumor-infiltrating immune cell analysis showed that patients with MUC16 mutations infiltrated more resting NK cells, which is consistent with immune cells and pathways that play an important role in the tumor microenvironment and promote immune responses [22,23]. These findings demonstrate that MUC16 has a certain research value in HCC.

MUC16 belongs to a type I transmembrane mucin that encodes cancer antigen 125 (CA-125) [24]. It was first described almost 40 years ago and was found to be a transmembrane mucin 20 years later [25]. MUC16 is an essential membrane protein that sustains normal cell function and plays a role in the development of numerous cancers [26,27].

Table 2: Demographic characteristics of the HCC patients from TCGA cohort.

Parameter	HCC patients
Age (years)	65.20 ± 10.59
Gender	
Male	251
Female	138
Grade	
G1	9
G2	138
G3	242
Stage	
I	51
II	126
III	175
IV	37
T stage	
T1	17
T2	80
T3	185
T4	107
M stage	
M0	348
M1	24
MX	17
N stage	
N0	122
N1	103
N2	79
N3	80
NX	5

Table 3: Univariate and multivariate overall survival analysis of HCC patients by the Cox proportional hazards.

Variables	Univariate		Multivariate	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age (≥65 vs. <65)	1.51 (1.08–2.10)	0.016	1.65 (1.18–2.31)	0.003
Gender (male vs. female)	1.01 (0.72–1.41)	0.967		
Grade (G3 vs. G2+G1)	1.37 (0.97–1.91)	0.071		
Stage (III + IV vs. I + II)	2.14 (1.51–3.02)	<0.001	2.18 (1.54–3.08)	<0.001
TMB (high vs. low)	0.99 (0.97–1.00)	0.055		
MUC16 (mutant vs. wild)	0.65 (0.44–0.94)	0.022	0.64 (0.44–0.93)	0.018

The expression of MUC16 is usually located in the cell membrane or scattered in bodily fluids as a soluble form [28]. A recent study revealed that MUC16 mutations are associated with a better OS in individuals with gastric cancer. One of possible mechanisms is that MUC16 mutations activate the p53 pathway and DNA repair pathway [24]. Previous studies in melanoma, colorectal cancer, and cervical cancer have demonstrated that individuals with high TMB scores show a favorable OS if treated with immune checkpoint inhibitors [29–32]. In our study, MUC16 mutation group presented higher TMB scores when compared to MUC16 wild-type group. Thus, it was possible that the MUC16 mutation group will benefit from immune checkpoint inhibitor treatment. Knockdown of MUC16 revealed the link between MUC16 and HCC cellular functions, demonstrating that tumor-derived MUC16 serves as a suppressor of the anti-tumor immune response [33]. MUC16 is a protein with a large molecular weight. The MUC16 gene covers many mutations in HCC derived from the TCGA portal [33]. Thus, we believe that such mutations may affect the structural stability of MUC16, which influences the expression of MUC16 protein.

Furthermore, regulatory T cells, activated NK cells, monocytes, and resting mast cells were more abundant in the wild type of MUC16 group, whereas resting NK cells were more abundant in the mutation type of MUC16 group. NK cells as an important component of innate immune system are labeled by releasing cytokines and cytolytic activity against target cells. It was demonstrated that NK cells can selectively kill cancer stem cells, which suggest that NK cell-based therapy can be used as an effective treatment to suppress cancer relapse and metastasis [34,35]. A majority of

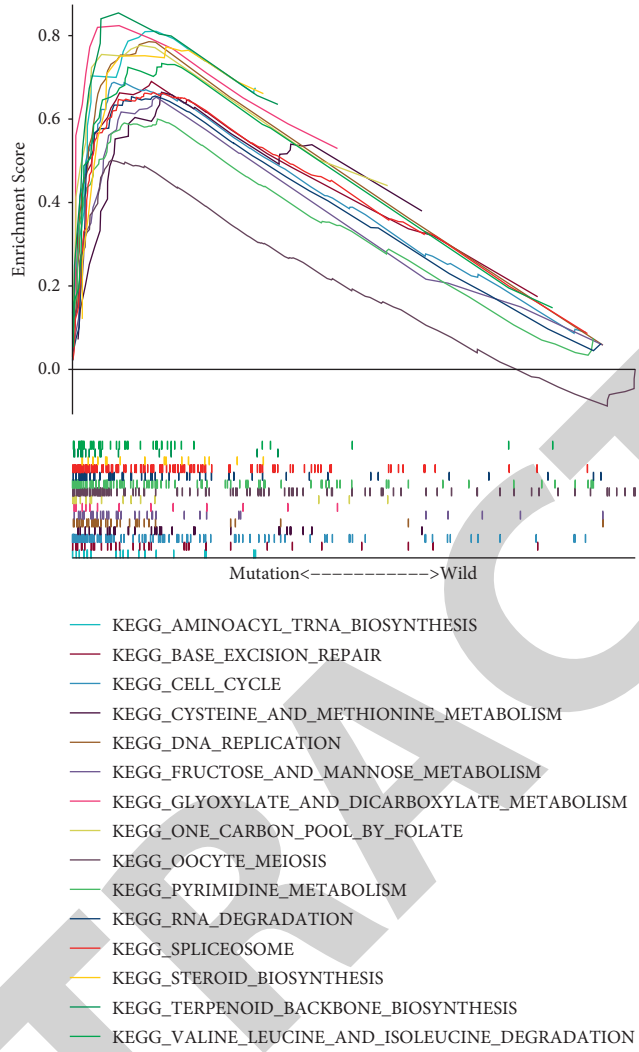

Figure 4: GSEA of the abnormally expressed genes in HCC in MUC16 mutation type.

the genes in MUC16 mutation were enriched in various cancer-related pathways, such as cell cycle and metabolic process, which demonstrated the critical role of the MUC16 gene in HCC.

The main limitation in our study is that the conclusions were drawn from bioinformatics analysis mainly about the prognostic value of MUC16 mutation and its correlation with immunity in HCC patients. Further research would be performed with larger sample sizes for exploring the prognostic value of MUC16 and FLG mutation in a clinical cohort as time and funding permit. Moreover, the role of MUC16 expression in the progression and metastasis in HCC was required to be confirmed by experiments in future. Nevertheless, MUC16 mutation is frequently mutated in HCC, and its mutation is associated with elevated TMB and contributes to anti-tumor immunity, which can act as a biomarker to forecast immune response.

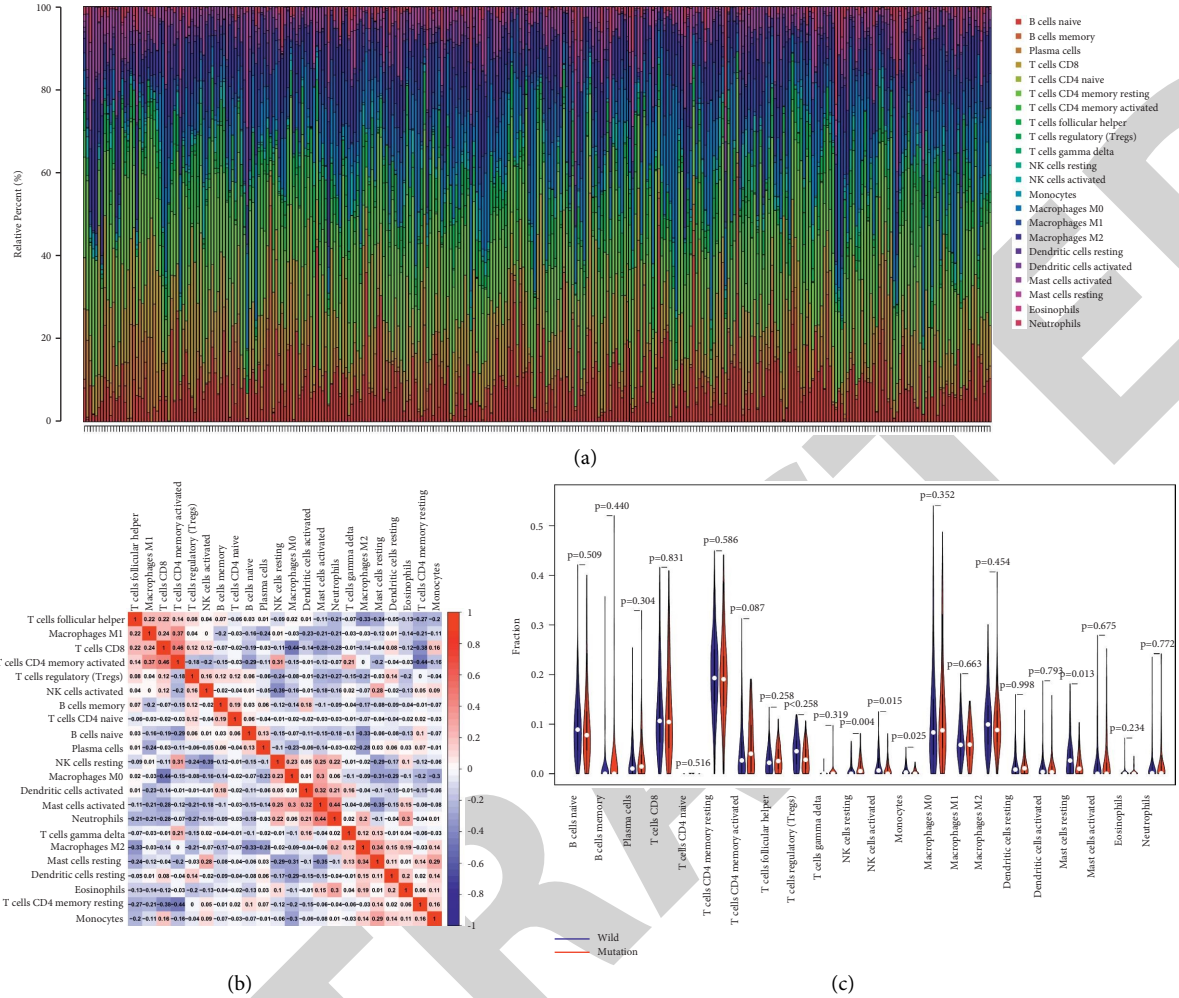

FIGURE 5: The landscape of immune cell infiltration in HCC samples. (a) Bar charts of 22 types of immune cells in HCC samples. (b) Correlation matrix of 22 types of immune cell proportions. (c) Differential expression of 22 types of immune cells in HCC samples between wild type and mutation type of MUC16.

Data Availability

The data used to perform the analyses described herein are publicly available from TCGA and ICGC data portals.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Bing Liu and Zhicheng Dong contributed equally to this study.

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Retraction

Retracted: Analysis of the B2M Expression in Colon Adenocarcinoma and Its Correlation with Patient Prognosis

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] H. Lin, K. Wang, K. Zou et al., "Analysis of the B2M Expression in Colon Adenocarcinoma and Its Correlation with Patient Prognosis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7264503, 13 pages, 2022.

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Research Article

Analysis of the B2M Expression in Colon Adenocarcinoma and Its Correlation with Patient Prognosis

Hailian Lin,[1,2,3] Kelang Wang,[1,2,3] Kebing Zou,[1,2,3] Yuanyuan Wang,[1,2,3] Gen xiang Que,[1,2,3] Xuefeng Yang ,[1,2,3] and Mengdan Liao [4]

[1]*Hunan Provincial Clinical Research Center for Metabolic Associated Fatty Liver Disease, the Affiliated Nanhua Hospital, Hengyang Medical School, University of South China, Hengyang 421002, Hunan, China*
[2]*The Affiliated Nanhua Hospital, Department of Gastroenterology, Hengyang Medical School, University of South China, Hengyang 421002, Hunan, China*
[3]*The Affiliated Nanhua Hospital, Department of General Practice, Hengyang Medical School, University of South China, Hengyang 421002, Hunan, China*
[4]*The Affiliated Nanhua Hospital, Department of Nephrology, Hengyang Medical School, University of South China, Hengyang 421002, Hunan, China*

Correspondence should be addressed to Xuefeng Yang; yxf009988@sina.com and Mengdan Liao; liaomengdan2021@163.com

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Colon adenocarcinoma (COAD) is one of the most common malignant tumors in clinics. It is often found at an advanced stage, with high incidence and poor prognosis; early diagnosis is difficult and treatment methods are limited. In order to find new methods for diagnosis and treatment of COAD, people pay more and more attention to the discovery and functional research of new oncogenes and tumor suppressor genes of COAD. β2-microglobulin (B2M) plays different physiological and pathological roles in tumor cells and nontumor cells. At present, there is no public report on the expression of B2M in COAD. In this study, the expression of B2M mRNA in COAD tissues was compared with that in normal tissues. The relationship between the expression of B2M mRNA and the stage, histological subtype, lymph node metastasis, TP53 mutation, and survival time of COAD was discussed. It was found that B2M is a potential tumor suppressor gene in COAD. The decreased expression of B2M after mutation can cause immune escape of COAD cells, thus affecting the therapeutic effect and prognosis. This study provides a new idea for the prevention and treatment of COAD.

1. Introduction

Colon adenocarcinoma (COAD) is one of the most common malignant tumors in the clinics. It is often found at an advanced stage, with high incidence and poor prognosis, and early diagnosis is difficult and treatment methods are limited. In order to find new methods for diagnosis and treatment of COAD, people pay more and more attention to the discovery and functional research of new oncogenes and tumor suppressor genes of COAD.

β2-microglobulin (B2M) is a serum protein composed of 119 amino acids with a size of 12 kDa [1]. B2M is expressed in all nucleated cells and is an important subunit of major histocompatibility complex (MHC) class I. It plays different physiological and pathological roles in tumor cells and nontumor cells, especially performing important biological functions in immune monitoring [2]. A large number of studies have found that serum B2M protein is closely related to infection [3, 4], cardiovascular and cerebrovascular diseases [5–7], inflammatory bowel disease [8], kidney injury [9], blood system diseases [10–12], amyloidosis [13, 14], and aging-related diseases [15]. At present, there is no public report on the expression of B2M in COAD. The purpose of this study is to use the TCGA database to analyze the difference of the B2M gene mRNA expression between colon cancer tissues and normal colon tissues and its correlation

with the survival prognosis of patients, so as to provide new diagnostic markers and therapeutic targets for colon adenocarcinoma.

2. Methods

2.1. Experimental Methods. The experimental methods are as follows:

(1) TCGA database was used to analyze the expression of B2M mRNA in pan-cancer tissues and corresponding normal tissues.

UALCAN (https://ualcan.path.uab.edu/index.html) is an effective online cancer data analysis and mining website based on relevant cancer data in TCGA database. We accessed the TCGA database through the UALCAN website [16] to analyze the expression of B2M mRNA in pan-cancer tissues and corresponding normal tissues.

(2) TCGA database was used to analyze the difference of the B2M mRNA expression between colon adenocarcinoma tissues and normal colon tissues.

We accessed the TCGA database through the UALCAN website [16], from which we downloaded 286 colon cancer tissue samples and 41 paracancer normal tissue samples to analyze the difference of the B2M mRNA expression between colon cancer tissues and adjacent normal tissues.

(3) TCGA database was used to analyze the difference of methylation level of a B2M gene promoter between colon adenocarcinoma tissues and normal colon tissues.

We accessed the TCGA database through the UALCAN website [16] to analyze the difference of methylation level of the B2M gene promoter between colon cancer tissues and adjacent normal tissues.

(4) TCGA database was used to analyze the relationship between B2M mRNA expression and colon cancer stage.

According to the latest TNM staging of malignant tumor, colon cancer can be divided into four stages according to the severity: Stage 1: The primary tumor is only confined to the mucosa or submucosa, and there is no tumor lymph gland metastasis or distant metastasis. Stage 2: The primary tumor invaded the muscular layer of intestinal wall, but there is no tumor lymph gland metastasis or distant metastasis. Stage 3: No matter the depth of primary tumor invasion, regional lymph node metastasis has occurred, but there is no distant metastasis. Stage 4: The tumor had distant metastasis, such as liver, lung, bone, and brain metastasis, peritoneal implantation metastasis, and distant lymph node metastasis(such as supraclavicular lymph node metastasis) [17]. We accessed the TCGA database through the UALCAN website [16] to analyze the relationship between the expression of B2M mRNA and the stage of colon cancer.

(5) TCGA database was used to analyze the relationship between B2M mRNA expression and histological subtypes of colon cancer.

The histological types of colon cancer can be divided into the following types: (1) Nonspecific adenocarcinoma. (2) Special types of adenocarcinoma, including mucinous adenocarcinoma, medullary carcinoma, serrated adenocarcinoma, signet-ring cell adenocarcinoma, cribriform acne adenocarcinoma, and micropapillary adenocarcinoma. (3) Squamous cell carcinoma. (4) Adenosquamous carcinoma. (5) Spindle cell carcinoma/sarcomatoid carcinoma. (6) Undifferentiated carcinoma. (7) Other special types of colon cancer. (8) Type undetermined colon cancer [18]. We accessed the TCGA database through UALCAN website [16] and mainly analyzed the differences of the B2M mRNA expression between adenocarcinoma and mucinous adenocarcinoma.

(6) TCGA database was used to analyze the relationship between the B2M mRNA expression and lymph node metastasis.

The status of lymph node metastasis was divided into four grades: N0: no regional lymph node metastasis; N1:1~3 axillary lymph nodes metastasis; N2:4~9 axillary lymph nodes metastasis; N3:more than 10 axillary lymph nodes metastasis. We accessed the TCGA database through the UALCAN website [16] to analyze the relationship between the B2M mRNA expression and lymph node metastasis.

(7) TCGA database was used to analyze the relationship between the B2M mRNA expression and TP53 mutation status.

We accessed the TCGA database through the UALCAN website [16] to analyze the relationship between the B2M mRNA expression and TP53 mutation status.

(8) TCGA database was used to analyze the relationship between the B2M mRNA expression and gender, age, weight, and race of patients with colon cancer.

We accessed the TCGA database through the UALCAN website [16] to analyze the relationship between the B2M mRNA expression and gender, age, weight, and race of patients with colon adenocarcinoma.

(9) TCGA database was used to analyze the relationship between the expression level of B2M mRNA in colon adenocarcinoma. tissues and the survival time of patients.

(10) TCGA database was used to analyze the genes related to the B2M gene expression in patients with colon adenocarcinoma.

We accessed the TCGA database through the UALCAN website [16] to analyze the genes related

to the B2M gene expression in colon adenocarcinoma patients.

2.2. Statistical Analysis. Wilcoxon assay was used to analyze the expression levels of B2M mRNA in colon cancer tissues and normal colon tissues. Kaplan–Meier analysis was used to compare the survival time of the B2M mRNA high expression group and low expression group. Log-ranch test was used to calculate the p value, $P < 0.05$ indicates statistical significance. All statistical analyses were performed using R (version x64 3.5.1).

3. Results

3.1. Clinical Characteristics of 286 Patients with Colon Cancer in the TCGA Database. We downloaded the clinical data of 286 patients with colon cancer from TCGA database, including patients' gender, age, weight, race, clinical stage, and histological subtype. After excluding the samples with incomplete clinical data, in the categories of gender, age, weight, clinical stage, and histological subtype, only 283, 283, 210, 274, and 280 samples were left to participate in the statistics; the clinical characteristics are shown in Table 1.

3.2. The Expression of B2M mRNA in Pan-Cancer Tissues and Corresponding Normal Tissues. The expression of B2M mRNA in pan-cancer tissues and corresponding normal tissues is shown in Figure 1. It can be seen that the expression of B2M mRNA is increased in most tumors, such as BRCA ($p = 1.604910E-03$), CHOL ($p = 7.43370000000354E-07$), ESCA ($p = 1.635010000000066E-05$), GBM ($p = 1.62447832963153E-12$), HNSC ($p = 1.62458935193399E-12$), KICH ($p = 3.87309999627661E-08$), KIRC ($p < 1E-12$), KIRP ($p = 1.5612000003884E-07$), PCPG ($p = <1E-12$), THCA ($p = 3.298400E-03$). In a few tumors, the expression of B2M mRNA was decreased, such as COAD ($p < 1E-12$), LUAD ($p = 1.62436730732907E-12$), LUSC ($p = 1.62458935193399E-12$), PRAD ($p = 1.757730E-02$), and READ ($p = 1.82229999978745E-08$). There was no statistically significant differences in the expression of other tumors in Figure 1.

3.3. The Expression of B2M mRNA in Colon Adenocarcinoma Tissues Was Significantly Lower Than That in Normal Colon Tissues. We downloaded 41 samples of normal tissues adjacent to cancer and 286 samples of colon cancer from the TCGA database. It can be seen that the expression of B2M mRNA in colon adenocarcinoma tissues was significantly lower than that in adjacent normal tissues ($p < 1E-12$) (Figure 2).

3.4. The Methylation Level of a B2M Gene Promoter in Colon Adenocarcinoma Tissues Was Lower Than That in Normal Colon Tissues. The results of TCGA database analysis showed that the methylation level of B2M gene promoter in colon cancer tissues was lower than that in normal colon tissues, and the difference was statistically significant ($p = 1.959910E-03$) (Figure 3).

β values indicate DNA methylation levels from 0 (unmethylated) to 1 (fully methylated). Different β value represents hypermethylation (β values: 0.7–0.5) or hypomethylation (β values: 0.3–0.25).

3.5. The Expression Level of B2M mRNA Was Correlated with the Stage of Colon Adenocarcinoma. The results of TCGA database analysis showed that the expression level of B2M mRNA was correlated with the stage of colon cancer. The difference of B2M mRNA expression between stage I and stage IV, and between stage II and stage IV was statistically significant. The higher the stage of colon cancer, the lower the expression of B2M mRNA (normal-vs-stage1: $p = 2.42909999892404E-08$; normal-vs-stage2: $p = 2.26879626197274E-11$; normal-vs-stage3: $p = 3.46889961200247E-10$; normal-vs-stage4: $p = 8.27404811332144E-12$; stage1-vs-stage4: $p = 1.609760E-02$; stage2-vs-stage4: $p = 3.202300E-03$) (Figure 4).

3.6. The Expression of B2M mRNA Was Correlated with Histological Subtypes of Colon Adenocarcinoma. The results of TCGA database analysis showed that the expression level of B2M mRNA was correlated with the histological subtypes of colon cancer, and the expression level of B2M mRNA in adenocarcinoma was lower than that in mucinous adenocarcinoma, and the difference was statistically significant (normal-vs-adenocarcinoma: $p = 1.34860012046545E-10$; normal-vs-mucinous-adenocarcinoma: $p = 2.019200E-04$; adenocarcinoma-vs-mucinous-adenocarcinoma: $p = 3.139800E-02$) (Figure 5).

3.7. The Expression of B2M mRNA Was Not Correlated with Lymph Node Metastasis. TCGA database analysis showed that B2M mRNA expression was not associated with lymph node metastasis (normal-vs-N0: $p = 1.79600001537494E-09$; normal-vs-N1: $p = 2.08109973698356E-10$; normal-vs-N2: $p = 1.10179976253733E-10$) (Figure 6).

3.8. B2M mRNA Expression Was Correlated with the TP53 Mutation Status. The results of TCGA database analysis showed that the expression level of B2M mRNA in colon adenocarcinoma tissues was correlated with the TP53 mutation status, and the expression level of B2M mRNA in TP53 mutated colon cancer tissues was lower than that in nonmutated colon adenocarcinoma tissues (normal-vs-tp53-mutant: $p = 5.69789770921147E-11$; normal-vs-tp53-nonmutant: $p = 6.83500001041892E-09$; tp53-mutant-vs-tp53-nonmutant: $p = 8.608400E-04$) (Figure 7).

3.9. The Expression Level of B2M mRNA Was Not Related to Gender, Age, and Weight of Patients with Colon Adenocarcinoma but Was Related to Race. The results of TCGA database analysis showed that the expression level of B2M mRNA in colon cancer tissues was not related to gender

Table 1: The clinical characteristics of the COAD patients in the TCGA.

Clinical features	Classification	Percentage (%)
Gender, *n* (%)	Male	156 (55.1%)
	Female	127 (44.9%)
Age, *n* (%)	21~60	102 (36.0%)
	61~100	181 (64.0%)
Weight, *n* (%)	Normal weight (BMI: 18.5~25)	70 (33.3%)
	Extreme weight (BMI: 25~30)	74 (35.2%)
	Obese (BMI: 30~40)	56 (26.7%)
	Extreme Obese (BMI > 40)	10 (4.8%)
Clinical stage, *n* (%)	Stage I	45 (16.4%)
	Stage II	110 (40.2%)
	Stage III	80 (29.2%)
	Stage IV	39 (14.2%)
Histological subtypes, *n* (%)	Adenocarcinoma	243 (86.8%)
	Mucinous adenocarcinoma	37 (13.2%)

Figure 1: Expression of the B2M gene in the tumor tissues of the TCGA database.

(normal-vs-male: $p = 2.39808173319034E - 14$; normal-vs-female: $p = 1.88882243179478E - 12$) (figure 8), age (normal-vs-age (21–40yrs): $p = 6.42129999999241E - 05$; normal-vs-age (41–60yrs): $p = 4.14730028097665E - 10$; normal-vs-age (61–80yrs): $p = 1.69331215715829E - 12$; normal-vs-age (81–100yrs): $p = 4.07770000000474E - 05$) (figure 9), and weight (normal-vs-normal weight: $p = 1.24109611476797E - 11$; normal-vs-extreme weight: $p = 8.13670020249901E - 10$; normal-vs-obese: $p = 2.16919999740384E - 08$; normal-vs-extreme obese: $p = 5.75699999999513E - 05$) (Figure 10), but was related to race, and the expression level of B2M mRNA in colorectal cancer

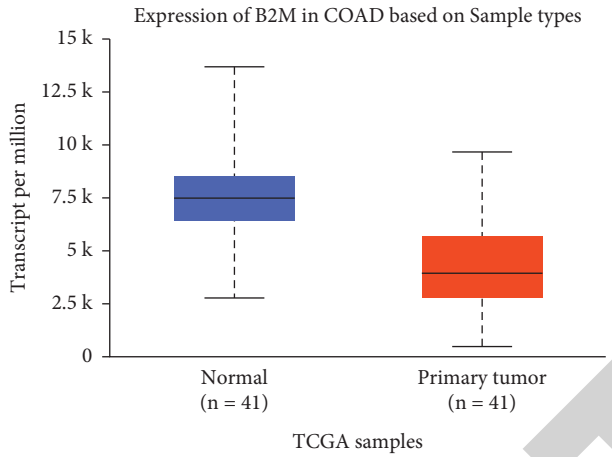

Figure 2: Expression of B2M in COAD based on sample types.

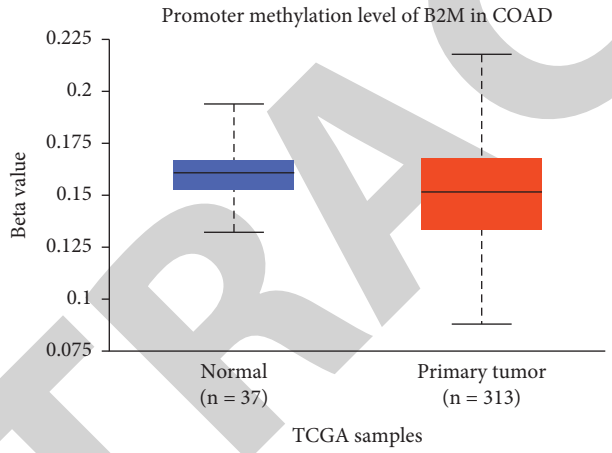

Figure 3: Promoter methylation level of B2M in COAD.

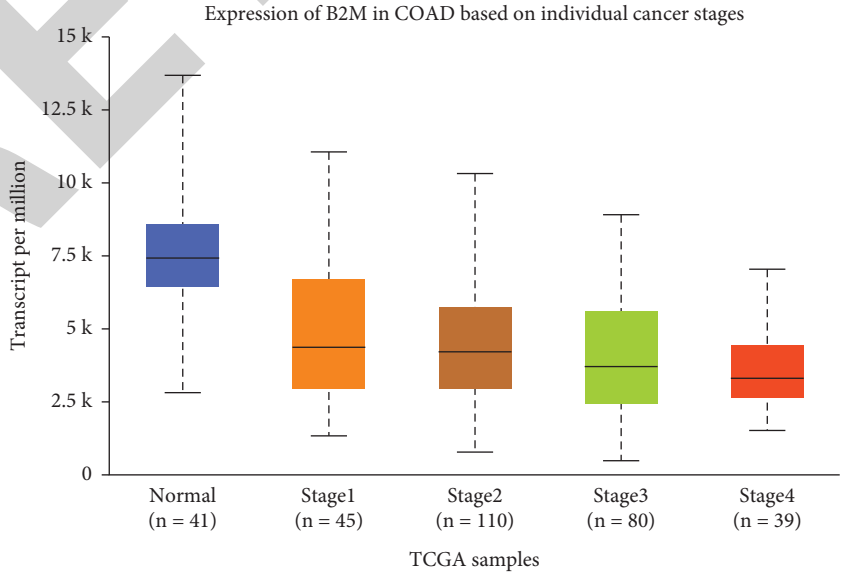

Figure 4: Expression of B2M in COAD based on individual cancer stages.

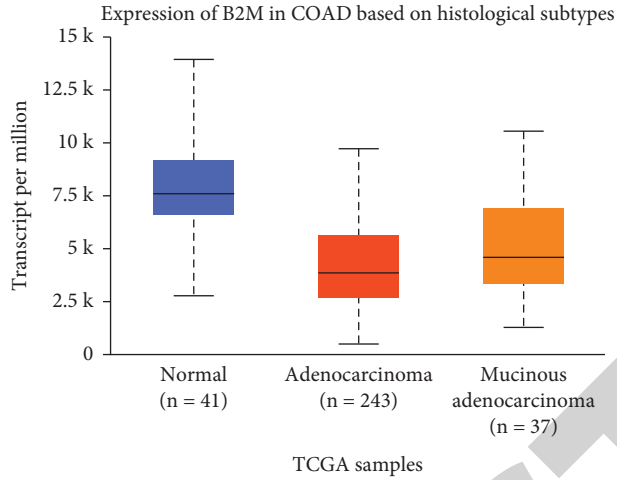

Figure 5: Expression of B2M in COAD based on histological subtypes.

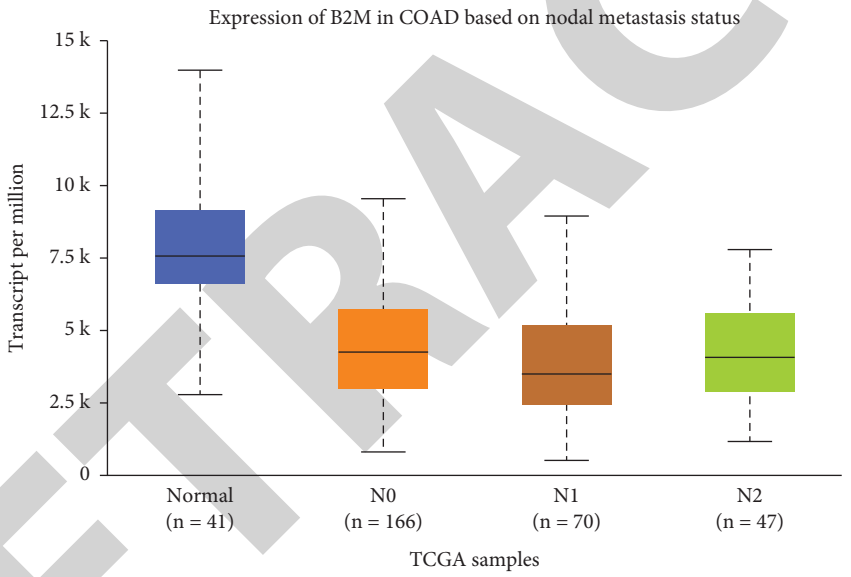

Figure 6: Expression of B2M in COAD based on nodal metastasis status.

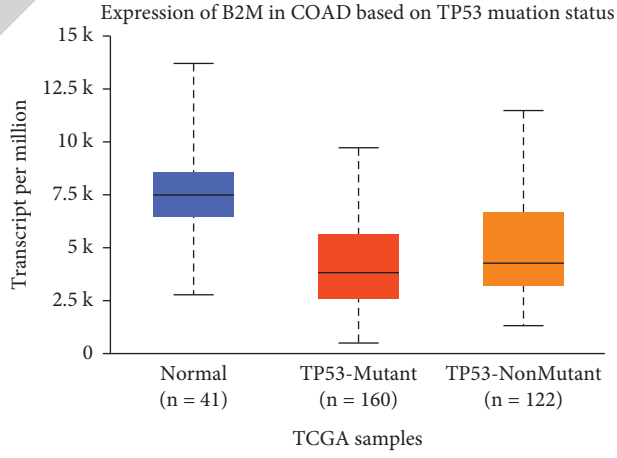

Figure 7: Expression of B2M in COAD based on TP53 mutation status.

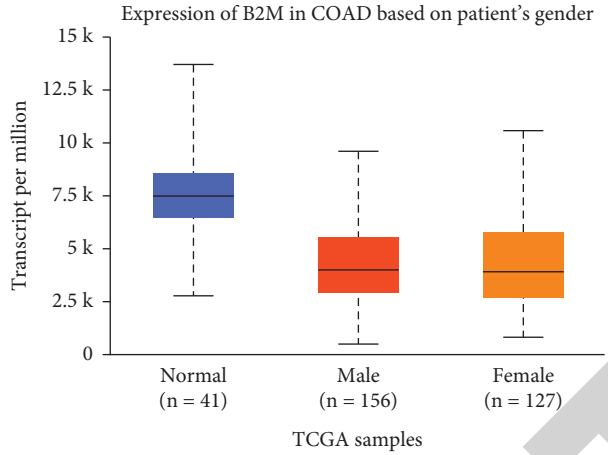

Figure 8: Expression of B2M in COAD based on patient's gender.

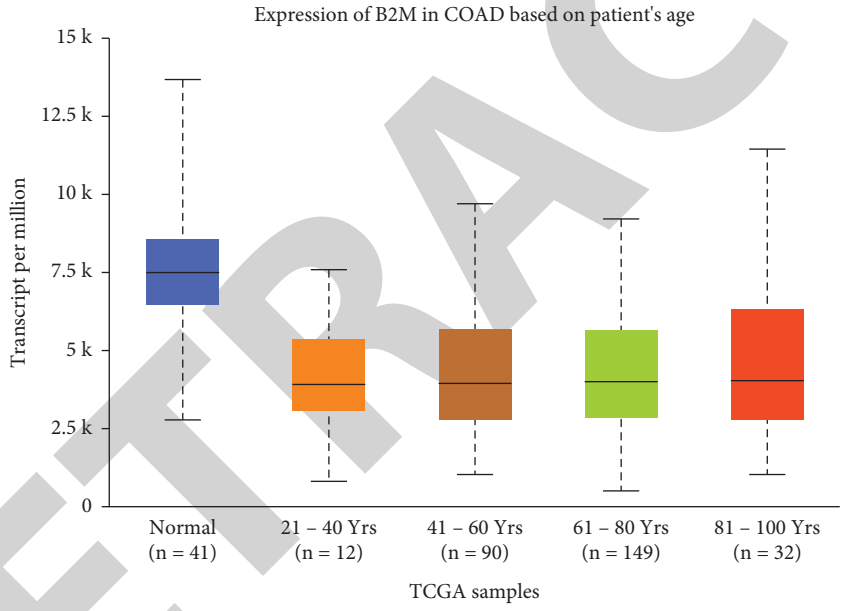

Figure 9: Expression of B2M in COAD based on patient's age.

tissues of African Americans was lower than that of Caucasians and Asians (normal-vs-Caucasian: $p = 1.7468\ 2490694522E-12$; normal-vs-African–American: $p = 1.28740351712509E-11$; normal-vs-Asian: $p = 5.421000E-03$; Caucasian-vs-African–American: $p = 1.956210E-02$; African–American-vs-Asian: $p = 2.269800E-02$) (Figure 11).

3.10. The Expression of B2M mRNA Was Not Associated with the Survival of Patients with Colon Adenocarcinoma. Analysis of TCGA database showed that the expression of B2M mRNA was not associated with the survival of patients with colon cancer($p = 0.75$) (Figure 12).

3.11. Genes Related to the B2M Gene Expression in Patients with Colon Adenocarcinoma. Using TCGA database, we analyzed the top 25 genes positively correlated (Figure 13) and negatively correlated with B2M gene expression in colon adenocarcinoma patients (Figure 14).

4. Discussion

The results of TCGA database analysis showed that the expression of B2M was increased in most tumors and decreased in a few tumors (Figure 1). Josson et al. reported that overexpression of B2M promotes the growth and progression of renal cell carcinoma, lung cancer, prostate cancer, and breast cancer [19]. Some researchers compared the preoperative serum B2M concentration of 40 patients with renal cell carcinoma and 23 normal controls and found that the preoperative serum B2M level increased in 70% of renal cell carcinoma patients [20]. Since then, researchers have demonstrated that B2M can promote the growth of human renal cell carcinoma [21] by activating the protein kinase A,

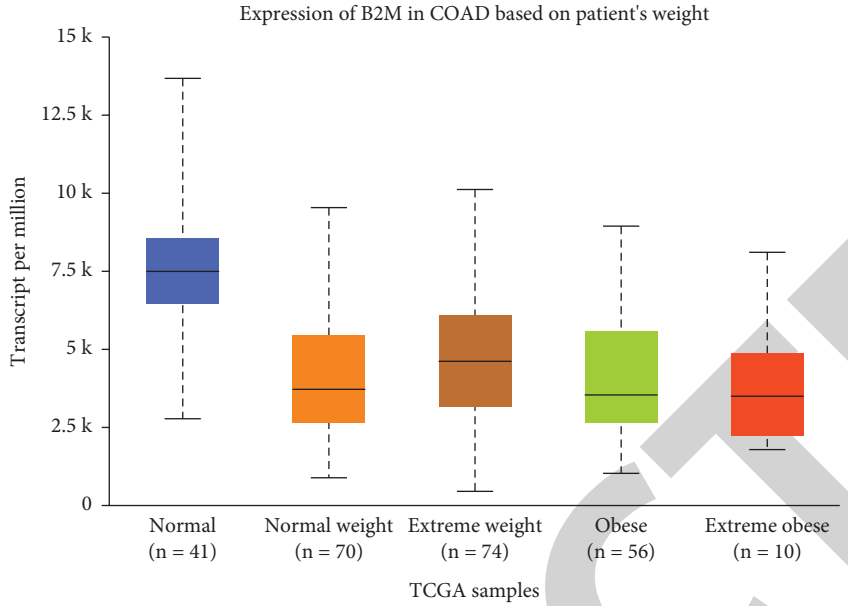

Figure 10: Expression of B2M in COAD based on patient's weight.

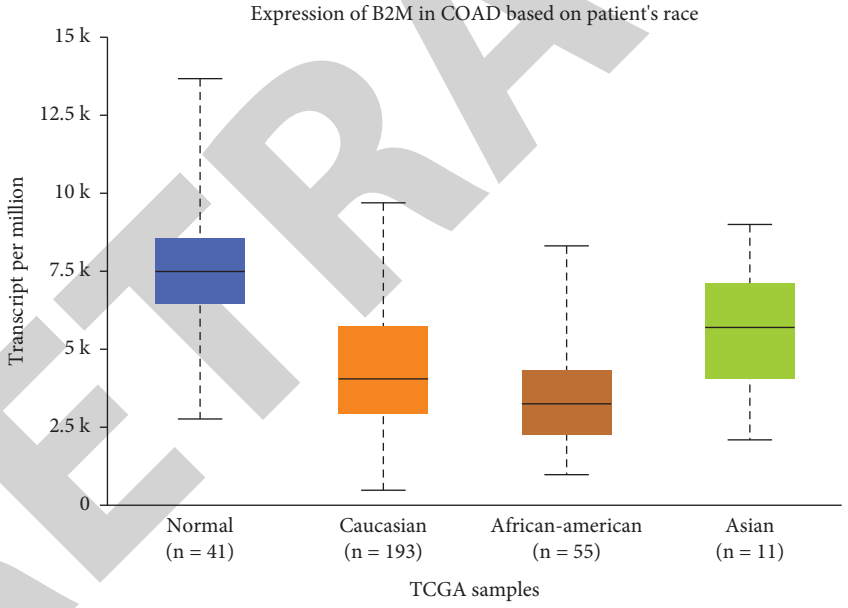

Figure 11: Expression of B2M in COAD based on patient's race.

cyclic adenosine monophosphate response element binding protein, and vascular endothelial growth factor axis. At the same time, a large number of studies have found that serum B2M levels in lung cancer [22, 23], prostate cancer [24–27], breast cancer [28, 29], and hematological malignancies have also increased [30–32]. We downloaded 41 samples of normal tissue adjacent to cancer and 286 samples of colon cancer from TCGA database. The results showed that the expression of B2M gene in colon cancer tissues was significantly lower than that in adjacent normal tissues.

DNA methylation status of the CpG island is often related to the transcriptional silence of related genes [33, 34]. Some researchers believe that DNA methylation plays a role in regulating HLA class I antigen presentation [35]. At present, there are only a few studies on the methylation status of tumor B2M gene. Gyorffy et al. found that epigenetic hypermethylation can cause loss or downregulation of HLAs and B2M expression in breast cancer [36]. At the same time, some researchers believe that hypermethylation of the B2M gene promoter may affect the antigen presentation of HLA class I molecules, which may lead to immune escape and immunotherapy resistance of colorectal cancer [37]. In addition, Cornelia et al. found that elimination of DNA methylation by DNMT inhibitors upregulated the

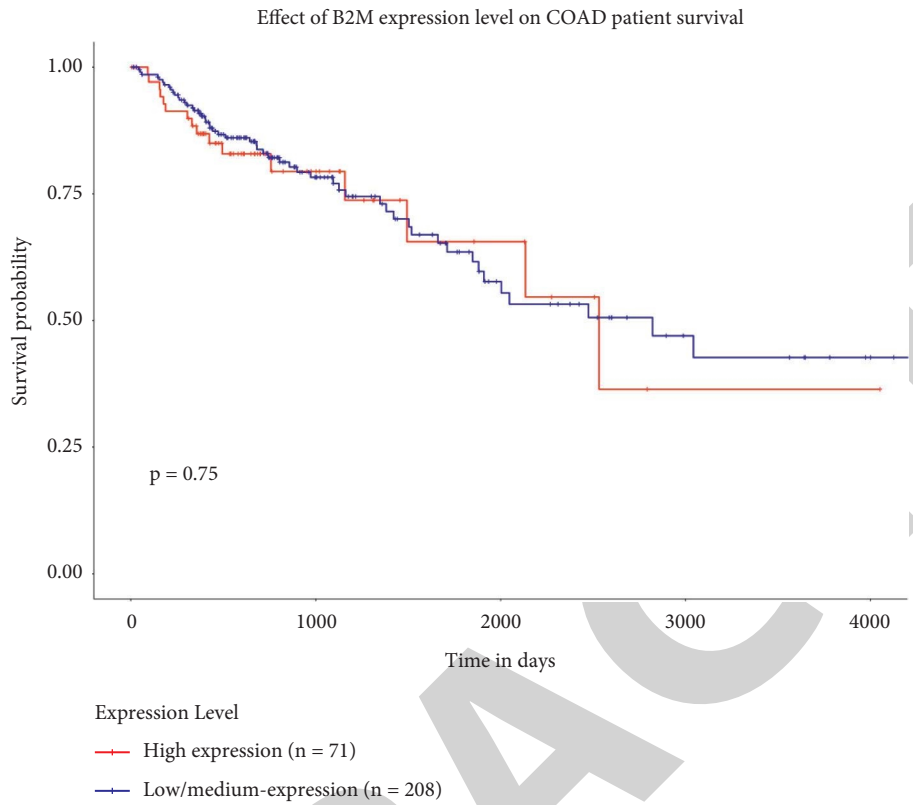

Figure 12: Effect of B2M expression level on COAD patient survival.

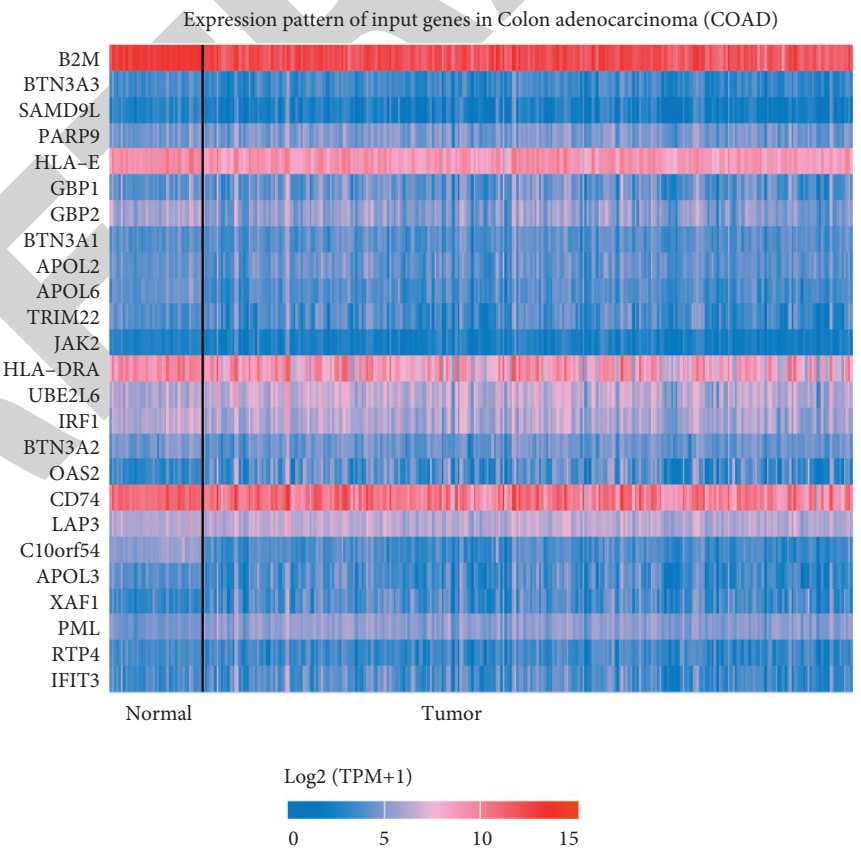

Figure 13: Genes positively correlated with B2M in COAD.

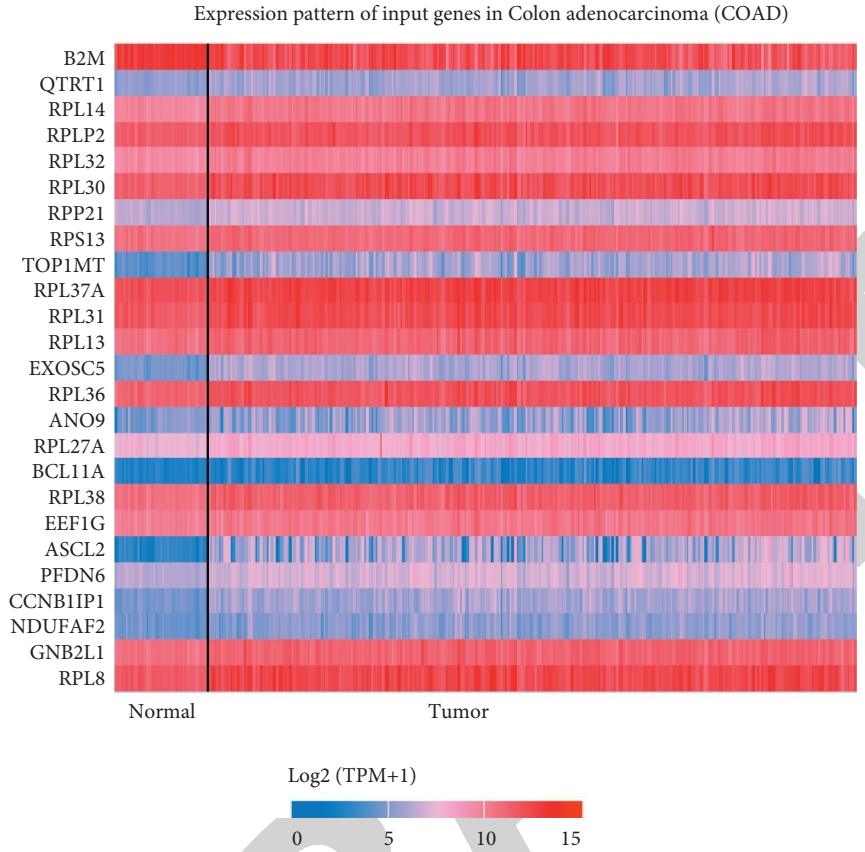

Figure 14: Genes negatively correlated with B2M in COAD.

expression of B2M at RNA and protein levels [38] in colon adenocarcinoma. However, the analysis of TCGA database showed that the methylation level of B2M gene promoter in colon adenocarcinoma tissues was lower than that in adjacent normal tissues. At the same time, the methylation of B2M gene promoter was at a very low level in both adjacent normal tissues and colon cancer tissues. This suggests that the low expression of B2M in colon cancer tissues may not be caused by methylation of the B2M gene promoter, but by B2M gene mutation [39, 40].

B2M is an important subunit of MHC class I molecules, which plays an antitumor role by promoting MHC class I molecules-mediated tumor antigen presentation and T cell recognition [2]. Therefore, we believe that B2M gene is a tumor suppressor gene in colon cancer, and its low expression in colon cancer tissue can promote the occurrence and development of colon cancer. We then analyzed the expression of B2M in different stages of colon cancer by TCGA database. The results showed that the expression level of B2M mRNA decreased with the progression of colon cancer stage, and the expression levels of B2M mRNA were different between stages I and IV, II and IV. In addition, we can also see that the expression level of B2M mRNA is different between colon adenocarcinoma and mucinous adenocarcinoma. The expression of B2M mRNA in colonic mucinous adenocarcinoma was higher than that in colonic adenocarcinoma.

TP53 is a common tumor suppressor gene, which plays a role in a variety of tumors. Mutations of TP53 are the most common in human tumors and are often associated with poor prognosis [41]. The missense mutation of TP53 is very common in human cancers, which can lead to the inactivation of the tumor suppressive effect of mutant p53 protein, which is conducive to the proliferation and survival of cancer cells, thus promoting tumor invasion, migration and chemotherapy resistance [42, 43]. The frequency of TP53 mutation in colorectal cancer ranged from 40% to 50% [44]. Through TCGA database analysis, we found that the expression level of B2M in colon cancer tissues with TP53 mutation was lower than that without mutation. It is suggested that the low expression of B2M in colon cancer is related to TP53 gene mutation. The expression level of B2M in colon cancer tissues with TP53 mutation is lower, and the tumor is easier to metastasize and more aggressive.

In addition, we also found that the expression level of B2M gene had racial difference, but it was not related to gender, age and weight of patients with colon cancer.

The effect of B2M expression level on the prognosis of cancer patients is different. The high expression of B2M gene is associated with poor prognosis in most cancer patients. It has been reported that elevated B2M can worsen the prognosis of patients with renal cell carcinoma [45], prostate cancer, breast cancer [29], hematological malignancy [30, 31, 46–48] and glioma [49]. At the same time, Kloor

et al. thought that the B2M mutation was associated with reduced metastasis and recurrence of colon cancer [40, 50, 51]. However, Shrout and Bianchini et al. found that the low expression of B2M was associated with lymph node metastasis and poor prognosis in patients with colorectal cancer [52, 53]. However, we found that the expression level of B2M was not related to the status of lymph node metastasis in patients with colon cancer through TCGA database analysis, which was inconsistent with the results reported in the literature. This may be because the TCGA database analyses tumor metastasis in axillary lymph nodes, while regional lymph node metastasis is the most common in colon cancer. At the same time, different researchers have drawn different conclusions on the impact of B2M expression level on lymph node metastasis and prognosis of colon cancer, so it is necessary to strengthen further research in this area.

To sum up, B2M may be a potential tumor suppressor gene in colon cancer. The decreased expression of B2M after mutation can cause immune escape of colon cancer cells, thus affecting the therapeutic effect and prognosis. However, there are still some contradictions about the role of B2M in colon cancer. Therefore, more research is needed to continue to explore the role of B2M in colon adenocarcinoma.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Hailian Lin and Kelang Wang contributed equally to this work.

Acknowledgments

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Retraction

Retracted: A Critical Scrutiny on Liposomal Nanoparticles Drug Carriers as Modelled by Topotecan Encapsulation and Release in Treating Cancer

Evidence-Based Complementary and Alternative Medicine

Received 12 December 2023; Accepted 12 December 2023; Published 13 December 2023

This article has been retracted by Hindawi, as publisher, following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of systematic manipulation of the publication and peer-review process. We cannot, therefore, vouch for the reliability or integrity of this article.

Please note that this notice is intended solely to alert readers that the peer-review process of this article has been compromised.

Wiley and Hindawi regret that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] H. Mills, R. Acquah, N. Tang et al., "A Critical Scrutiny on Liposomal Nanoparticles Drug Carriers as Modelled by Topotecan Encapsulation and Release in Treating Cancer," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7702512, 7 pages, 2022.

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Review Article

A Critical Scrutiny on Liposomal Nanoparticles Drug Carriers as Modelled by Topotecan Encapsulation and Release in Treating Cancer

Hilla Mills,[1] **Ronald Acquah**,[1] **Nova Tang**,[2] **Luke Cheung**,[2] **Susanne Klenk**,[3] **Ronald Glassen**,[3] **Magali Pirson**,[4] **Alain Albert**,[4] **Duong Trinh Hoang**,[5] **and Thang Nguyen Van**[5]

[1]*Department of Medical Science, University for Development, Accra, Ghana*
[2]*RD Lab, The Hospital Institute for Hebal Research, Toluca, MEX 50200, Mexico*
[3]*Research Institution of Clinical Biomedicine, Hospital University Medical Centre, Ulm 89000, Germany*
[4]*Industrial Research Group, International College of Science and Technology, Route de Lennik 800, CP 590, Brussels 1070, Belgium*
[5]*Clinical Analysis Lab, Center of Bio-Medicine, Hanoi, Vietnam*

Correspondence should be addressed to Hilla Mills; hilla.mills@hotmail.com, Luke Cheung; luke.cheung@hotmail.com, Ronald Glassen; ronald.glassen@ricbm.de, Alain Albert; alain.albert@ricbm.de, and Thang Nguyen Van; tn.van@cbm.asia

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The medical field is looking for drugs and/or ways of delivering drugs without harming patients. A number of severe drug side effects are reported, such as acute kidney injury (AKI), hepatotoxicity, skin rash, and so on. Nanomedicine has come to the rescue. Liposomal nanoparticles have shown great potential in loading drugs, and delivering drugs to specific targeted sites, hence achieving a needed bioavailability and steady state concentration, which is achieved by a controlled drug release ability by the nanoparticles. The liposomal nanoparticles can be conjugated to cancer receptor tags that give the anticancer-loaded nanoparticles specificity to deliver anticancer agents only at cancerous sites, hence circumventing destruction of normal cells. Also, the particles are biocompatible. The drugs are shielded by attack from the liver and other cytochrome P450 enzymes before reaching the desired sites. The challenge, however, is that the drug release is slow by these nanoparticles on their own. Scientists then came up with several ways to enhance drug release. Magnetic fields, UV light, infrared light, and so on are amongst the enhancers used by scientists to potentiate drug release from nanoparticles. In this paper, synthesis of liposomal nanoparticle formulations (liposomal-quantum dots (L-QDs), liposomal-quantum dots loaded with topotecan (L-QD-TPT)) and their analysis (cytotoxicity, drug internalization, loading efficiency, drug release rate, and the uptake of the drug and nanoparticles by the HeLa cells) are discussed.

1. Introduction

Drugs were invented to treat a plethora of diseases. However, the drugs pose some undesired effects. In the case of chemotherapy, normal cells are damaged because the drugs do not specifically hit the cancer cells [1]. Consequently, the doses are limited (the therapeutic window is the primarily targeted dose). Chronic chemotherapy might coerce cancer cells to resist the anticancer agents, which is very common [2, 3]. Drug efficacy has to be achieved; otherwise, toxicity is inevitable in the event that drug concentration overshoots the therapeutic window [4]. The human body itself has barriers that serve to protect the system from intrusion by poisonous substances. Amongst such barriers is the blood-brain barrier (BBB), which makes it difficult to treat neurodegenerative diseases [5]. Drugs are considered foreign and are thus subject to expulsion. The cytochrome P40 enzymes, glutathione, the liver, kidney, and many other biological molecules like

P-glycoproteins are responsible for xenon compound expulsion. These affect drug bioavailability (F), and reaching a steady-state concentration is daunting [6].

According to Du et al. [4], nano drug carriers have been shown to greatly counteract the highlighted challenges. It is reported that a number of endogenous and exogenous drug carriers are under scrutiny. Endogenous drug carriers like exosomes and cell membranes are being studied [7, 8]. Exogenous drug carriers such as nanoparticles [9], dendrimers [10], starch microspheres, ethyl cellulose microspheres, albumin microspheres, gelatin microspheres [11, 12], and liposomes [13].

Figure 1 shows some of the liposomal nanoparticle enhancers, among others. Nano delivery systems mitigate toxicity while improving bioavailability. It is reported that liposomes are characterized by biodegradability, biocompatibility, and low toxicity [14–16]. The liposomes can be modified by enveloping them with stable polymers such as oligosaccharides, polysaccharides, glycoproteins, and synthetic polymers with the intention of increasing their half-lives [17]. A controlled process can be used to synthesize liposomes that are capable of carrying either water-soluble or fat-soluble drugs. Such drug carriers are of the magnitude of 100–150 nm. The modified liposomes stealth phagocytosis of the reticuloendothelial system during circulation in the blood, thus toxicity is reduced [18]. It was observed that liposomes, based on the retention effect and tumor enhanced permeability, can accumulate at the cancer site, thus improving drug efficacy [19–21]. Notwithstanding, the rate at which the liposomes release drugs is relatively slow. As a result, a number of response triggers have been studied that enhance drug release. Examples of such response triggers are temperature [22], microwave [23], photodynamic conversion [24], pH [25], and ultrasound [4, 26].

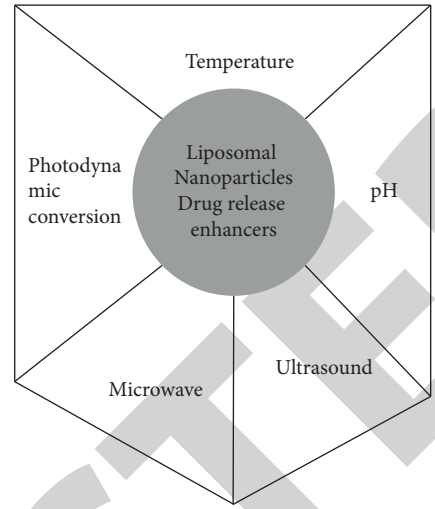

Figure 1: Some of the liposomal nanoparticle enhancers, among others.

2. Topotecan

Figure 2 shows the structure of the topotecan. Topotecan is a hydrophilic anticancer drug that is semisynthetic. It is known that TPT is derived from camptothecin. The drug works by interfering with the protein topoisomerase 1. The drug specifically affects the Topo-1 DNA, forming a ternary complex known as the "drug-Topo1-DNA" complex [4]. The FDA approved the use of TPT for treating small cell lung cancer and ovarian cancer. It is reported that TPT has a broad spectrum of anticancer activities (i.e., it kills a variety of tumors). One of the major disadvantages of the drug under physiological conditions is that the ring opening of the drug structure results in ineffectiveness, thus affecting drug efficacy [27, 28]. To circumvent the aforementioned drawback, Tarhan et al. [29] prepared special nanoparticles, which were referred to as magnetic dextran nanoparticles branched with NαNα-Bis (carboxymethyl)-L-lysine hydrate. Seleci et al. [30] prepared a variety of lipid nanoparticles, including LQ-Dots, which were loaded with TPT.

This review article serves to highlight the theragnostic role played by liposomes in drug delivery systems, enhancing drug bioavailability and efficacy while lowering drug toxicity. In this paper, a very close investigation of the preparation of TPT-loaded quantum dots and the use of

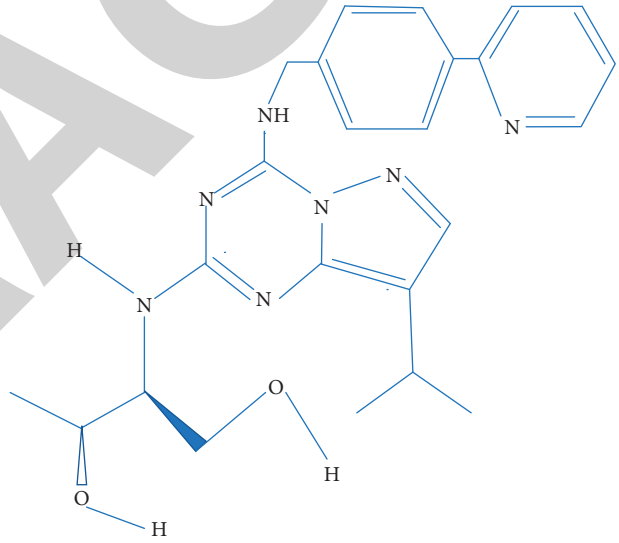

Figure 2: The structure of topotecan.

liposomes in cancer treatment is carried out. Table 1 shows some of the lipid-encapsulated drugs approved by the FDA.

2.1. Liposome-Nanoparticle Hybrids. Seleci et al. [30] acknowledged that nanomedicine is a multifunctional discipline. The team probed the preparation, characterization, and *in vitro* evaluation of theragnostic liposomes. The team used topotecan (TPT), a hydrophilic drug analogous to camptothecin, as a model drug. The Quantum dots (QDs) are exceptional promising nanoparticles characterized by fluorescent properties such as high photochemical stability, narrow emission spectra, broad absorption spectra, high quantum yields, and resistance to photobleaching [32–34]. Owing to these properties, QDs have been studied for biochemical applications as fluorescent probes. It is reported that QDs are

Table 1: Some of the lipid-encapsuled drugs approved by the FDA [31].

Drug	Date of first approval	The drug treats:	Company
Doxil	1995	Kaposi's sarcoma, ovarian cancer, multiple myeloma	Janssen
DaunoXome	1996	Kaposi's sarcoma	Galen
Marqibo	2012	Acute lymphoblastic leukaemia	Acrotech Biopharma
Onivyde	2015	Metastatic pancreatic cancer	Ipsen
Vyxeos	2017	Acute myeloid leukaemia	Jazz Pharmaceuticals
Onpattro	2018	Transthyretin-mediated amyloidosis	Alnylam Pharmaceuticals

particularly useful for *in vivo* cell labeling and imaging [35–38]. Table 2 shows some of the applications of nanoparticles (NPs) in the medical field.

2.2. Preparation of Liposome-QD Hybrids. A number of modifications are made with the intention of surmounting the aforementioned drawbacks. It is reported that a broad spectrum can improve QDs [39]. Notwithstanding, surface modifications decrease fluorescence photostability and intensity [30, 40].

According to Muthu et al. [41], LQD exhibited excellent potential. It is reported that Tian et al. loaded with LQD [42]. In addition, in one study, L-QDs loaded with apomorphine were investigated for bioimaging and brain targeting. It was observed that the liposomes accumulated in the brain to a large extent [43]. Moreover, Muthu et al. tailor-made the folic acid-conjugated theragnostic liposomes purporting to carry out the targeted co-delivery of quantum dots and docetaxel [30, 41].

2.3. Methodologies. Reference [30] used the thin film hydration method to synthesize L-QD hybrids [44]. In a round-bottomed flak that contained chloroform (an organic solvent) [45].

2.4. TPT Encapsulation. The drug (TPT) was loaded into the L-QD vesicles using a pH-gradient technique [46]. The lipid-QD dried thin film obtained, things can be determined by a ratio of drug weight encapsulated to the initial drug weight before encapsulation.

$$\%\,\mathrm{EE} = \frac{W\mathrm{en}}{W\,\mathrm{total}} \times 100. \quad (1)$$

The above equation was used to calculate encapsulation efficiency, where W_{en} is the drug weight encapsulated in the L-QDs and W_{total} is the initial drug weight [47]. Encapsulation efficiency was determined following L-QD-TPT hybrid vesicles lysis by diluting purified liposomes in acidic methanol (1% trifluoroacetic acid in methanol). Known concentrations of free TPT were used for curve calibrations by measuring fluorescence emission at 530 nm using a fluorospectrometer (NanoDrop 3300, Thermo Fisher Scientific Inc., Waltham, MA, USA).

Formulation fluorescence spectra were determined by a spectrofluorometer while an Olympus BX41 fluorescence microscope was used to capture TPT and QD localizations in a big liposome. Zetasizer Nano-ZS (Malvern Instruments, Malvern, UK) was used to analyze the zeta potential (ζ) and particle size distribution of the liposomes. A parameter known as the polydispersity index (PDI) was reported as the size distribution width. In their study, the samples were diluted using a 1 : 100 (v/v) ratio with $\mathrm{ddH_2O}$. These diluted samples were first equilibrated for 3 minutes prior to measurements. At room temperature, measurements were taken in triplicates. The team tested and examined the stability of the samples (liposomal formulations) by storing them [30].

2.5. In Vitro Drug Release Assay. Reference [30] carried out a drug release experiment using the dialysis technique. The team prepared the LQD. The release medium was replenished by the same amount of fresh buffer. A calibration curve was used to quantify the TPT released. The concentrations were studied at 530 nm using a spectrofluorometer.

2.6. Cell Culture. Reference [30] cultured it. In a medium that contained 1.0% penicillin/streptomycin (P/S) and 10% fetal calf serum (FCS), cells were grown. The medium conditions were 5.0% $\mathrm{CO_2}$ and 37°C.

2.7. Cytotoxicity Assay. Cytotoxicity of liposome formulations was carried out using the MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) assay. In a 96-well tissue plate (Sarstedt, Newton, MA, USA), 8×10^3 cells were seeded in a volume of 200 μl and then grown for 72 hours. Cells produced a formazan complex during the incubation period. Purple-colored salts were removed from the cells. Then UV-Vis absorption was measured using a reference wavelength in the range of 570–630 nm [30].

2.8. Cellular Uptake. The cellular uptake of liposomal formulations and TPT by HeLa cells was studied through flow cytometry. Cells (5×10^5) were collected, incubated with the samples for 2 h, and then washed twice with PBS. Flowing Software 2 was used to analyze dot plot and histogram data [30].

3. Discussion

Focusing on the study conducted by Seleci et al. [30], the liposomes were formulated using distearoylphosphatidylcholine (DSPC) and cholesterol in the ratio of 7 : 3 respectively.

Table 2: Some of the applications of nanoparticles (NPs) in the medical field [31].

Application	Description
Genome editing	NPs carry CRISPR components to the nucleus
Stratification of patients basing on genetic information and biomarkers	Antibody-targeted NPs reach cancer cell with complementary receptors
Modulation of the immune system and response	NPs deliver mRNA vaccines in the system
Determination of pharmacokinetics changed by disease states	NP-based imaging unveils levels of enhanced permeation and retention (EPR).
Autologous cell therapies creation	NPs generate chimeric antigenic receptor (CAR) T cells for cancer immunotherapy

The team wanted membrane rigidity and thus chose DSPC over any other possible phospholipids like dimyristoylphosphatidylcholine (DMPC) and egg phosphatidylcholine (EPC). The DMPC increases liposomal drug retention [48, 49]. It was observed that sufficient cholesterol (≤30%) prevented leakage of encapsulated contents by decreasing contents' solubility and increasing contents' stability [50, 51]. It is reported that cholesterol could also enhance membrane hydrophobicity [52]. Seleci et al. [30] chose the simple and commonly used method of liposomal synthesis, which is a thin layer hydration. The pH technique works on the basis that a pH gradient is a driving force that accumulates weakly basic molecules in acidic vesicles. TPT was loaded using this approach, and its active lactone form was retained till release. Liposomal and free drug fluorescence spectra revealed both TPT and QD peaks simultaneously, thus confirming the coexistence of the two in the vesicles. The team carried out molecules' fluorescence localizations in a large liposome.

It is emphasized that the nanoparticles' physicochemical properties are crucial in protein interactions [53]. Piling evidence supports those nanoparticles in magnitude. There are some other studies [54, 55]. In this regard, Seleci et al. [30] determined liposomes' surface charge and hydrodynamic parameters by carrying out Dynamic Light Scattering (DLS) and ζ-potential analysis. The average size of the plain liposomes was found to be 132 nm. An increase in liposome size by 6 nm was detected following entrapping the QD in the lipid bilayer. This could only be explained by the successful encapsulation of molecules. Encapsulation of the TPT did not alter the size of the L-QD. The researchers examined liposomal stability upon storage. The observations were that at 4°C in a space of over 2 months, there were no significant changes in ζ-potential, size distribution, and polydispersity index (PDI).

According to Deng et al. [56] and Gessner et al. [57], the higher surface charge of nanoparticles has effects on the amount of protein adsorption.

Protein corona composition on the surface. A number of studies revealed the mechanism [58–61]. In the study conducted by Seleci et al. [30], efficiency was found to be approximately 40%. The QD integration was found to have affected it. Furthermore, the hybrid liposomes had better physicochemical properties.

An important aspect of treatment, drug release, was analyzed *in vitro* by Seleci et al. [30]. The team came up with an L-QD-TPT drug release profile following its determination using the dialysis method, which is the most common approach for nanoparticle drug release analysis. The researchers created an environment that mimics normal human tissue conditions with a pH of 7.4 and a tumor microenvironment (pH 5.6) at a temperature of 37°C. It was observed that TPT release was higher in an acidic environment as compared to a neutral one. In the first 4 hours, the drug release was rapid due to the modest initial burst of the L-QD-TPT nanoparticles, with the acidic-environment nanoparticles reaching about 33% cumulative drug release while neutral-environment nanoparticles scored 25%. Slower rate release occurrs for up to 32 hours. Thereafter, TPT release rates were observed to be 39 and 45% for the neutral and acidic conditions, respectively. Higher cumulative drug release in acidic conditions is attributed to the protonation of TPT, hence increasing its solubility [61].

Seleci et al. [30] observed that cells treated with samples (TPT, L-QD, L-TPT, and L-QD-TPT) had higher fluorescence signals as compared to control cells, which were not subjected to samples. The observed fluorescence signal measurements for TPT, L-TPT, and L-QD-TPT were 2472 a.u., 3839 a.u., and 4007 a.u., respectively. The discrepancies in fluorescence signal measurements are explained by different mechanisms by which HeLa cells take in the formulations. It is reported that free TPT enters the cells and makes its way into the cells via endocytosis [62, 63].

Seleci et al. [30] examined the L-QD-TPT-treated cells by fluorescence microscopy. The fluorescent model drug (TPT) was found unsurprising in the nuclei of the cells since it is a topoisomerase-I inhibitor, to execute its toxicity [64, 65]. In their study, the blue and green fluorescence from 4′, 6-diamidino-2-phenylindole (DAPI), and TPT, respectively, matched very well. The DAPI was used to stain the nuclei of the cells.

Furthermore, the researchers determined the cytotoxicity of TPT and free liposomal formulations on HeLa cells using a 3-(4, 5-Dimethylthiazol-2-yl)-2, 5 diphenyltetrazolium bromide (MTT) assay. The assay works based on the principle that only viable cells with active metabolism convert MMT into formazan, a purple-colored substance. The quantification of formazan is carried out by taking absorbance readings at 570–630 nm reference wavelengths. Seleci et al. [30] found out that L-QD caused no cytotoxicity. The reason is that the lipid bilayer shielded the cells from harm effectively. The same results were reported by Chinnathambi and colleagues. In their study, phosphoethanolamine (polyethylene glycol)-based phospholipid micelles were used to envelope CdSe/ZnS QDs. The QDs in the

concentration range of 0–25 μg/ml almost showed no toxicity in A546 and HeLa cell lines following 24 hour-exposure. However, in the case of Seleci and colleagues, L-QD-TPT and L-TPT obviously posed toxicity on HeLa cells after 24 hour-exposure. This is due to high L-QD-TPT and L-TPT intake by the cells, and the TPT concentration delivered was obviously higher than that of free TPT. It is reported that the same results were obtained by Hao and colleagues [66].

Versions of the liposomal nanoparticles exist. These include magnetic nanoparticles [67]; thermosensitive liposome-in-gel [5]; transferrin receptor (TR)-targeted liposomal cisplatin [68]; magnetic thermosensitive cationic liposomes [69] and so on. Novel technologies have also been reported [70, 71].

4. Conclusion

Liposomal nanoparticles increase drug bioavailability while lowering drug toxicity. Controlled drug release is also achieved and is an important aspect of treatment where steady-state concentrations are maintained, hence drug efficacy is achieved. Therefore, nanomedicine is improving the diagnosis and treatment of patients tremendously. In this paper, the synthesis of liposomal nanoparticle formulations (liposomal-quantum dots (L-QDs), liposomal-quantum dots loaded with topotecan (L-QD-TPT)) and their analysis (cytotoxicity, drug internalization, loading efficiency, drug release rate, and the uptake of the drug and nanoparticles by the HeLa cells) were discussed.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

HM and RA contributed to the conception and design of the study, and wrote the first draft of the manuscript. NT, LC, SK, RG, MP, AA, DTH, and TNV contributed to the data collection and analysis. All authors approved the submitted version.

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Retraction

Retracted: Type 2 Diabetes Mellitus (T2DM) and Carbohydrate Metabolism in Relation to T2DM from Endocrinology, Neurophysiology, Molecular Biology, and Biochemistry Perspectives

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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Review Article

Type 2 Diabetes Mellitus (T2DM) and Carbohydrate Metabolism in Relation to T2DM from Endocrinology, Neurophysiology, Molecular Biology, and Biochemistry Perspectives

Hilla Mills,[1] **Ronald Acquah**,[1] **Nova Tang**,[2] **Luke Cheung**,[2] **Susanne Klenk**,[3] **Ronald Glassen**,[3] **Magali Pirson**,[4] **Alain Albert**,[4] **Duong Trinh Hoang**,[5] **and Thang Nguyen Van**[5]

[1]*Department of Medical Science, University for Development, Accra, Ghana*
[2]*RD Lab, The Hospital Institute for Hebal Research, Toluca 50200, MEX, Mexico*
[3]*Research Institution of Clinical Biomedicine, Hospital University Medical Centre, Ulm 89000, Germany*
[4]*Industrial Research Group, International College of Science and Technology, Route de Lennik 800, CP 590, Brussels 1070, Belgium*
[5]*Clinical Analysis Lab, Center of Bio-Medicine, Hanoi, Vietnam*

Correspondence should be addressed to Hilla Mills; hilla.mills@hotmail.com, Luke Cheung; luke.cheung@hotmail.com, Ronald Glassen; ronald.glassen@ricbm.de, Alain Albert; alain.albert@ricbm.de, and Thang Nguyen Van; tn.van@cbm.asia

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Type 2 diabetes mellitus (T2DM) is a severe disease caused by metabolic disorders, particularly carbohydrate metabolism disorders. The disease is a fatal global trouble characterised by high prevalence rates, causing death, blindness, kidney failure, myocardial infarction, amputation of lower limps, and stroke. Biochemical metabolic pathways like glycolysis, gluconeogenesis, glycogenesis, and glycogenolysis are critical pathways that regulate blood glucose levels with the glucokinase (GK) enzyme playing a central role in glucose homeostasis. Any factor that perturbs the aforementioned biochemical pathways is detrimental. Endocrinological, neurophysiological, and molecular biological pathways that are linked to carbohydrate metabolism should be studied, grasped, and manipulated in order to alleviate T2DM global chaos. The challenge, howbeit, is that, since the body is an integration of systems that complement one another, studying one "isolated" system is not very useful. This paper serves to discuss endocrinology, neurophysiology, and molecular biology pathways that are involved in carbohydrate metabolism in relation to T2DM.

1. Introduction

According to Tramunt et al. [1], diabetes is more prevalent in men, especially in the middle-aged individuals, than in women. This is a general trend all over the world except some few parts like North Africa and the Middle East. The International Diabetes Federation's last global estimates in 2017 indicated that diabetes prevalence is larger in men than in women (9.1% vs. 8.4%, respectively). This information suggested that approximately 12.3 million more men lived with diabetes than women. The clinical and experimental evidence that support the discrepancies in diabetes prevalence are mainly based on sex hormones endocrinology. The postpubertal sex steroid hormones in particular account for different diabetes prevalence rates in men and women. Premature ovarian sufficiency and early menopause in women correlate with an increased risk of developing T2DM more than premenopausal ones. A documented reduction in diabetic menopausal women incidence of about 21–35% was due to an oestrogen-based hormonal therapy. Hypogonadism men are at risk of developing T2DM and vascular ailments. It is reported that testosterone supplements

improve both glucose and lipid homeostasis. It is beyond dispute that the highlighted endocrinology triggers and influences other biological pathways like glucogenesis, glycolysis, and neuropathways that are associated with homeostasis, particularly glucose and lipid homeostasis. Besides, herbal medicine and nanomaterials have also been used in medical engineering [2, 3].

2. Challenges Associated with T2DM Studies

Gender, as highlighted above, is one of the challenges in treating T2DM. A thorough understanding of male and female physiology in relation to T2DM is imperative. Tramunt et al. [1] asserted that gender governs energy storage and use. Females can withstand undernutrition periods better than males, and this enables females to preserve their reproductive functions. Most importantly, gender determines carbohydrate and lipid metabolism. It is reported that females are more insulin sensitive than males. The list of differences goes on and on. This means glucose and lipid metabolism in men and women is not the same. Tramunt et al. [1] argued that there should be sex-specific medicine for T2DM. Achieving this goal is very expensive considering that research projects are done for men and women separately. This sounds to be the major drawback of the idea of sex-specific T2DM medicine. Notwithstanding, if the goal is achieved, a number of T2DM patients will lead almost a normal life.

Other daunting factors when it comes to T2DM treatment are age, race, health status, and so on. Focusing on health status, recent studies showed that angiotensin-converting enzyme 2 (ACE2) is a receptor of the severe acute respiratory syndrome corona virus (SARS-CoV). The ACE2 is overexpressed in diabetic and hypertension patients due to the use of angiotensin-converting enzyme 1 (ACE1) inhibitors. Consequently, patients suffering from T2DM and hypertension are at risk of acquiring the COVID-19 diseases, and once such patients get sick, death rates for this group are high. It is imperative to monitor glucose levels in SARS-CoV patients. Needless to say, the job is irksome [4]. Studying T2DM is complex considering factors that affect glucose homeostasis. Healthy T2DM animal models are of great help in studying the disease. However, in the world, comorbidity is a great challenge.

According to Timer et al. [5], T2DM affects many body systems like cardiovascular and nervous systems. A plethora of studies revealed that T2DM is a risk factor for vascular dementia and Alzheimer's disease. Studies that aimed to investigate the correlation between T2DM and cognitive impairment have been done, and they focused on the presence of apolipoprotein allele, mitochondrial malfunction, oxidative stress, macrovascular mechanisms, the formation of advanced glycosylation end-products, inflammation, and insulin resistance [6]. Patients who suffer from diabetic retinopathy showcased a poor cognitive skill compared with disease-free patients. The observation is attributed to microalbuminuria in T2DM patients. Timer et al. [5] conducted a study to compare T2DM-peripheral-neuropathy patients and T2DM-peripheral-neuropathy-free patients concerning cognitive functions based on the notion that peripheral neuropathy may also correlate with microvascular impairment in the brain. The team observed no significant differences between the TDM patient groups. Such investigations still need to be expanded since only a handful studies have been done. Howbeit, polyneuropathy manifests in the early phases of T2DM, and needless to say, T2DM interferes with the nervous system.

Feng et al. [6] designed an experiment to probe the relationship between TSH (thyroid-stimulating hormone) and serum uric acid (SUA) in T2DM patients with early-stage diabetic kidney disease (ESDKD). A negative correlation of 0.35 (95% confidence interval) between SUA and TSH was reported. This implies that T2DM patients with ESDKD whose SUA levels are high have decreased TSH levels. Uric acid (UA) is produced following purine metabolism. The kidney eliminates about 70% of UA. Recent studies reveal that SUA causes the development of microvascular diseases. According to De Cosmo et al. [8], SUA significantly correlates with albuminuria in T2DM patients. As a result, hyperuricemia has been used as a "biomarker" for DKD prediction. It is documented that thyroid dysfunction can exacerbate glucose metabolism and induce hyperglycaemia in T2DM patients, thus promoting the risk of diabetic complications. Hyperglycaemia lowers the level of thyroid-stimulating hormone (TSH) and mitigates the conversion of thyroxine to triiodothyronine in the peripheral tissues. This piece of evidence without doubt proves that there is a link between endocrinology and T2DM.

According to Stoll et al. [9], secretion of insulin is governed by a circular RNA that contains a lariat sequence of the second intron insulin gene. A decrease in the expression of key components of the secretory machinery of β-cells that leads to impaired glucose or KCl-induced insulin release and calcium signalling was reported following silencing of this intronic circular RNA in pancreatic islets. The effect of the circular RNA was observed to be exerted at the transcriptional level. It is reported that this effect involves an interaction with the RNA-binding protein TAR DNA-binding protein 43 kDa (TDP-43). The level of this circularised intron is mitigated in the islets of rodent diabetes models and of T2DM patients. This is possibly due their impaired secretory capacity. Type 2 diabetes mellitus, therefore, can be studied from a molecular biology perspective.

The xenobiochemistry concept of T2DM with respect to ω-6 PUFA-rich vegetable cooking oil we use almost daily to cook our meals at home is elucidated by Yamashima et al. [10]. Hydroxynonenal is a compound that forms following lipid peroxidation. It is also formed during vegetable oil deep-frying. The phenomenon is frequent when using soybean, rapeseed, and sunflower vegetable oil that contain a lot of linoleic acid. Reactive oxygen species attack membrane ω-6 PUFAs to generate endogenous hydroxynonenal. It is reported that hydroxynonenal forms adducts with 4 amino acids, namely, arginine, lysine, histidine, and cysteine. It is thought that the compound might be able to interfere with proteins. Therefore, hydroxynonenal is capable of causing neuron dysfunction and degeneration by altering membrane-associated glucose and glutamate transporters, ion-

motive ATPases, enzymes involved in amyloid metabolism, and cytoskeletal proteins. Recently, hydroxynonenal is increasingly recognised as a particularly important mediator and marker of cellular dysfunction and degeneration in diverse disorders such as T2DM, arteriosclerosis, cardiovascular disease, and stroke.

This paper serves to shade some light on the critical neurophysiological, endocrinological, biochemical, and molecular biological aspects in relation to T2DM. It is imperative that the readers should bear in mind that the study assumes the only disease in *the test subjects* is T2DM. The major enzyme GK and its activities, the CNS and carbohydrate metabolism, and some mechanisms related to T2DM are discussed herein.

2.1. Carbohydrates. Simple sugars are either monosaccharides or disaccharides that are easy to break down resulting in a rapid increase of blood sugar. Consequently, a rapid secretion of insulin occurs. Examples of such sugars are ribose, fructose, galactose, maltose, glucose, lactose, and sucrose. Sources of such sugars are carbonated beverages, honey, table sugar, fruit juice, candy, and corn syrup [11].

There are sugars that are either disaccharides or polysaccharides having a complex chemical structure. These sugars are not easy to break down, and thus they do not cause a rapid blood sugar escalation following consumption. Sugars such as amylose, dextrin, cellulose, cellobiose, and rutinulose fall under complex sugars. The sugars are found in foods like apples, brown rice, unrefined whole grains, broccoli, spinach, and lentils. Thousands of glucose units are joined together within starches. The starches fall under complex sugars. Wheat, pasta, potatoes, and chickpeas are sources of starches [11].

Complex carbohydrates that are not digestible belong to this group of sugars. The sugars encourage bacterial growth in the colon. As a result, defecation is made easy. It is reported that fibre is a bulking agent. Pectin, hemicellulose, and cellulose are examples of fibre. Fibre can be soluble or insoluble. Insoluble fibre is known for softening and bulking stool by absorbing water in the intestines. The risk of developing diverticulosis is reduced, and bowel movement is regularised. Sources of insoluble fibre include potato skins, brans, seeds, brown rice, and vegetables. Soluble fibres aid in reducing the levels of low-density lipoprotein (LDL) cholesterol and postprandial blood glucose and reduce straining with defecation [11].

According to Holesh et al. [11], carbohydrate metabolism starts in the mouth where salivary amylase begins to degrade the sugars. Glucose is one of the final products produced following carbohydrate breakdown by the digestive system. The monomers are now ready for absorption. Below are two major monomers discussed.

It is reported that, in normal human beings, approximately 15–25% of the ingested glucose is metabolised in the liver and the gut. The glucokinase enzyme "activates" glucose by phosphorylation whereby the glucose-carbon-atom on position six links with a phosphate group via its hydroxyl group. This happens in the liver. The glucose-6-phosphate molecule formed undergoes a series of biochemical reactions in a glycolytic pathway to produce two pyruvate molecules. Phosphofructokinase-1 (PFK-1) tightly governs the amount of glucose that undergoes glycolysis. The PFK-1 is inhibited by intracellular excess amounts of ATP (adenosine triphosphate) and citrate. Reports say that the glucose concentration that survives the splanchnic metabolism reaches the systemic circulation. Consequently, a transient increase in the arterial blood glucose level arises from approximately 5 mM/L fasting glucose to 8–10 Mm/L postprandial. Insulin secretion is inevitable therefore, and the arterial glucose is taken up by peripheral organs either independently of insulin (say brain) or under the control of insulin (adipose tissue, skeletal muscle).

Pure fructose ingestion does not trigger insulin secretion or cause markable glycaemia. It is reported that, in case of fructose ingestion, a momentary increment of about 0.5 mM/L in arterial blood glucose takes place. Such a small increment in arterial blood glucose implies that most of glucose is extracted by splanchnic organs. Fructose metabolism takes place mainly in the liver, gut, and kidney. It is reported that, in the aforementioned organs, fructolytic enzymes are present like fructokinase, triokinase, and aldolase B. Fructolysis does not depend on insulin. It is just a biochemical pathway that breaks down fructose to form triose-phosphates viz. dihydroxyacetone phosphate and glyceraldehyde phosphate. Fructokinase and aldolase B are not inhibited by any of the fructolytic products or by signals that arise from cellular energy status [12].

The ingestion of fructose leads to an increment in blood glucose and insulin, compared to an isomolar glucose load. Howbeit, the ingestion of fructose potentiates complete carbohydrate oxidation and energy expenditure in lean healthy volunteers to a larger extent, then in T2DM patients and obese insulin-resistant individuals. In addition, postprandial blood lactic concentrations escalate. The fructolytic pathway converts fructose into lactate and glucose in the splanchnic organs. The glucose produced in the splanchnic organs awaits a secondary oxidation in peripheral tissues. Oral or intravenous fructose boosts glucose synthesis (gluconeogenesis). Surprisingly, glycaemia does not ensue. Also, infusion of gluconeogenic precursors like alanine, lactate, or glycerol leads to gluconeogenesis, but hepatic glucose levels are not affected [12].

2.2. Central Nervous System (CNS) and Carbohydrate Metabolism Studies in Relation to T2DM. Defects in insulin secretion cause a metabolic ailment known as diabetes. In addition, insulin resistance is capable of inducing diabetes [13–15]. Hyperglycaemia is a primary indication of diabetes manifestation caused by an abnormal glucose metabolism. A lot of health complications "come along" with diabetes. Type 2 diabetes mellitus (T2DM) affects quality of life and health of patients intensely owing to its high mortality and prevalence. Pathologically and physiologically, the autonomous nervous system (ANS) might take part in nutrient metabolism. Generally, the sympathetic system could potentiate catabolism, while the parasympathetic system could

Table 1: P2Y receptor subtypes' distribution, G-proteins, and agonists.

Subtype	Distribution	G-protein	Agonist
$P2Y_1$	Broad including skeletal tissue, heart, CNS, platelets	G_q	ADP
$P2Y_2$	Brain, kidney, skeletal muscle, heart, lungs	G_q	ATP/UTP
$P2Y_4$	Vascular smooth muscle, lung, placenta	G_q	UTP
$P2Y_6$	Intestines, spleen, lung, heart, placenta, brain, etc.	G_q	UDP
$P2Y_{11}$	Dendritic cells, intestine, spleen	G_S and G_q	ATP
$P2Y_{12}$	Hepatocytes, platelets, brain	G_i	ADP
$P2Y_{13}$	Spleen, brain	G_i	ADP
$P2Y_{14}$	Haematopoietic cells, intestine, placenta, adipose tissue, heart, brain, etc.	G_i	UDP/UDP-glucose

promote anabolism. Evidence is piling up, which support that an escalated sympathetic nervous system activity is associated with pathogenesis of metabolic disorders. Sympathetic denervation improves glucose metabolism and insulin sensitivity; consequently, this implies that the sympathetic nervous system can affect glucose metabolism. When the sympathetic nervous system is activated, acute hyperglycaemia ensues. Such a phenomenon can be prevented by exendin-4. Insulin resistance induced by hypoxia can be relieved by sympathetic nervous system inhibition. Catecholamines mitigate insulin secretion [16, 17].

The prevertebral sympathetic ganglion known as celiac ganglion (CG) and its postganglionic fibres release neurotransmitters like ATP targeting purine receptors [18, 19]. Purine receptors are categorised into two classes, namely P1 and P2. Purinoceptors play a crucial role in the regulation of lipid and glycogen metabolism. In addition to that purinoceptors are involved in the release of insulin [20, 21]. The G-protein-coupled metabolic receptors (P2Y) and the ligand-gated ion channel receptors (P2X) belong to P2 class receptors. The P2Y12 is expressed in both peripheral tissues and central nervous system (CNS). The excitability of sympathetic nerve is controlled by the P2Y12 receptor and is associated with autonomic neuropathy [22]. The receptor might be involved in liver fibrosis, autoimmune pathologies, and platelet aggregation. There is not much information known about the P2Y12 receptor function in nutrient metabolism [16, 23–25]. Table 1 shows P2Y receptor subtypes' distribution, G-proteins, and agonists.

Regulation of nutrient metabolism is carried out by the liver, a key organ. Purinergic signalling controls the pathophysiology and physiology of the liver. The sympathetic CG projects its postganglionic fibres to the liver. In the liver, there is P2Y12 receptor distribution and function [26]. Sympathetic ganglia-P2Y12 receptor is involved in diabetic autonomic neuropathy. The receptor is reported also to be involved in other diabetic disorders [27, 28]. Reduced hepatic glycogenesis, escalated blood glucose, and decreased hepatic glucose uptake may be caused by an excited sympathetic nerve. The function and expression of P2 receptors have been studied in the liver. Nonetheless, it is still ambiguous whether changes in P2Y12 receptor expression have an effect on the CG or liver [16]. Figure 1 shows the purinergic receptors' role in governing the secretion of insulin and the survival of β-cells.

Documented reports prove that inflammation plays a key role in the origination and development of a number of metabolic disorders, namely T2DM, obesity, insulin resistance, etc. Neuroinflammation that is related to the autonomic nervous system is capable of contributing to the progression of diabetes. A principal feature of insulin resistance and obesity is presented as a chronic, systemic, low-grade state of inflammation [29, 30]. Activation of inflammasomes is the main molecular mechanism that underlies induction of the inflammatory responses and liver damage under a number of pathological conditions. The pathological conditions include T2DM and development of insulin resistance. There was a suggestion made that inflammasomes link inflammation to insulin resistance [31]. The nod-like receptor protein 3 (NLRP3) inflammasome is a complex that institutes NLRP3, caspase 1, and apoptosis-associated spot-like protein (ASC) [31, 32]. The activation of the NLRP3 inflammasome may lead to cellular inflammatory necrosis and a new kind of a programmed cell death that relies on the activated caspase 1. The above phenomenon is accompanied by the release of proinflammatory factors like interleukin 1-β (IL-1β). Such proinflammatory factors are known for exaggerating inflammatory response and cell dysfunction [16].

Li et al. [16] carried out research on how the P2Y12 receptor is linked to T2DM. The team made use of short hairpin RNA (shRNA) technology to cut down the P2Y12 receptor in T2DM rats and then probed hepatic glycogen content, inflammatory responses, GK expression, celiac ganglia sympathetic activity, and lipid and glucose profiles. The team noted changes in the hepatic P2Y12 receptor expression and in the celiac ganglia. At the mRNA level, P2Y12 receptor expression was significantly higher in rat livers and celiac ganglia in the T2DM rats than in the control group. The T2DM rats were then injected with the P2Y12 shRNA plasmid, and then a significant decrease in P2Y12 mRNA levels was observed. The results show that shRNA could "undo" the high expression of P2Y12 receptor in T2DM rats. In addition, the team observed that the postganglionic celiac sympathetic nerve discharge of the celiac ganglia markedly increased in the T2DM-rat group compared with the control group. The finding suggests that escalated excitability of the celiac sympathetic nerve is a common phenomenon in T2DM. Nevertheless, treatment with P2Y12 shRNA plasmid normalises the situation. Moreover, principal typical features of metabolic disorders were observed at the early stage of T2DM. Fasting blood glucose (FBG) and fasting plasma insulin (FINS) levels were higher in T2DM rats than in control. In contrast, FINS and FBG levels in T2DM rats treated with the P2Y12 shRNA

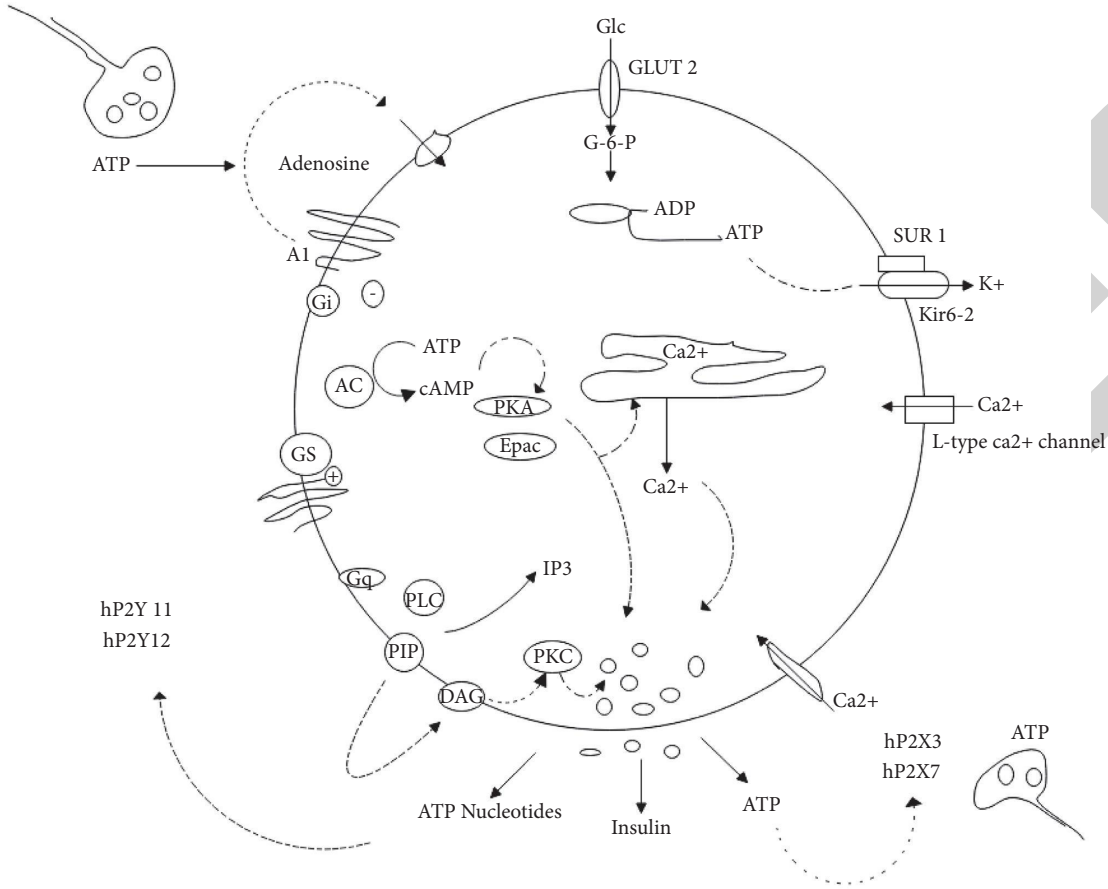

Figure 1: The purinergic receptors' role in governing the secretion of insulin and the survival of β-cells. The GLUT2 facilitates the entrance of glucose. Glycolysis yields ATP. The ATP produced is used to close up the ATP-sensitive channel, K_{ATP}. The K_{ATP} channel is made up of 4 (four) Kir6.2 and SUR1 subunits. When the K_{ATP} closes, the cell membrane potential depolarises and this leads to the opening of the voltage-gated L-type Ca^{2+} channels, generating Ca^{2+} action-potentials. An increase in the cellular Ca^{2+} triggers ATP-insulin-containing secretory vesicles exocytosis. Parasympathetic and sympathetic nerves may also release ATP. Membrane depolarisation and Ca^{2+}/Na^{+} influx are facilitated by P2X receptors. P2Y receptors elevate cellular Ca^{2+} and "turn on" protein kinase C (PKC) pathways. Also, other P2Y and adenosine receptors affect the cAMP pathway and possibly Epac signalling. High adenosine concentrations are a "force" that coerces adenosine translocation into the β-cell, thus exerting metabolic effects.

plasmid were significantly lower. The finding implies that P2Y12 shRNA treatment could normalise changes in FBG and FINS levels and improve insulin resistance in T2DM rats. Furthermore, it was observed that P2Y12 shRNA treatment reduced levels of triglyceride, total cholesterol, and LDL in T2DM rats. A lower hepatic glycogen profile was observed in T2DM rats. Howbeit, upon treatment with the P2Y12 shRNA, the hepatic glycogen significantly increased. A lower hepatic expression of GK mRNA was observed from RT-PCR analysis in the T2DM rats than in the control group. In contrast, hepatic GK mRNA levels in T2DM rats treated with P2Y12 shRNA increased significantly. Western blot results revealed lower GK protein levels in T2DM rats than that in control rats. The GK levels increased upon P2Y12 shRNA treatment. Also, Western blot analysis showed that hepatic NK-$\kappa\beta$ p65 levels were higher in T2DM rats than in the control group. A markable decease in the hepatic NF-$\kappa\beta$ p65 levels were noted upon treatment of T2DM rats with the P2Y12 shRNA. Finally, the team examined the effects of P2Y12 shRNA on NLRP3 inflammasome and interleukin-1β (IL-1β) in T2DM rats. The observation was that, at both mRNA and protein levels, the expression of NLRP3 subunits (ASC, NLRP, and caspase-1) and IL-1β was increased substantially in T2DM rats compared with the control group. Notwithstanding, P2Y12 shRNA treatment reversed the escalated levels of NLRP3 and IL-1β, exhibiting the beneficial properties of P2Y12 shRNA in playing an inhibitory role of IL-1β production and NLRP3 inflammasome. Figure 2 shows the P2Y12 receptor allows the entrance of a signal from excited CG.

Glucagon is a glucose-elevating hormone that is secreted by pancreatic alpha-cells in the event that blood glucose concentration falls. The hormone then triggers a cascade of biochemical signalling pathways in the hepatocytes that stimulate glucogenesis. The glucose produced then supports the fallen blood glucose level to normalise. Extrinsic electric signals from the parasympathetic and sympathetic ANS also stimulate glucagon secretion. A combination of intrinsic mechanisms, paracrine and juxtacrine, suppress glucagon secretion under normo- and hyperglycaemic conditions.

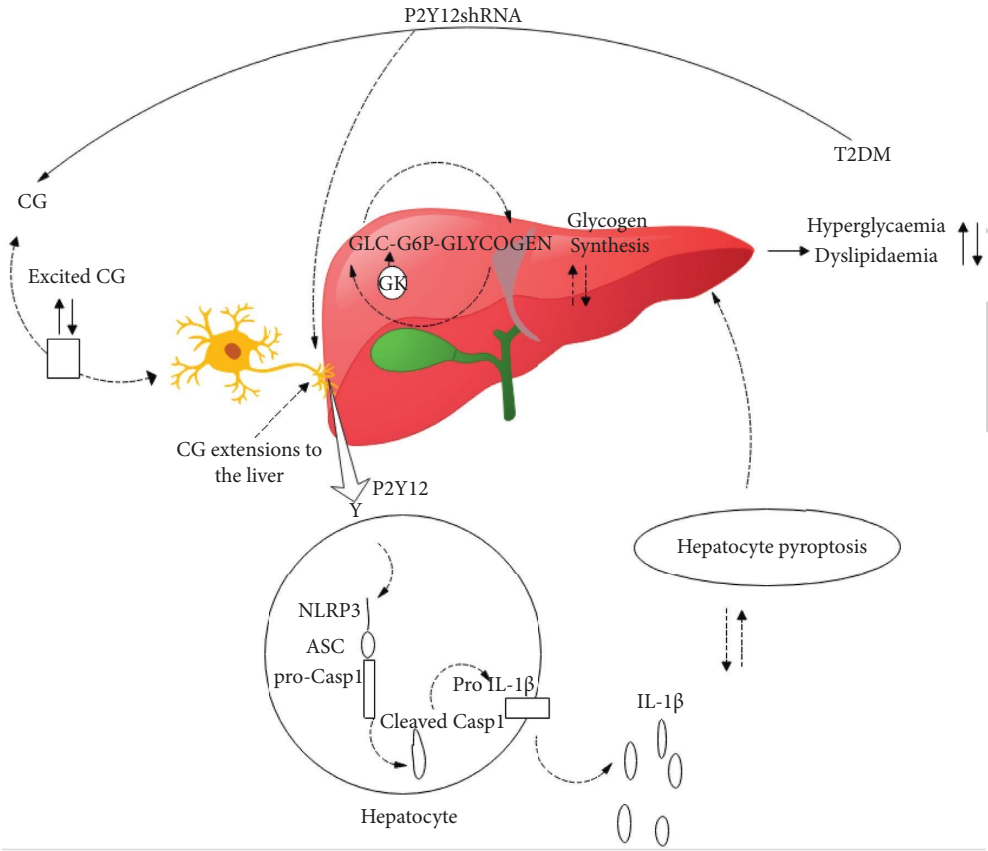

Figure 2: The P2Y12 receptor allows the entrance of a signal from excited CG. Cleavage of the Casp1 from the NLRP3 leads to cellular inflammatory necrosis. The above phenomenon is accompanied by the release of proinflammatory factors like interleukin 1-β (IL-1β). Such proinflammatory factors are known for exaggerating inflammatory response and cell dysfunction. The celiac ganglia take part in carbohydrate metabolism, which in turn is linked to neuroinflammation. The P2Y12 shRNA therapy inhibits the excitation of the celiac ganglia, which is associated with overexpression of P2Y12 receptors and then hepatic glucose homeostasis is restored. GLC is glucose, and G6P is glucose-6-phosphate.

Hypoglycaemia induces glucagon secretion by a mechanism that involves a fall in the ATP/ADP cytosolic ratio and escalated activity of P/Q-type Ca^{2+} channels, causing Ca^{2+} influx. These findings illustrate the crucial vitality of the electrophysiological mechanisms that link glucose metabolism to electrical activity and hormone secretion [33].

Basco et al. [34] conducted an experiment using mice with alpha-cell-specific knockout GK genes. The findings illustrated the crucial role of GK in regulating glucagon secretion from intact islets and *in vivo*. Honzawa et al. [35] came up with a different suggestion concerning glucose-dependent intrinsic mechanism for the control of glucagon secretion. The team mentioned that glucose uptake by sodium-glucose co-transporter 1 (SGLT1) can cause intracellular Na^+ ion concentrations to be a higher than that of the extracellular compartment. Consequently, secretion of glucagon is triggered. This mechanism is deemed relevant particularly for the paradoxical hypersecretion of glucagon in T2DM. A lot of scientific reports serve as evidence to illustrate that alpha-cells in intact cells are capable of responding to hypoglycaemia by releasing glucagon. In addition, the importance of GK during such phenomena is also documented. Notwithstanding, it is still ambiguous whether alpha-cells are capable of regulating secretion of glucagon intrinsically and whether GK is the glucose sensor linking glucose metabolism to the regulation of glucagon secretion [33].

Moede et al. [33] addressed the above unanswered questions by conducting an experiment where they manipulated GK activity and expression in purified single alpha-cells accompanied with measurements of glucagon release by total internal reflection fluorescence (TIRF) microscopy. In 1996, GK expression in alpha-cells has been done. However, the findings are debatable since the sample that was analysed contained approximately 87% alpha-cells and the rest were other kinds of cells, including beta-cells, which would be suffice to detect GK transcripts. Moede and colleagues managed to obtain $96.6 \pm 14\%$ purity of the functional rat alpha-cells. The team examined the hexokinase isoforms that were expressed in rat pancreatic alpha-cells. The results came out as expected: cells that were identified as β-cells were positive for GK and negative for hexokinase I, II, and III expression. The most important observation was that all α-cells analysed tested positive for GK. Pancreatic alpha-cells were found to express the neuroendocrine GK isoform. Verification of this finding was done by isolating RNA from sorted alpha-cells and performing real-time polymerase chain reaction (RT-PCR)

using primers located in the first and seventh exons [36]. The resulted PCR products were subcloned and sequenced. The sequence analysis showed that 60% GK mRNA is encoding the functional B1 neuroendocrine isoform [37]. The rest, that is, 40%, encode neuroendocrine GK nonfunctional variants. Heimberg et al. [38] and Segerstolpe et al. [39] support Moede et al. [33] findings.

The GK enzyme has become a primary target in treating T2DM. Permanent neonatal diabetes mellitus is a severe ailment that occurs as a result of homozygous inactivating mutations in GK. Heterozygous inactivating mutations elevate the threshold for insulin secretion [40, 41]. Glucose kinase regulatory protein (GKRP), as the name says, is a protein that regulates GK in the hepatocytes. The GKRP binds the GK, hence switching off the glycolytic pathway in the event of hypoglycaemia. Many research articles highlight that GKRP mutations that affect its activity, localisation, and expression do not only have impact on glucose homeostasis but also on triglyceride (TG) metabolism [42, 43]. A number of small molecules that serve as GK activators (GKAs) have been found and used in the medical field. Notwithstanding, the activators posed some disadvantageous effects like loss of efficacy over time, increase in TG concentrations, and hypoglycaemia [44, 45]. These effects were linked to ongoing activation of β-cells and peradventure related to the development of hepatic steatosis [46–48]. Figure 3 shows glucokinase (GK) phosphorylates glucose during glycolysis.

Patients with GK-activating mutations or GKRP loss-of-function mutations require hepatoselective GKAs that affect neither the GK-GKRP interactions nor GK in β-cells. Such "ideal" small-molecule activators can circumvent the adverse effects posed by the GKAs, which have been used in the medical field. Therefore, Vella et al. [48] developed a hepatoselective GKA namely TTP399. The GKA improved glycaemic regulation both in T2DM animal models and patients. Adverse effects like dyslipidaemia, hypoglycaemia, and pathological accumulation of glycogen and TG in the liver were not induced. In addition, TTP339 administration did not seem to perturb GK-GKRP interactions in the presence of normoglycaemia, maybe thus justifying the absence of altered liver function and dyslipidaemia. There was a reduction in hepatic fat in response to TTP399 administration [48].

Hexokinase isoenzyme, known as glucokinase (GK), is expressed specifically in pancreatic islet beta-cells and mature hepatocytes [49, 50]. The GK is a pacemaker enzyme in a glycolytic pathway. It catalyses the first irreversible reaction of glycolysis. The enzyme adds a phosphate group to the carbon atom number six of a glucose molecule, forming glucose-6-phosphate. The product formed can then be metabolised further and stored as glycogen in the liver for future use. GK plays a vital role in regulating glycogenesis and gluconeogenesis in the liver. Therefore, abnormalities in the structure and function of the GK enzyme definitely cause metabolic disorders like T2DM [16].

There is what is referred to as diet-induced diabetes [54, 55]. Scientists have been studying T2DM using high-fat-diet (HFD)-fed mouse models. GK expression in β-cells decreased in HFD-induced diabetes according to Lu et al. [27]. Nevertheless, the contribution of decreased

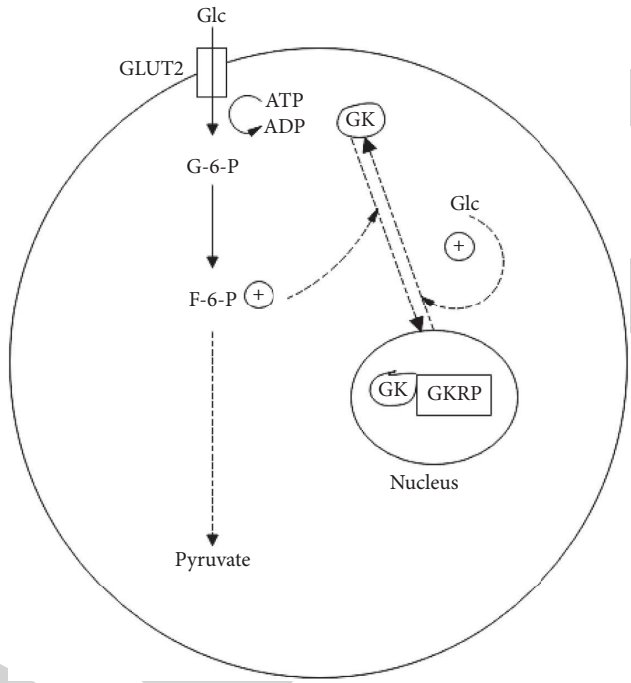

Figure 3: Glucokinase (GK) phosphorylates glucose during glycolysis. High glucose concentrations cause the release of a bound GK in the nucleus by GKRP. Conversely, high fructose-6-phosphate (F-6-P) concentrations cause GK to be bound in the nucleus by the GKRP.

GK expression to HFD-induced diabetes is ambiguous. It is reported that HFD-induced defect in β-cell function is associated with the downregulation of islet GK. HFD feeding decreases GK mRNA and GK protein by approximately 45%, compared with isoenergetic high-carbohydrate feeding in rats. Previous *ex vivo* studies of islets also showed a decrease in GK mRNA and GK protein following co-culture with palmitic acid [51]. Patients with T2DM were found to have reduced GK expression in the islets [22, 55, 56]. The challenge, however, is that GK is expressed in both hepatocytes and β-cells. Therefore, probing the correlation between GK expression and HFD is daunting [57]. Table 2 shows comparison between hexokinase and glucokinase (GK) enzymes.

Regardless of a challenge highlighted above, Lu et al. [57] designed an experiment where they targeted a β-cell gene, transferred it into a vector, and then investigated β-cell-specific GK expression on β-cell function in HFD-induced diabetes. The team made use of the adeno-associated viral (AAV) vector system. The crew observed that overexpression of GK promoted glycolytic flux, activation of ATP-sensitive potassium channel, membrane depolarisation, and an increase in proliferation of Min6 cells. The transduction of β-cell GK showed no difference in terms of glucose handling in chow-fed C57BL/6 mice. Adult mice fed with a HFD were found to have reduced islet GK expression, glucose-stimulated insulin secretion (GSIS), and impaired glucose tolerance. Nevertheless, β-cell-targeted GK transduction reinstated GSIS and improved glucose tolerance. Perfusion experiments of the islets confirmed

Table 2: Comparison between hexokinase and glucokinase (GK) enzymes.

Attributes	GK	Hexokinase
Biological importance	Blood glucose homeostasis	Intracellular glucose homeostasis
Clinical significance	Low activity in diabetic patients	Deficiency results in haemolytic anaemia
Inducibility	Determined by the insulin in the liver	Not inducible
Substrate affinity	Lower ($K_m = 10$ Mm/L)	Higher ($K_m = 0.05$ Mm/L)
V_{max}	Higher	Lower

restoration of GSIS in isolated HFD islets upon GK gene transduction.

2.3. Mechanisms. Based on the studies conducted by Lu et al. [57], restoration of β-cell function by β-cell-targeted GK overexpression suggests that GK suppression plays an etiological role in β-cell dysfunction in HFD-induced diabetes. It is thought that this mechanism is most likely to be regulated through PDX-1, which plays a regulatory role in GK expression [58]. The PDX-1 is downregulated in diabetic victims [59]. A decrease in PDX-1 expression, which leads to reduced GK expression, was observed in rat islets that were incubated in fatty acids. Restoration of GK expression increases glycolytic flux and leads to the induction of glucose response genes like PDX-1 [54, 60, 61]. The mechanism behind increased glycolytic flux by overexpression of the GK is vague. Howbeit, glucose plays a regulatory role in β-cell proliferation and GSIS [62, 63]. Overexpression of β-cell GK above physiological levels in chow-fed β-cells increased glucose utilisation. Glucose induces β-cell proliferation via IRS2 and cyclin D2 [64].

According to Vella et al. [48], GK is the target enzyme for T2DM treatment due to the vital role it plays in glucose homeostasis. A number of GKAs have been designed, assessed, and evaluated. At least 30 GKAs are discussed in published preclinical data. GKAs studies in humans and animals showed hypoglycaemia and enhanced β-cell function and proliferation. Nonetheless, the clinical trials did not come out well due to adverse effects like hyperlipidaemia, hypoglycaemia, and declining efficacy after prolonged treatment [65]. The proposed mechanism of the above highlighted side effects is that hepatic overexpression escalates hepatic lipogenesis and plasma triglycerides levels in rats [66]. GKAs can be categorised into GKAs that target both the pancreas and liver, hepato-selective GKAs and partial GKAs. Vella and colleagues studied a hepatoselective GKA, TTP399. It is proposed that GK-GKRP interaction is maintained in the presence of TTP399. The TTP399 increased the GK activity in its active conformation. Consequently, TG levels are kept normal. Heavier individuals lost weight upon administration of TTP399. The mechanism underlying this finding requires further studies, including the potential impacts of TTP399 on food intake and appetite.

Reduction in fasting plasma glucagon is a mystery in relation to the study of Vella et al. [48]. Insulin secretion impairment has been the explanation for increased plasma glucagon levels. Notwithstanding, a number of scientists challenged this idea and suggested that insulin signalling impairment explains the elevation of plasma glucagon levels [67]. According to Lee et al. [64], the accumulation of ceramide in α-cells of *ob*/*ob* hyperglycaemic rodents inhibits the suppression of glucagon. The reduction in FBG levels by the TTP399 therapy with no changes in insulin concentrations suggests an improvement in the action of insulin. It is ambiguous if the mechanism highlighted above explains the reduction in fasting glucagon. Needless to say, further studies should be conducted.

According to Li et al. [16], hepatic P2Y12 receptor protein expression was increased in the T2DM rats and the inhibition of the protein (P2Y12) by P2Y12 shRNA caused restoration of glycogen content in the liver. The finding suggests that P2Y12 might be involved in the hepatic dysfunction pathogenesis in diabetic rats. Cell bodies of the sympathetic neurons in the celiac ganglia (CG) project axons to the liver, indicating that the neurotransmission across CG may activate the sympathetic afferents of the liver. The solution, therefore, is the downregulation of the P2Y12 receptor protein expression in both the CG and liver, resulting in the inhibition of the unusual sympathetic excitability, promotion of hepatic glycogenesis, and normalisation of hyperglycaemia. The NLRP3 subunits (ASC, NLRP, and caspase-1) that assemble and activate NLRP3 complex were increased in T2DM rats. This finding is most likely explained by upregulated P2Y12 in the liver of T2DM rats since P2Y12 shRNA mitigated the increments of ASC, active caspase-1, and NLRP. In addition, NF-κB plays a vital role in the inflammatory responses and might be involved in the activation of the NLRP3 inflammasome. Activation of NLRP3 inflammasome complex induces the secretion of IL-1β, leading to cell injury and pyroptosis. The P2Y12 shRNA therapy suppressed IL-1β release. Therefore, a downgrade of sympathetic purinergic excitability could prevent hepatic inflammation of the T2DM rats, thereby improving dysfunctional metabolism and hepatic insulin resistance [32].

3. Conclusions

Type 2 diabetes mellitus (T2DM) is caused by a number of factors namely gene mutations that lead to "underexpression" or overexpression of the GK, GKRP, glucagon, insulin, and PDX-1; β-cell dysfunction, hepatic inflammation, unusual excitability of sympathetic nerves, and diet-inducing factors like taking high fat content. Molecular therapy is a promising potent solution to T2DM since the P2Y12 shRNA treatment in T2DM rats mitigated a P2Y12 receptor expression at the mRNA level significantly; increased postganglionic sympathetic nerve discharge (SND); normalised FBG and FINS; improved insulin resistance, triglyceride (TG) levels, total cholesterol (TC) levels, and

hepatic glycogen; and reduced NLRP3 complex expression. GKAs are also another good option, particularly hepatoselective GKA like TTP399.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

HM and RA contributed to conception and design of the study and wrote the first draft of the manuscript. NT, LC, SK, RG, MP, AA, DTH, and TNV contributed to the data collection and analysis. All the authors approved the submitted version.

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Research Article

Mechanistic Investigation of Curcuma Protection against Oral Submucous Fibrosis

Haiyan Peng,[1,2] Xiaowen Jiang ,[1,2] Linna Cui,[1,2] Yali Zhu,[1,2] Zhikui Ye,[1,2] and Zhiming Zhang[1,2]

[1]*Department of Stomatology, The First People's Hospital of Chenzhou, the First Affiliated Clinical Medical College, Xiangnan University, Chenzhou, China*
[2]*Department of Oral and Maxilofacial Surgery, The Stomatology College, Southern Medical University, Guangzhou, China*

Correspondence should be addressed to Xiaowen Jiang; jxw0927@163.com

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Objective. Oral submucous fibrosis (OSMF) is a chronic, fibrotic disease that affects the oral cavity, showing a high rate of malignant transformation. Curcuma exerts therapeutic potentials in many diseases including OSMF. However, the potential targets and pathways to explain the therapeutic effects of curcuma on OSMF are outside the scope of present knowledge. Herein we intend to reveal the predictive targets and potential pathways of curcuma against OSMF by a network pharmacology-based approach followed by molecular docking technology. *Methods*. We searched the SymMap, GeneCards, and OMIM database to obtain curcuma and OSMF common targets. The protein-protein interaction (PPI) of curcuma and OSMF common targets were then analyzed, followed by functional enrichment analysis. The best binding mode of curcuma and target proteins was analyzed by molecular docking technology. *Results*. We collected 290 putative targets of curcuma molecules and 600 known therapeutic targets of OSMF, with 64 curcuma and OSMF common targets sorted out. In the PPI network, there were 63 nodes with 922 edges. The node indicates protein and the line indicates PPI relation. The most enriched GO term in the BP level is "gland development", followed by "cellular response to chemical stress", and then "response to oxygen levels", while the most enriched GO term in CC and MF is "membrane raft" and "cytokine receptor binding", respectively. We also found 131 KEGG pathways significantly enriched by curcuma and OSMF common targets. The binding energy of curcuma to ALB, TNF, TP53, IL6, and VEGFA was −9.5 kcal/mol, −3.9 kcal/mol, −3.5 kcal/mol, −3.6 kcal/mol, and −8.9 kcal/mol, respectively, which suggested ALB and VEGFA were regarded as main targets involving in the potential mechanism of curcuma against OSMF. *Conclusion*. The present study illustrated that the therapeutic effects of curcuma on OSMF were achieved by targeting ALB and VEGFA, which giving reference to further drug design and development for OSMF.

1. Introduction

Oral submucous fibrosis (OSMF) is defined as a chronic scarring disease that severely affects the oral cavity, oropharynx, and sometimes the oesophagus [1, 2]. It represents a precancerous disorder and the transformation into oral squamous cell carcinoma has been found in 6%–30% cases of OSMF [1, 3]. OSMF is characterized by abnormal accumulation of collagen concomitant with progressive fibrosis in the submucosal connective tissues and limit mouth opening and tongue movement, leading to impingement on speech and swallowing [4]. OSMF is described as a multifactorial disease and mainly results from the habit of chewing betel quid and other areca nut containing products especially in Asian countries, lack of vitamin and iron, overconsumption of spicy food, and genetic susceptibility [5]. In China, men present a higher predisposition to OSF than women [6, 7]. The World Health Organization statistics, more than 5 million individuals are afflicted by OSMF worldwide, with age ranging from 8 to 80 years [8]. The mainstay of OSMF management is to minimize the annoying symptoms and increase the mouth opening to

improve the quality of life of patients and further prevent malignant transformation. The current treatment strategies for OSMF mainly includes drug treatment, mouth exercise physiotherapy, and elective surgery [9]. The primary clinical drugs to treat OSMF are corticosteroids, mainly focusing on ameliorating the inflammation and reducing the collagen formation in the oral tissue [10]. Several adjuvant agents including vitamins and vasodilators, aid to relive the symptoms [11]. Mouth exercise physiotherapy alone or plus other modalities has been found to significantly increase the mouth opening [12]. Laser therapy has been introduced as a promising non-invasive technique to treat OSMF in modernized dentistry [13]. Recently, herbal derivatives or extracts have been studied by oral physicians to treat OSMF rather than commonly practiced intralesional steroids due to better patient compliance and better performance [14].

Curcumin, as a main bioactive polyphenolic compound, is extracted from the curcuma longa (also known as tumeric) that is a plant belonging to the ginger family (Zingiberaceae), originated from India, and currently grown in Southeast Asia and China [15]. Curcuma has attracted broad attention from ancient times as it owns profound biochemical and biological activities, such as antiviral, antimicrobial, anti-inflammatory, and antioxidant activities [16, 17]. Several investigations have revealed therapeutic implications of curcuma in several human diseases including diabetes [18], cancers [19], wound healing [19], rheumatic diseases [20], and ulcers [21]. Curcuma was previously studied in animal oral ulcer model, showing enhanced mucosal healing potentials [22]. Researchers treated rat models of OSMF with curcumol-loaded collage scaffold [23]. However, the potential targets and pathways to explain the therapeutic effects of curcuma on OSMF are outside the scope of present studies. Network pharmacology is burgeoning as an effective method to provide a systemic analysis of the pharmacokinetic properties of traditional Chinese medicine (TCM) by uncovering the interrelationship among drugs, targets, pathways, and disease [24]. Molecular docking is a drug design technology that simulates the geometric structure of molecules and estimates the best binding mode of small molecule drugs and its potential targets. Using both techniques in this study, we attempt to (i) construct OSMF interaction network with the targets of curcumol, (ii) decipher the mechanism elucidating the preventive role of curcuma against OSMF, and (iii) verify the potential targets of curcuma in treating OSMF.

2. Methods

2.1. Common Targets Mining. The SymMap database, accessed at http://www.symmap.org/, was retrieved to collect putative targets of curcuma. The proteins (only "*Homo sapiens*") corresponding to the above active components were transformed into gene symbols using the UniProt database (https://www.UniProt.org/). The targets of OSMF were acquired from two public databases the GeneCards database (https://www.genecards.org/) and Online Mendelian Inheritance in Man database (OMIM, https://omim.org/). Briefly, we used "oral submucous fibrosis" as the search term to obtain disease targets (only "*Homo sapiens*") in these two databases, with duplicates removed. The Venn diagram of the OSMF-associated targets and the putative targets of curcuma molecules was made using the R software to obtain curcuma and OSMF common targets and the corresponding network was visualized using Cytoscape software.

2.2. Protein-Protein Interaction (PPI) Network Construction. The curcuma and OSMF common targets were mapped into the STRING database, accessed at https://www.string-db.org/, to perform the PPI analysis. The PPI network was visualized by importing the tsv-based file to Cytoscape software (3.8.1). The species must be "*Homo sapiens*" and high confidence for interaction score must not less than 0.4. In the PPI network, nodes reflect proteins and connecting lines represent PPIs. The core genes ranked according to degree value obtained using cytoHubba plug-in of Cytoscape.

2.3. Functional Classification and Pathway Enrichment. Gene ontology (GO) functional analysis and pathway analysis based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) were implemented to harvest the potential functions of the disease-drug common targets by using the "clusterProfiler" package in the R software. The results of GO analysis were presented at the three levels: biological processes, molecular functions, and cellular components. The GO terms at three levels and significant KEGG pathways enrichments were ranked by P value, and the top 20 pathways and top 10 GO functions were visualized as bar plots and bubble plots using the "Pathview" package in R software.

2.4. Molecular Docking Technology. Molecular docking technology is a well-recognized method to examine receptor-ligand interactions along with binding patterns and affinities. Therefore, we performed molecular docking analysis between curcuma and the top core target genes in the PPI network. The pdb format of the 3D structure of the proteins encoded by the top core target genes were downloaded from the RCSB Protein Data Bank (PDB) database, accessed at https://www.rcsb.org/. Then, we converted the pdb-based files containing curcuma and the proteins encoded by core targets into pdbqt-based files and search for active pockets. The AutoDockTools was employed to determine the binding ability of ligands and receptors. The binding energy less than 0 indicates spontaneous binding of ligand and receptor, and smaller values reflect higher binding activity.

3. Results

3.1. Identification of Curcuma and OSMF Common Targets. After searching the SymMap database, we collected 290 putative targets of curcuma molecules in total and then convert these molecule names into gene symbols in the

UniProt database. With regard to the known therapeutic targets of OSMF, 600 targets were identified, with 578 collected in the GeneCards and 22 collected in the OMIM. Then, by using Venny 2.1 drawing software, we sorted 64 druggable targets of curcuma which were also therapeutic targets of OSMF (Figure 1(a)). We then used Cytoscape software to present disease-target-compound network (Figure 1(b)).

3.2. Key Targets in the PPI Network. We imported 64 curcuma and OSMF common targets into the STRING database for PPI analysis. As shown by the PPI network in Figure 2, there were 63 nodes with 922 edges, and those with higher degree values were regarded as corer target genes.

3.3. Enrichment Analysis for Curcuma and OSMF Common Targets. Next, we further analyzed 64 curcuma and OSMF common targets by GO annotation and KEGG pathway analyses. After GO analysis, 1736 GO terms, in total, were found to be significantly enriched by curcuma and OSMF common targets ($P < 0.05$). Figure 3(a) lists the top 10 most enriched GO terms in the levels of BP, CC, and MF. The most enriched GO term in the BP level is "gland development", followed by "cellular response to chemical stress", and then "response to oxygen levels", while the most enriched GO term in CC and MF is "membrane raft" and "cytokine receptor binding", respectively. After KEGG pathway analysis, we found 131 KEGG pathways were significantly enriched by curcuma and OSMF common targets ($P < 0.05$). Figure 3(b) lists the top 10 most enriched KEGG pathways.

3.4. Molecular Docking of Key Targets. The corresponding three-dimensional structures were downloaded from RCSB PDB to perform molecular docking and analysis in the AutoDockTools. ALB, TNF, TP53, IL6, and VEGFA as top 5 targets in the core PPI network were selected for molecular docking and analysis. The binding energy of curcuma to ALB, TNF, TP53, IL6, and VEGFA was −9.5 kcal/mol, −3.9 kcal/mol, −3.5 kcal/mol, −3.6 kcal/mol, and −8.9 kcal/mol, respectively. According to the principle of binding energy, a more negative docking score indicates a higher binding force between the compound and the protein. The affinity energy ≤ −5 kcal/mol is considered as high affinity, and thus ALB and VEGFA were regarded as main targets involving in the potential mechanism of curcuma against OSMF. The docking results are presented in a three-dimensional manner in Figure 4.

4. Discussion

Curcumin is the main component of turmeric (also known as curcuma longa), which is considered to be a non-toxic and safe substance for food uses and therapeutic purposes. Previous studies has proved its efficacy on various diseases such as type 2 diabetes mellitus [25], nonalcoholic fatty liver disease [26], and head and neck squamous cell carcinoma [27]. Although evidence indicated that Curcumin inhibited migration and metastasis of oral cancer cells [28], and turmeric oil and turmeric oleoresin exhibited antitumor activity in OSMF [29], few investigations have been done on the potential targets and pathways to clarify therapeutic value of curcuma against OSMF. Network pharmacology is a new and effective method, which changes the dogma of "one disease-one target-one drug", and designs and analyses multi-target drug molecules to elaborate the mechanism of drug actions [30] in diseases such as diabetic nephropathy [31] and T-cell acute lymphoblastic leukemia [32]. As a silico structure-based approach, molecular docking strategies have been broadly applied to drug discovery process and identified new compounds with therapeutic significance [33].

In our study, according to network pharmacology method, we identified 64 common targets both acting on curcuma and OSMF through Venny 2.1 drawing software, and sorted the top 5 targets including ALB, TNF, TP53, IL6, and VEGFA as a result of PPI network. Human ALB gene encodes 609 amino acids and its expression is regulated by its promoter, transcription factor and intron. A case report of familial dysalbuminemic hyperthyroxinemia revealed that the patient showed extremely high serum free thyroxine concentration due to p.R242P mutation in the ALB gene [34]. Barasa et al. demonstrated that reduced serum ALB levels was found in HIV-1-infected patients following antiretroviral treatment, and this results might be attributed to rs1445776009 variants in the human ALB gene [35]. Furthermore, the role of ALB in cancers has been explored, for instance, the endometrial cancer patients with poor overall survival presented low serum ALB concentration, and ALB concentration was the independent prognostic factor for patients [36]. As reported by Bao et al. this prospective study concluded that ALB levels were negatively related to overall survival of oral cancer patients, exposing prognostic significance of ALB in oral cancer [37]. Similarly to previous study, elevated CRP/ALB ratio was observed in oral squamous cell carcinoma patients with poor overall survival [38]. TNF cytokine is a central regulator of immunity, which can promote inflammation. In the presence of pathogens, and inflammation and stress signals, TNF gene transcription is activated in a variety of cell types such as T cells, macrophages, and fibroblasts [39]. TNF-alpha located in the class III region of human leukocyte antigen belongs to TNF/TNFR cytokine family, and is involved in the malignant progression of disease. Like TNF cytokine, IL 6 type cytokine is essential for homeostasis and immunity maintenance. It is produced rapidly and instantaneously during infection and tissue injury, which promotes host defense by stimulating acute phase reaction, hematopoiesis and immune response [40]. TNF-alpha acts as a pathogenic role in the development of OSMF, a condition of precancerous lesions [41]. Increased risk of oral precancerous lesions, such as leukoplakia, oral lichen planus, and OSMF, was induced by TNF-α (−308) and IL-6 gene polymorphism [42]. Compared with healthy controls, the patients with oral lichen planus, oral leukoplakia, or OSMF all had elevated serum and salivary levels of TNF-α and IL-6 [43], and the findings were supported by another research, revealing that

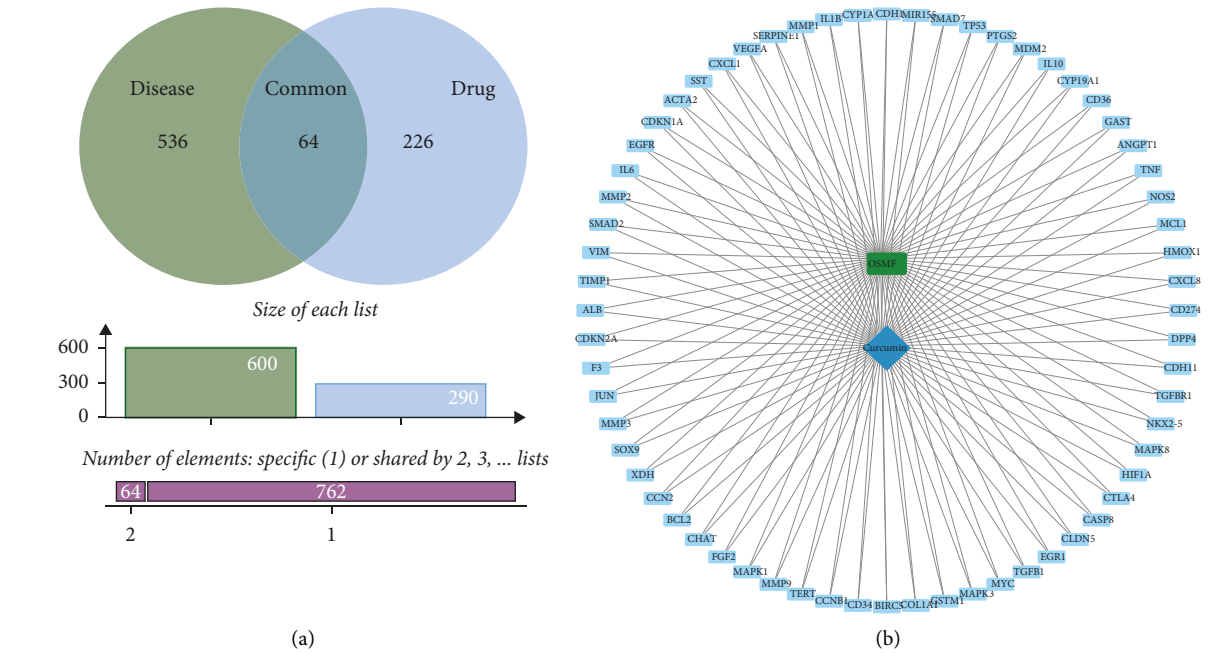
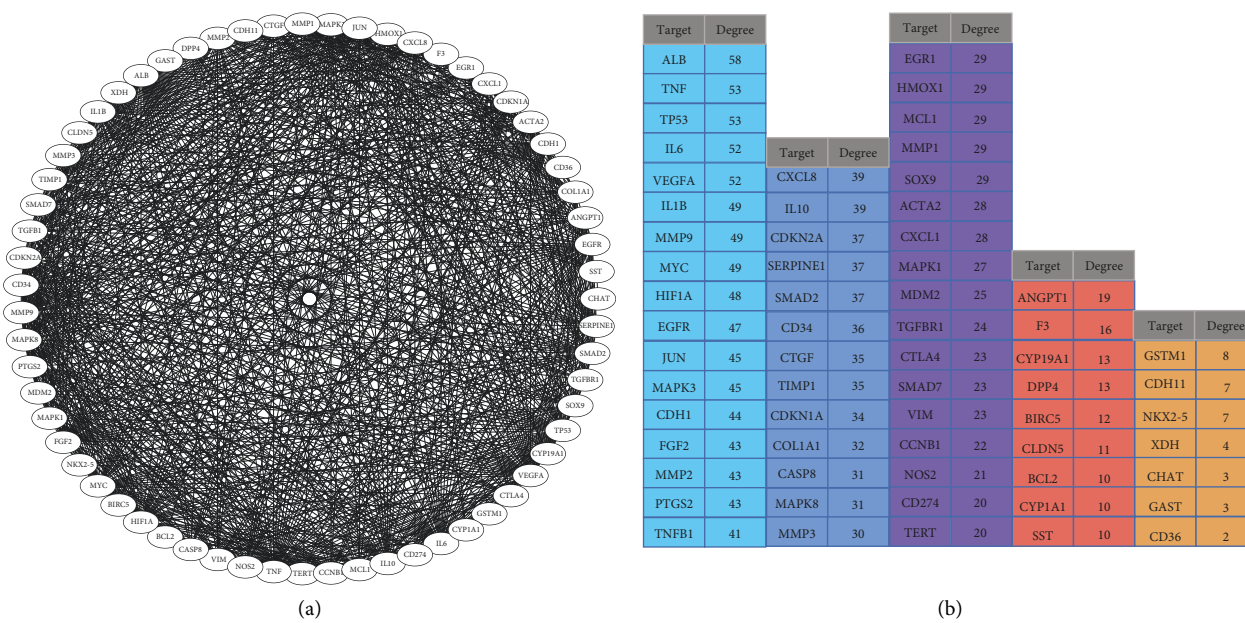


Figure 1: Venny diagram of 64 curcuma and OSMF common targets (a) and disease-target-compound network (b).



Target	Degree
ALB	58
TNF	53
TP53	53
IL6	52
VEGFA	52
IL1B	49
MMP9	49
MYC	49
HIF1A	48
EGFR	47
JUN	45
MAPK3	45
CDH1	44
FGF2	43
MMP2	43
PTGS2	43
TNFB1	41

Target	Degree
CXCL8	39
IL10	39
CDKN2A	37
SERPINE1	37
SMAD2	37
CD34	36
CTGF	35
TIMP1	35
CDKN1A	34
COL1A1	32
CASP8	31
MAPK8	31
MMP3	30

Target	Degree
EGR1	29
HMOX1	29
MCL1	29
MMP1	29
SOX9	29
ACTA2	28
CXCL1	28
MAPK1	27
MDM2	25
TGFBR1	24
CTLA4	23
SMAD7	23
VIM	23
CCNB1	22
NOS2	21
CD274	20
TERT	20

Target	Degree
ANGPT1	19
F3	16
CYP19A1	13
DPP4	13
BIRC5	12
CLDN5	11
BCL2	10
CYP1A1	10
SST	10

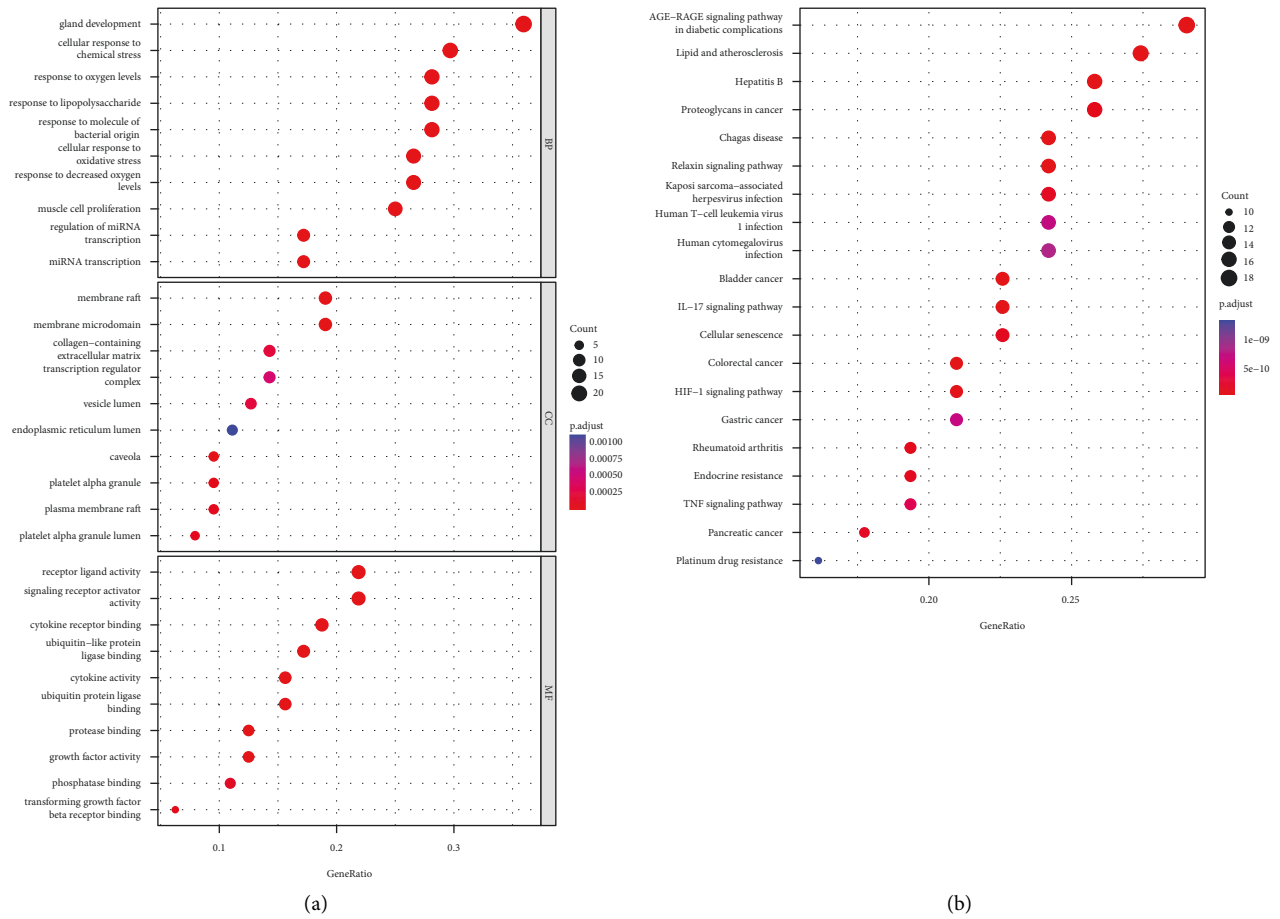
Target	Degree
GSTM1	8
CDH11	7
NKX2-5	7
XDH	4
CHAT	3
GAST	3
CD36	2

(a)
(b)

Figure 2: PPI analysis for curcuma and OSMF common targets (a) and their degree in the PPI network (b).

TNF-α and IL-6 levels increased in OSMF patients [44]. TP53 is a tumor suppressor gene and TP53 gene mutations, especially somatic mutation of TP53 gene, are responsible for more than 50% of human tumors [45]. TP53 mutation is considered as a potential prognostic and predictive marker along with a target of drug intervention in cancers. Varun et al. pointed out that mean labeling index of P53 for OSMF and normal mucosa was 34.6 ± 8.7 and 15.1 ± 9, respectively, indicating increased P53 was associated with malignant lesions of the oral cavity [46]. VEGFA is involved in the regulation of angiogenesis and vascular permeability. A systematic review and meta-analysis presented by Almangush et al. suggested that no direct correlation was found between VEGFA and oral tongue squamous cell carcinoma through the meta-analyses. However, VEGFA could be used as a prognostic indicator of oral tongue squamous cell carcinoma via the pooled analysis [47]. Furthermore, the patients with OSMF showed significantly higher mean serologic levels of VEGFA than that in healthy controls ($P < 0.001$) [48].

In the present study, we performed molecular docking method to evaluate the binding energy of curcuma to the top



(a) (b)

Figure 3: The top 10 most enriched GO terms at the levels of BP, CC, and MF (a) and the top 20 most enriched KEGG pathways (b).

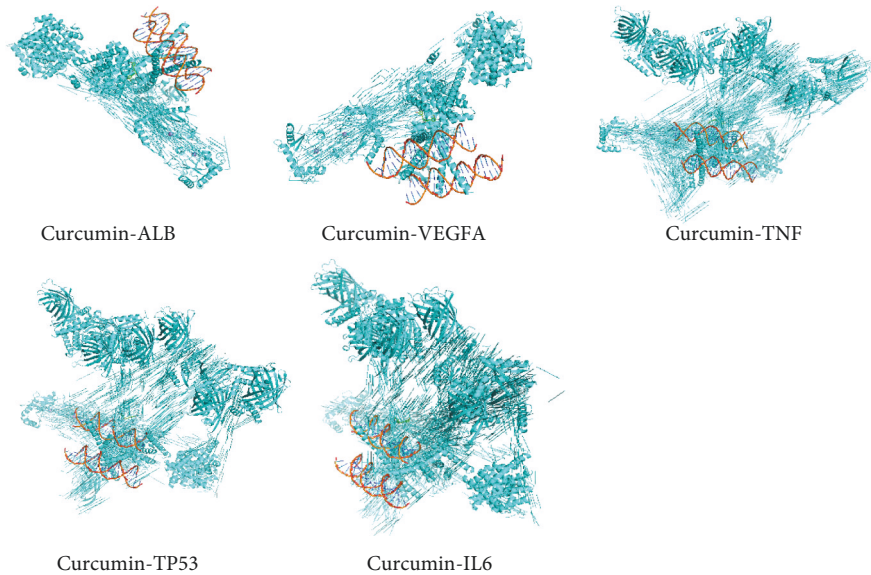


Figure 4: Molecular docking analysis of curcuma to ALB, TNF, TP53, IL6, and VEGFA.

5 targets, and ALB with -9.5 kcal/mol and VEGFA with −8.9 kcal/mol stood out. Previous studies manifested that the conjugation of curcuma and ALB increased the aqueous solubility of the drug, leading to favorable immunomodulatory activity with increase in total leukocyte count, platelet count, and viable cell count in bone marrow. Besides, this

conjugation was helpful to inhibit tumor deterioration in model of mice with Dalton's lymphoma ascites [49]. Oral administration of curcumol-based supplement is a safe and effective anti-VEGF treatment in age-related macular degeneration, resulting in functional outcome improvement [50]. The results in our study revealed that ALB and VEGFA might be the main targets participating in the potential mechanism of curcuma against OSMF.

Of note, our study has several limitations. First, the findings in our study obtained by a network pharmacology-based approach followed by molecular docking technology need to be verified in cellular and animal model. Second, we need more database screening common targets to improve the reliability of analysis or gene expression profiling of OSMF sample compared to control can be used to obtain more validated targets of OSMF. Third, the expression patterns of ALB, TNF, TP53, IL6, and VEGFA, the regulation of curcuma on these targets in the setting of OSMF are warranted to receive experimental validation. Forth, the exact therapeutic mechanism of curcuma against OSMF should be clearly explained in the future, such as anti-inflammatory, antioxidant, or wound healing effects. Network pharmacology has been widely used for drug-target-pathway analysis [51], where we again emphasize the importance of this field for medical research.

5. Conclusion

In conclusion, the study illustrated that the therapeutic effects of curcuma on OSMF were achieved by targeting ALB and VEGFA. Accordingly, the study thoroughly elucidated the molecular mechanism responsible for the therapeutic effects of curcuma on OSMF, which not only can facilitate the design and application of curcuma but also may bring more profound therapeutics for minimize the symptoms and healing oral mucosal lesion thus improving mouth opening in the context of OSMF.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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Research Article

Succinimide Derivatives as Antioxidant Anticholinesterases, Anti-α-Amylase, and Anti-α-Glucosidase: In Vitro and In Silico Approaches

Osama M. Alshehri,[1] Mater H. Mahnashi,[2] Abdul Sadiq,[3] Rehman Zafar,[4] Muhammad Saeed Jan,[5] Farhat Ullah,[3] Mohammed Ali Alshehri,[6] Saleh Alshamrani,[1] and Elhashimi E. Hassan[1]

[1]*Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Najran University, Najran, Saudi Arabia*
[2]*Department of Pharmaceutical Chemistry, College of Pharmacy, Najran University, Najran, Saudi Arabia*
[3]*Department of Pharmacy, Faculty of Biological Sciences, University of Malakand, Chakdara, KP 18000 Dir (L), Pakistan*
[4]*Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad 44000, Pakistan*
[5]*Department of Pharmacy, University of Swabi, Swabi, KP, Pakistan*
[6]*Department of Medical Genetics, Collage of Applied Medical Sciences, Najran University, Najran, Saudi Arabia*

Correspondence should be addressed to Abdul Sadiq; sadiquom@yahoo.com and Muhammad Saeed Jan; saeedjanpharmacist@gmail.com

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Based on the diverse pharmacological potency and the structural features of succinimide, this research considered to synthesize succinimide derivatives. Moreover, these compounds were estimated for their biological potential in terms of anti-diabetic, anti-cholinesterase, and anti-oxidant capacities. The compounds were synthesized through Michael addition of various ketones to *N*-aryl maleimides. Similarly, the MOE software was used for the molecular docking study to explore the binding mode of the potent compounds against different enzymes. In the anti-cholinesterase activity, the compounds **MSJ2** and **MSJ10** exhibited outstanding activity against acetylcholinesterase (AChE), i.e., 91.90, 93.20%, and against butyrylcholinesterase (BChE), i.e., 97.30, 91.36% inhibitory potentials, respectively. The compounds **MSJ9** and **MSJ10** exhibited prominent α-glucosidase inhibitory potentials, i.e., 87.63 and 89.37 with IC_{50} value of 32 and 28.04 μM, respectively. Moreover, the compounds **MSJ2** and **MSJ10** revealed significant scavenging activity against DPPH free radicals with IC_{50} values of 2.59 and 2.52, while against ABTS displayed excellent scavenging potential with IC_{50} values 7.32 and 3.29 μM, respectively. The tentative results are added with molecular docking studies in the active sites of enzymes to predict the theoretical protein-ligand binding modes. Further detailed mechanism-based studies in animal models are essential for the in vivo evaluation of the potent compound.

1. Introduction

Diseases adversely affect the health and well-being of human population [1]. In the 21st century, non-communicable diseases have become the main public concern [2]. Nature gave unexhaustive bounties to explore, experiment, analyze, and utilize to cure and treat human and animal ailments successfully such as hepatitis, diabetes, malaria, jaundice, inflammation, skin disorders, and depression [3, 4]. Recently, extensive research is still ongoing to find remedies to many concerning pathological conditions including diabetes, hepatitis, and cancer, which are not only effective in complete amelioration of the diseased condition but are also safe and economical [5, 6]. Day by day, there is an increasing demand for medicine and treatment of many diseases [7]. Continual use of some drugs may lead to side effects or drug

interactions when used to treat such ailments [8]. There is a need to look for new purpose-based research work, using their therapeutic values because various drugs cause various side effects [9], e.g., sulfonamides inhibit the metabolism or excretion of anti-diabetic drug sulfonylureas, resulting in hypoglycemia, while rifampicin increases their metabolism to reduce their hypoglycemic effect [10].

Diabetes mellitus (DM) can cause illness for prolonged time due to which the premature mortality ratio is high as compared to HIV-AIDS with approximately one death in every ten seconds across the globe [11]. This particular metabolic disease is characterized by defects in insulin secretion with subsequent effects displayed in the spectrum of hyperglycemia [12]. Diabetes mellitus can worsen in a few years due to which it is a main threat for human health worldwide [13]. In developed countries, diabetes is the fourth to fifth major cause of mortality, and signifies one of the most common non-communicable diseases worldwide [14, 15]. The current estimate revealed that among 150 to 220 million people were affected in 2010, with a forecast of 300 million individuals in 2025 worldwide [16]. Developing countries had maximum increases in the last few years. It has been estimated that there will be the largest number of diabetic subjects in the world by 2025 [17, 18]. DM is one of the major killers in Asian and Western Pacific peoples as described by the World Health Organization [19].

Free radicals have been involved in several diseases such as in cancer, liver cirrhosis, diabetes mellitus, and atherosclerosis [20], and those compounds which can easily remove these free radicals have great potential in amending the subject disease progression [21]. In diabetes mellitus, free radicals production like ROS (reactive oxygen species) is increased in all tissues from protein glycosylation and glucose auto-oxidation due to persistence hyperglycemia [22]. Different studies have shown that DM is mostly associated with oxidative stress, as a result of high production of ROS [23], superoxide radicals (O_2), hydroxyl radicals (OH), hydrogen peroxide (H_2O_2), and/or decrease in the anti-oxidant defense system. In the pathogenesis of DM (diabetes mellitus), the effect of oxidative stress is not only due to the presence of free radicals but also due to decreased anti-oxidant enzyme, glucose auto-oxidation, non-enzymatic protein glycosylation, and formation of peroxides [24, 25].

In the progression of Alzheimer's disease, oxidative stress is one of the initial events before the formation of AD plaques; to counteract this effect with interrelated factors is to raise the conation of ACH through the inhibition of AChE (acetylcholinesterase) and BChE (butyrylcholinesterase), which are responsible for the breakdown of acetylcholine in the synaptic clefts [26]. On the other hand, cholinesterase inhibitors have proven to be inadequate to stop or slow down the neurodegenerative process but partially compensate the lost cognitive functions [26]. It is proposed that the treatment of Alzheimer's would benefit with the use of multipotent drugs with cholinesterase (AChE or BChE) and β-secretase activities as well oxidative stress-reducing capability [27].

Succinimides have been observed to play a significant role in therapeutic strategies [28]. However, the use of succinimide derivatives is supposed to be a virtuous way to improve metabolic stability and pharmacokinetic properties. Various nitrogen-containing derivatives use succinimide derivatives as the building blocks. Reagents are required for the irregular addition [14, 29]. Succinimides are the well-known class of compounds possessing anti-Alzheimer potential through dual inhibitory pathways. They follow the cholinesterase inhibition at one side and behave as antioxidants on the other [30]. These classes of compounds also have been reported for other pharmacological activities. Succinimide has the basic nuclei of pyrrolidine-2,5-dione which is a five-member heterocyclic ring having nitrogen as the heteroatom and two carbonyl groups attached as functional groups. This basic skeleton can be altered to form carbon- or nitrogen-substituted derivatives with various aryl or alkyl groups that can formulate potential drug molecules [30]. The various synthetic and natural drugs commonly employed in neurological diseases like Alzheimer's possess an aromatic ring, a nitrogen atom, or a carbonyl group in their structure. Likewise, compounds used as free radical scavengers should have electron-rich moieties like hydroxyl groups in conjugation with their structures. This is the reason why these synthesized succinimide derivatives have been tested for enzyme inhibitory potential against cholinesterase enzymes including acetylcholinesterase and butyrylcholinesterase, α-amylase, α-glucosidase, and antioxidant activities. The as acquired derivatives were then *in vitro* screened in enzymes assays for AChE, BChE, ABTS, DPPH, alpha glucosidase, and alpha amylase inhibition. The enzyme interactions were then further validated using molecular docking studies.

2. Material and Methods

All of the chemicals, solvents, and drugs used in the analyses were obtained from Sigma Aldrich's local seller. Tween 80 (CAS no; 9005-65-6), Alloxan (CAS no: 50-71-5), E.A (CAS no; 141-78-6), maleimides (CAS no; 541-59-3), chloroform (CAS no; 67-66-3), silica gel (CAS no; 7631-86-9), n-hexane (CAS no; 110-54-3), α-glucosidase (CAS no; 9001-42-7), KOH (CAS no; 1310-58-3), α-amylase (CAS no; 9000-90-2), creatinine (CAS no; 67-7-5), phosphate buffer, glibenclamide, and other important chemicals were purchased from the standard quality supplier.

2.1. Compounds' Synthesis. The synthesis of the compounds (**MSJ 1—10**) was carried out by organocatalytic Michael addition. Various cyclic and acyclic ketones were added to N-substituted aryl-maleimides. Initially, 2.0 equivalent of ketone was added to chloroform (1 M) in the presence of catalytic amounts of L-isoleucine and KOH (each 0.2 equivalent) in a small reaction vial. This was stirred for a short time to produce the nucleophilic enamine species of the respective ketones. Afterwards, the maleimides were added to the respective reaction as the limiting reagent (1 equivalent) to precede the reaction. The reaction was

routinely checked by TLC analysis. The reaction was quenched with distilled water when the limiting reagent disappeared on the TLC analysis. The upper layer (organic) was separated 3 times from the water layer. The materials were dried and subjected to flash chromatography for the isolation of pure compounds [31].

2.2. Anti-Oxidant Activity

2.2.1. DPPH Radical Scavenging Assay. A previously reported method for DPPH radical scavenging activity was used to determine the anti-oxidant activity of the synthetic compounds with insignificant modification [12]. A solution of DPPH, e.g., (50 μL of 1.0×10^{-3} M), was prepared freshly and then added to CH_3OH (methyl alcohol). A solvent like methanol was used as a control group. The mixture was then incubated for 30 minutes at 25°C. A spectrophotometer is used to calculate the DPPH free radicals at specific wavelength like 517 nm. After the incubation period, Trolox (drug) was used as the control group (positive). The anti-oxidant activity was determined using the following formula:

$$\text{Percent Inhibition} = \left[\frac{\text{Absorbance (control)} - \text{Absorbance (test sample)}}{\text{Absorbance (control)}}\right] \times 100. \quad (1)$$

2.2.2. ABTS Radical Scavenging Assay. A previously reported method for ABTS radical scavenging assay was used to determine the anti-oxidant activity of the synthetic compounds with negligible modification [32]. The stock solution was prepared, e.g., 7 mM ABTS solution and 2.4 mM of potassium persulfate solution, and then mixed in equal amounts for about 16 hours. The stock solution was then diluted with methyl alcohol. Using a spectrophotometer, the absorption (0.7 ± 0.02) units at 734 nm wavelength were identified. In this assay, the solution was prepared freshly. The ABTS solution (150 μl) was mixed with the synthesized compounds (50 μl) and then reserved in darkness for about 10 minutes. The same procedure was repeated 3 times and then the results were verified using mean ± standard deviation. A solvent, e.g., methanol, was used as blank and the standard (butyl hydroxytoluen in methanol) were run at the same time. The absorbance was checked at a wavelength of 734 nm by utilizing a microplate reader.

2.2.3. Anti-Cholinesterase Assay. In Ellman's test, enzymes like (BChE) butyrylcholinesterase from equine serum and (AChE) acetylcholinesterase from electric eel were designated for studying the enzyme inhibitory capacity of the new synthesized compounds [33, 34]. This test is performed on hydrolyzed butyrylthiocholine or acetylthiocholine iodide through equivalent enzymes; as a result, 5-thio-2-nitrobenzoate anion was formed with DTNB and gives yellowish color compounds that were observed by a spectrometer alongside reaction time.

2.3. Preparation of Solutions. Synthetic compounds in concentration ranging from 31.25 to 500 μg/ml, KH_2PO_4 (13.6 g/L) and K_2HPO_4 (17.4 g/L), were dissolved in 0.1 M phosphate buffer solution. After mixing, they were combined in 6 and 94% ratio, to make 0.1 M and 8.0 phosphate buffer solutions having 0.1 pH. Potassium hydroxide was used to change the pH. The freshly prepared buffer pH 0.8, AChE (518 U/mg solid), and BChE (7–16 U/mg) were diluted to achieve final absolute concentrations of 0.01 U/ml and 0.03 U/ml, respectively. In distilled water, BChI (0.0005 M), DTNB iedithio bis-nitrobenzoic acid solution (0.0002273 M), and AChI were prepared and then kept in the refrigerator [35].

2.4. Spectroscopic Analysis. In this assay, introduce 5 μl of the enzyme solution into a cuvette which has 205 μl of the synthesized compound solution; then, add 5 μl of the DTNB iedithio bis-nitrobenzoic acid reagent. After that, the substrate solution (5 μl) was added into the solution present in mixture form and was held in a water bath for 15 minutes at 30°C. Absorbance was measured at 412 nm using a double beam spectrophotometer [24]. In this assay, galanthamine (cholinesterase inhibitor) was used as a positive control drug while all components except the compound have been used as the negative control group. At 30°C, the absorbance and the time of the reaction were measured at 30°C for four minutes and repeated three times. Finally, the activity of the control groups, enzymes, and test sample were assessed using the following formula ($V = \text{Abs}/t$)

$$\begin{aligned} \%\text{of enzyme inhibition} &= 100 - \%\text{activity of enzyme}, \\ \%\text{of enzyme activity} &= 100 \times \frac{V}{V_{\max}}, \\ V_{\max} &= \text{enzyme activity in the absence of potent inhibitory drug.} \end{aligned} \quad (2)$$

2.5. Anti-Diabetic Assay

2.5.1. α-Glucosidase Activity. In this assay, glucopyranoside is added to the solvent (phosphate buffer). Various concentrations of the synthetized compounds like 500, 250, 125, 62.5, and 31.25 μg/ml were used for preparing the sample solutions. Glucosidase in distilled water (0.5 μg/ml) was added to the above mixture. This mixture was then incubated for 20 minutes at 37°C [36]. After the incubation period, the reaction mixture was ceased by the addition of hydrochloric acid. The color intensity was determined at 540 nm wavelength using a spectrophotometer. The formula which was used to determine percentage inhibition is:

$$\text{Percent Inhibition} = \frac{\text{Absorbance (Control)} - \text{Absorbance (Sample)}}{\text{Absorbance (Control)}} \times 100. \quad (3)$$

2.5.2. In Vitro Assay of α-Amylase Activity. In this assay, previously documented protocols were used [37]. For preparing the sample solution, alpha amylase was mixed with the solvent (phosphate buffer) and also various concentrations of the synthesized compounds (500 μg/ml, 250 μg/ml, 125 μg/ml, 62.5 μg/ml, and 31.25 μg/ml) were mixed in this solution. Starch solution was then mixed with the above solution and then incubated for about 20 minutes at 37°C. After incubation, the reactant mixture was then kept in a water bath for some time at 100°C. Color intensity was measured using a microplate reader at 656 nm. To determine percentage inhibition, the following formula was used:

$$\text{Percent Inhibition} = \frac{\text{Absorbance (Control)} - \text{Absorbance (Sample)}}{\text{Absorbance (Control)}} \times 100. \quad (4)$$

2.5.3. In Silico Docking Studies. Docking studies of the synthesized compounds were carried out to analyze the stabilizing interactions of all synthesized compounds **MSJ (1-10)** inside the protein pockets of selected targeted macromolecules. Docking studies were performed through Autodock Vina 1.1.2 interlinked with PyRx Software that has excellent authenticity to perform. The Pdb IDs of all targeted protein moieties (AChE-1EVE, BChE-4BDS, α-amylase-5U3A, and α-glucosidase-5NN3) were downloaded from an online data bank server https://www.rcsb.org/pdb and saved in the Pdb format. LGA (Lamarckian genetic algorithm) and the empirical energy-free function were employed for docking scoring through PyRx. The three-dimensional structures of all the synthesized compounds were generated through the latest version 20.0.0.41 of PerkinElmer Chem Draw professional software. Files were saved in the mol. Format. Furthermore, these structures were converted to the Pdb format through BioVia Discovery Studio Visualizer 20.0 after the addition of polar hydrogen. Meanwhile, the Pdb IDs of all targeted proteins were purified by removing the co-crystallized ligands and adding polar hydrogen, in addition to energy minimization. Docking runs were generated by adjusting the grid box with dimensions (Å) X: 52.21, Y: 51.98, Z: 48.12. Out of top-10 postures generated, the one having a greater negative binding energy was selected for each of the synthesized compounds and analyzed to understand the nature of the binding interactions.

3. Results

3.1. Chemistry of the Compounds. Ten different ketone derivatives of succinimides (**MSJ 1—10**) have been synthesized and evaluated in this study as shown in Figure 1. The compounds **MSJ1** and **MSJ2** have been synthesized with cyclohexanone additions to N-phenyl and N-benzylmaleimides with isolated yields of 90 and 69%, respectively. **MSJ1** was a white solid while **MSJ2** was half white. The compounds **MSJ4** and **MSJ5** are the extended structures/modifications of **MSJ1** and **2** where a 4-methylcyclohexanone has been used in the synthesis of both. The isolated yields for MSJ4 and 5 were 79 and 63%, respectively. MSJ4 was a white solid while MSJ5 was yellowish in color. The compound **MSJ3** is synthesized by reacting cyclohexanone with N-(4-bromo) phenylmaleimide with 75% isolated yield and with yellowish color. The compound **MSJ6** has been synthesized with a derivative of cyclohexanone having a heteroatom (oxygen) at the para position. The compound was half white in color with 73% isolated yield. Similarly, in structures **MSJ7** and **8**, the ketone ring is increased and decreased by a methylene unit, respectively. The isolated yields of compounds **MSJ7** (white) and **8** (yellowish) were 78 and 74%, respectively. The last two compounds (**MSJ9** and **MSJ10**) have been synthesized with acyclic ketones, i.e., acetone (for **MSJ9**) and 3-methyl-2-butanone (for **MSJ10**). Both of these compounds were yellowish in color with isolated yields of 76 (**MSJ9**) and 70% (**MSJ10**). The 1H and 13C NMR spectra are provided in the supplementary material, Figures S1–S10.

3.2. Results of the Anti-Oxidant Assays. In the DPPH scavenging assay, the succinimide derivatives **MSJ (1–10)** were tested at different concentrations of 31.25, 62.5, 125, 250, and 500 μmol/mL, respectively. In this assay, the most potent compound was **MSJ10** which caused a percent radical scavenging of 93.03 ± 0.48, 90.90 ± 0.48, 85.79 ± 0.63, 79.67 ± 0.61, and 75.69 ± 0.77 (IC_{50} 2.52 μM), the second

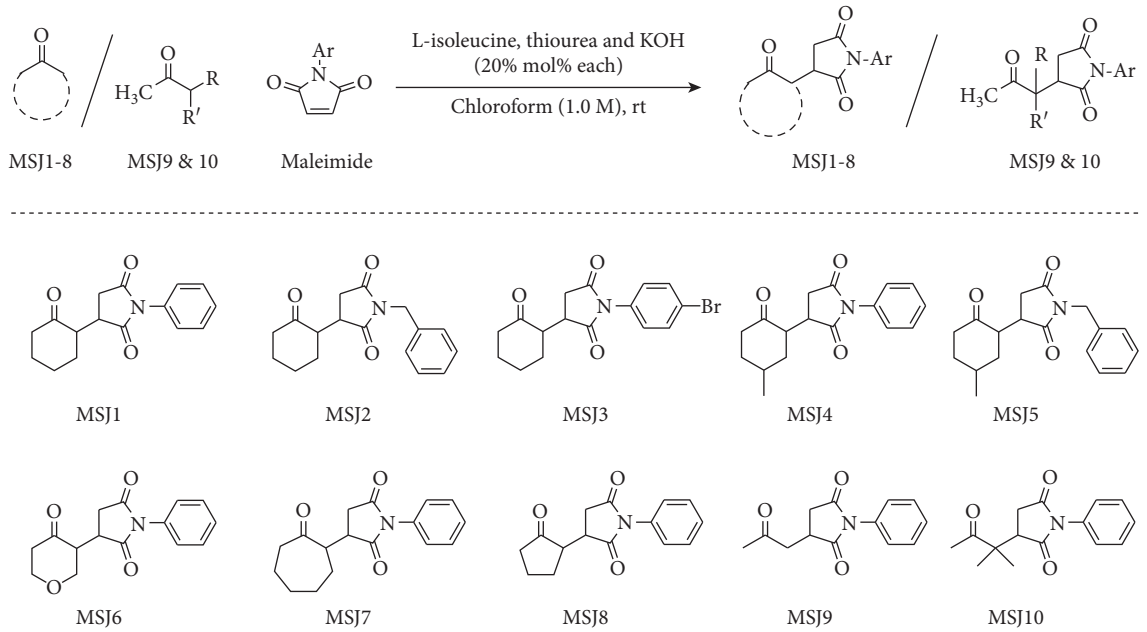

Figure 1: Structures of the synthesized compounds (**MSJ 1—10**).

highest activity was displayed by **MSJ2** causing 86.47 ± 0.70, 84.47 ± 0.46, 81.50 ± 0.61, 78.23 ± 0.44, and 73.45 ± 0.65 (IC_{50} 2.59 μM), respectively. All the other compounds like **MSJ1**, **MSJ3**, **MSJ4**, **MSJ5**, **MSJ6**, **MSJ7**, **MSJ8,** and **MSJ9** also exhibited significant results causing IC_{50} 34.57 μM, 33.47 μM, 31.96 μM, 39.01 μM, 44.86 μM, 31.44 μM, 29.23 μM, and 53.02 μM, respectively. The standard drug, ascorbic acid, displayed 98.65 ± 1.32, 93.56 ± 0.45, 91.52 ± 0.66, 88.22 ± 1.28, and 86.42 ± 0.43 at various concentrations with IC_{50} 6.25 μM as shown in Table 1. The percent inhibition values at concentrations ranging from the 500 to 31.25 μmol/ml of the various synthesized compounds are exhibited in Figure S11.

In comparison to ABTS, the compounds exhibited significant DPPH free radical scavenging activity. Using this assay, all the 10 compounds were tested at concentrations (31.25–500 μmo/mL). In the DPPH anti-radical assay, again, the compounds **MSJ10** and **MSJ2** had the highest activity with percent inhibitions of 93.03 ± 0.48, 90.90 ± 0.48, 85.79 ± 0.63, 79.67 ± 0.61, and 75.69 ± 0.77 (IC_{50} 3.29 μM), and 90.09 ± 0.32, 88.67 ± 1.20, 83.40 ± 0.25, 78.58 ± 1.12, and 74.65 ± 1.34 (IC_{50} 7.32 μM) correspondingly (Table 1). Ascorbic acid (positive control) inhibition was (IC_{50} 4.66 μM). All the other compounds also displayed good to moderate activity (Figure S12).

3.3. Results of the Anti-Cholinesterase Assay. The results of the anti-cholinesterase assay of the tested compounds as well as the positive control galantamine IC_{50} values are summarized in Table 2. The compound **MSJ10** exhibited outstanding anti-cholinesterase potential against both AChE and BChE. The percent anti-AChE and anti-BChE potentials displayed by the tested compound were very comparable 93.20 ± 0.10, 90.09 ± 0.32, 88.67 ± 1.20, 83.40 ± 0.25, 78.58 ± 1.12 and 91.36 ± 0.39, 87.15 ± 1.07, 83.00 ± 0.44, 78.26 ± 0.43, 73.89 ± 0.49 to that of the galantamine which is used as the standard drug. The IC_{50} value of the test compound against AChE and BChE was deliberated to be 4.97 and 10.72 μM, while the positive control displayed IC_{50}

Table 1: DPPH and ABTS free radicals scavenging IC_{50} values of the synthesized compounds.

Compound	IC_{50} (μM)	IC_{50} (μM)
MSJ1	34.57	29.41
MSJ2	2.59	7.32
MSJ3	33.47	24.04
MSJ4	31.96	48.71
MSJ5	39.01	51.24
MSJ6	44.86	55.11
MSJ7	31.44	36.27
MSJ8	29.23	25.19
MSJ9	53.02	38.10
MSJ10	2.52	3.29
Ascorbic acid	6.25	4.66

Table 2: IC_{50} values of the synthesized compounds against the anti-cholinesterase inhibitory assay.

Compound	IC_{50} (μM)	IC_{50} (μM)
MSJ1	13.60	31.26
MSJ2	8.73	11.26
MSJ3	24.32	39.39
MSJ4	19.49	17.31
MSJ5	20.28	11.62
MSJ6	24.30	20.35
MSJ7	13.07	6.34
MSJ8	14.15	41.90
MSJ9	27.24	17.43
MSJ10	4.97	10.72
Galantamine	0.762	6.31

values of 0.762 μg/mL against AChE and 6.31 μM against BChE, respectively. This shows the effectiveness of the synthesized succinimide derivatives against Alzheimer's disease. All the other compounds also exhibited well to moderate activity against both AChE and BChE. The anti-AChE scavenging potential of the tested compounds were in an ascending order of MSJ10 > MSJ2 > MSJ7 > MSJ1 > MSJ8 > MSJ4 > MSJ5 > MSJ6 > MSJ3 > MSJ9, respectively (Figures S13 and S14).

3.4. Results of the Anti-Diabetic Assay

3.4.1. α-Glucosidase Inhibitory Assay. As α-glucosidase is an enzyme responsible for diabetes, it has been used for the assessment of the anti-diabetic potential of the subject compounds. Analysis of the tested samples against α-glucosidase revealed that the highest scavenging effect is shown by compound **MSJ10**, which shows 89.37 ± 0.54, 84.44 ± 0.50, 77.51 ± 0.72, 72.28 ± 0.61, and 67.46 ± 0.62 activity at concentrations of 500, 250, 125, 62.5, and 31.25 μmol/mL, respectively (Figure S15) with the IC_{50} value 28.04 μM. The standard drug acarbose exhibited 94.40 ± 0.03, 85.03 ± 2.16, 80.90 ± 1.11, 76.44 ± 0.28, and 71.22 ± 0.47% inhibition at 500-31.25 μmol/mL, respectively, with 9.76 μM IC_{50} value. The lowest α-glucosidase scavenging activity was recorded for **MSJ6** possessing the IC_{50} value 155.59 μM. The second highest activity was displayed by **MSJ9** with the IC_{50} value 32 μM as shown in Table 3.

3.4.2. α-Amylase Inhibition Assay. In the α-amylase inhibition assay, the highest activity was shown by **MSJ10**. It displayed 86.91 ± 1.30, 81.26 ± 1.27, 76.00 ± 0.30, 71.54 ± 0.50, and 68.76 ± 0.58 percent inhibitions at concentrations from 500 to 31.25 μmol/mL with the IC_{50} of 16.62 μM. The compound **MSJ9** showed the second highest activity, resulting in 94.40 ± 0.03, 85.03 ± 2.16, 80.90 ± 1.11, 76.44 ± 0.28, and 71.22 ± 0.47 with an IC_{50} of 27.24 μM. Acarbose as a standard drug showed an activity of 91.90 ± 0.96, 87.08 ± 0.47, 82.40 ± 0.20, 77.61 ± 0.43, and 75.45 ± 0.90 percent inhibition (Figure S16) with an IC_{50} value of 3.86 μM against α-amylase (Table 3). All the other tested compounds in this assay displayed good to moderate α-amylase inhibition potential.

3.5. Results of In Silico Molecular Docking. Docking studies acquired a convinced position in scrutinizing and calculating the right way of ligand binding into active site (Ref). They provide an accurate approach of identification of ligand behavior inside the binding pockets of macromolecules (Ref). All the synthesized compounds **MSJ1** to **MSJ10** were docked with targeted proteins: acetylcholinesterase, butyrylcholinesterase, α-amylase, and α-glucosidase whose active sites were identified through co-crystallized ligands. The resultant binding energies of best postures are mentioned in Table 4.

All of the synthesized compounds performed satisfactorily with the targeted macromolecules, but the results were excellent in the case of **MSJ2** and **MSJ10,** showing increased binding affinities with the protein moieties. These results were validated through comparison with co-crystallized ligands of each targeted macromolecule. The results were compared in terms of RMSD values, binding posture of ligands, and interactions like conventional hydrogen bonds, pi-pi bonds, pi-sigma interaction, carbon-hydrogen bonds, and others appearing. Regarding the binding behavior of **MSJ2** with acetylcholinesterase, it gave −8.7 Kcal/mol binding energy in its best pose, while in the case of other targets, it gave −8.9 Kcal/mol, −8.2 Kcal/mol, and −8.5 Kcal/mol when interacting with butyryl cholinesterase, α-amylase, and α-glucosidase, respectively, a satisfactory comparison with in vitro results. All the visual parameters have been described in Figure 2.

Table 3: In vitro anti-diabetic inhibitory activity of the synthesized compounds.

Compound	IC_{50} (μM)	IC_{50} (μM)
MSJ1	149.35	144.48
MSJ2	94.73	86.46
MSJ3	173.89	93.01
MSJ4	96.90	84.99
MSJ5	50.98	27.29
MSJ6	155.59	127.34
MSJ7	64.87	55.62
MSJ8	113.38	76.26
MSJ9	32.00	27.24
MSJ10	28.04	16.62
Acarbose	9.76	3.86

When interacting with acetylcholinesterase, the cyclohexanone side chain established strong pi-sigma bond with TYR A: 334, while the aromatic ring observed a carbon-hydrogen bond with TRP A: 84. This interaction becomes more prominent in the case of butyrylcholinesterase, in which the cyclohexanone formed four alkyl and pi-alkyl linkages with TRP A: 231, LEU A: 286, PHE A: 329, and PHE A: 398. Amide pi-stacked was observed with GLY A: 115. One strong conventional hydrogen bond with ALA A: 199 further stabilized the linkages. The other prominent amino acid residues at the active site that were involved in the interaction in the case of α-amylase and α-glucosidase were PHE A: 229, PHE A: 252, PHE A: 335, ARG A: 398, TYR A: 360, ARG A: 594, and HIS A: 717.

Figure 3 represents the behavior of MSJ9 with all targeted proteins. This compound was stabilized inside the binding pocket through conventional hydrogen bonds. It formed carbon-hydrogen bonds with HIS A: 440 and GLY A: 441 in the case of acetylcholinesterase, with the best pose giving a binding affinity of −6.6 Kcal/mol. This ligand gave more interesting linkages with GLY A: 116, Gly A: 117, and ALA A: 199 in butyrylcholinesterase through three conventional hydrogen bonds. The prominent linkage was butan-2-one side chain with TRP A: 82 that stabilized this linkage further. Moreover, this ligand formed conventional hydrogen bonds with GLN A: 776 in α-amylase PDB ID: 5U3A with a bond length of 2.24 Å. The aromatic ring in this ligand formed pi-sigma linkages with LEU A: 701 and pi-alkyl linkages with VAL A: 816 and LEU A: 775.

Table 4: Binding energy scoring of the synthesized ligands (**MSJ 1-10**) with targeted proteins.

Ligands	Binding energies (Kcal/mol)			
	Acetylcholinesterase 1EVE	Butyrylcholinesterase 4BDS	α-amylase 5U3A	α-Glucosidase 5NN3
MSJ1	−6.5	−6.7	−7.1	−7.4
MSJ2	−8.7	−8.9	−8.2	−8.5
MSJ3	−6.9	−7.2	−7.4	−7.8
MSJ4	−7.5	−7.8	−7.1	−7.2
MSJ5	−6.9	−6.5	−6.5	−6.6
MSJ6	−7.1	−7.5	−7.4	−7.8
MSJ7	−7.4	−7.5	−7.4	−7.7
MSJ8	−6.9	−6.5	−6.4	−6.8
MSJ9	−6.6	−6.6	−6.7	−6.7
MSJ10	−9.5	−9.1	−8.2	−8.8
Galantamine	−9.9	−9.6	—	—
Acarbose	—	—	−9.1	−9.5

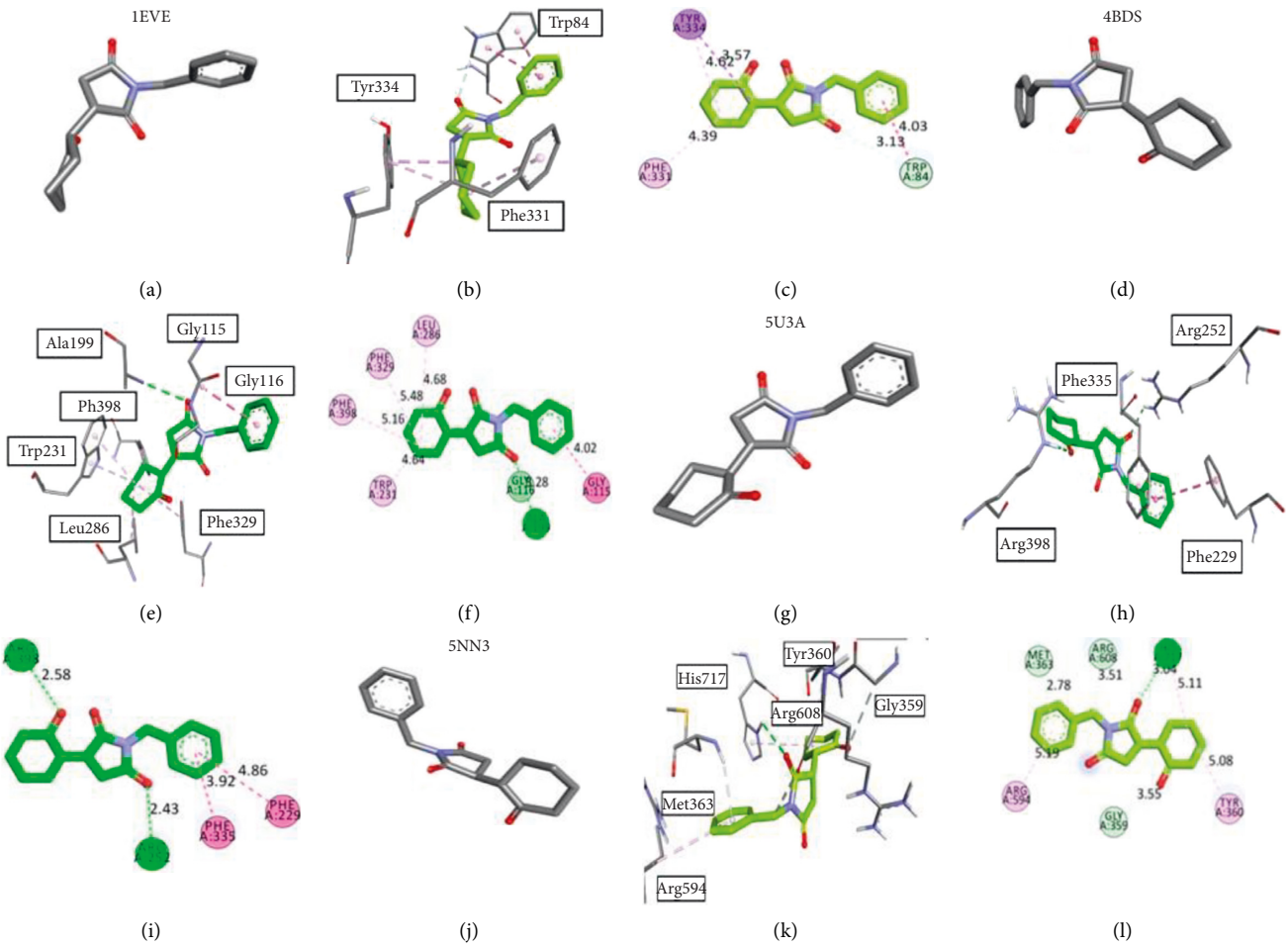

Figure 2: Docking 3-dimensional and 2-dimensional poses of ligand **MSJ2** inside the binding pockets of the targeted proteins. (a–c) indicate the best binding postures with acetylcholinesterase, (d–f) with butyrylcholinesterase, (g–i) with α-amylase, and (j–l) with α-glucosidase.

The protein-ligand complex of the synthesized chemical moiety **MSJ10** with all the targeted proteins including acetylcholinesterase, butyrylcholinesterase, α-amylase, and α-glucosidase displayed interesting features with binding affinities of −9.5 Kcal/mol, −9.1 Kcal/mol, −8.2 Kcal/mol, and −8.8 Kcal/mol, respectively Figure 4.

This compound consists of 3,3-dimethylbutan-2-one side chain that provides a prominent interaction in the form of pi-sigma with PHE A: 331 and TYR A: 334 in the case of acetylcholinesterase. Conventional hydrogen bonds were formed with TYR A: 121 through the cyclopentane-1,3-dione structure. This complex established three conventional

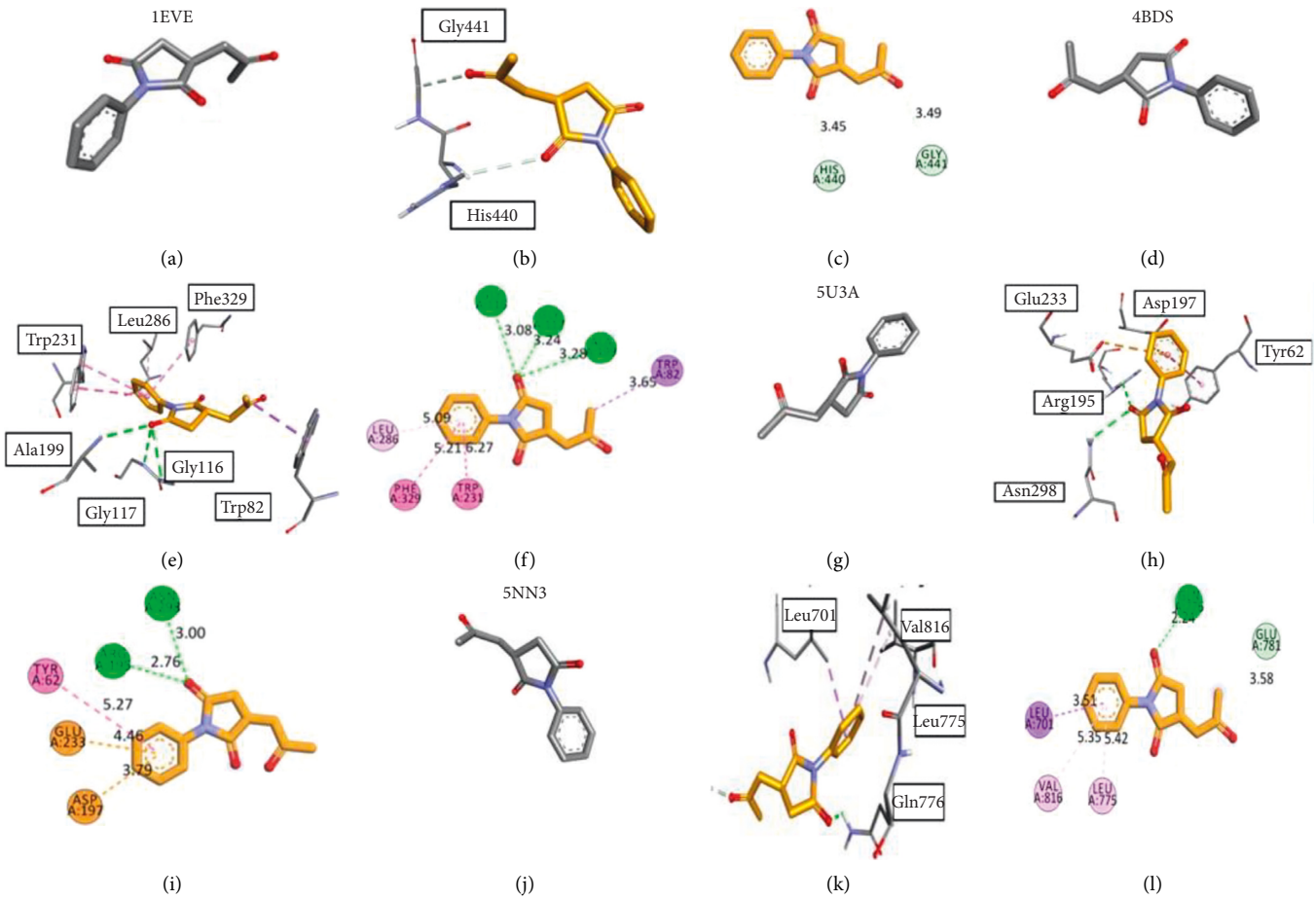

FIGURE 3: Docking 3-dimensional and 2-dimensional poses of ligand **MSJ9** inside the binding pockets of the targeted proteins. (a–c) indicate the best binding postures with acetylcholinesterase, (d–f) with butyrylcholinesterase, (g–i) with α-amylase, and (j–l) with α-glucosidase.

hydrogen bonds in butyrylcholinesterase with GLY A: 117, Gly A: 116, and ALA A: 119 through the cyclopentane-1,3-dione ring. The aromatic ring in this ligand formed pi-pi T-shaped linkages with PHR A: 329 and TRP A: 231, and pi-alkyl linkages with LEU A: 286 with a bond length of 5.25 Å, 6.21 Å, and 5.05 Å, respectively. Furthermore, TRP A: 82 formed pi-sigma linkages with 3,3-dimethylbutan-2-one. Further visualizing the binding affinity and interaction of this compound in α-amylase, it formed two conventional hydrogen bonds with ARG A: 195 and HIS A: 299 through the cyclopentane-1,3-dione ring. Pi-anion linkage provided more stability through ASP A: 197 interaction with an aromatic ring. This structural unit formed conventional hydrogen bonds with ILE A: 780 and GLN A: 776 through the side chain 3,3-dimethylbutan-2-one in the case of the α-glucosidase macromolecular structure. The interaction of the standard drug galantamine with the active site of butyrylcholinesterase has been elaborated in Figure 5. It gave the binding energy −9.6 Kcal/mol in its best pose. The interacting amino acid (AA) residues were TRP A: 82, THR A: 120, TYR: A 128, ALA A: 328, TRP A: 430, MET A: 437, and TRP A: 440. This interaction showed the important binding amino acid (AA) residues of the targeted macromolecule interacting with the standard drug that played an important role in initializing the response. This butyrylcholinesterase inhibition by the standard drug galantamine provides promising information that is used to compare the results with the synthesized succinimide derivatives.

4. Discussion

In pharmacological research, the most interesting fields are the discovery and development of multi-target drug-able moieties. Oxygen is an important component of the aerobic life, but it also has a negative effect on our health by initiating the development of free radicals like ROS (reactive oxygen species), which are responsible for diseases like cancer, diabetes, inflammation, neurodegenerative disorders (Alzheimer's and dementia), ulcers, immune suppression, aging, and atherosclerosis [38, 39]. The most common free radicals are lipid peroxyl, hydroxyl, nitric oxide, and superoxide. On the other hand, the most frequent non-free radicals are hydrogen peroxide and singlet oxygen [40]. However, our immune systems protect us from all these free radicals using the anti-oxidant defense system that slows the formation of free radicals while another system generates chain-breaking antioxidants to stabilize and scavenge free radicals [41, 42]. However, when the production of free radicals increases from the incompetency of the body's defense mechanisms,

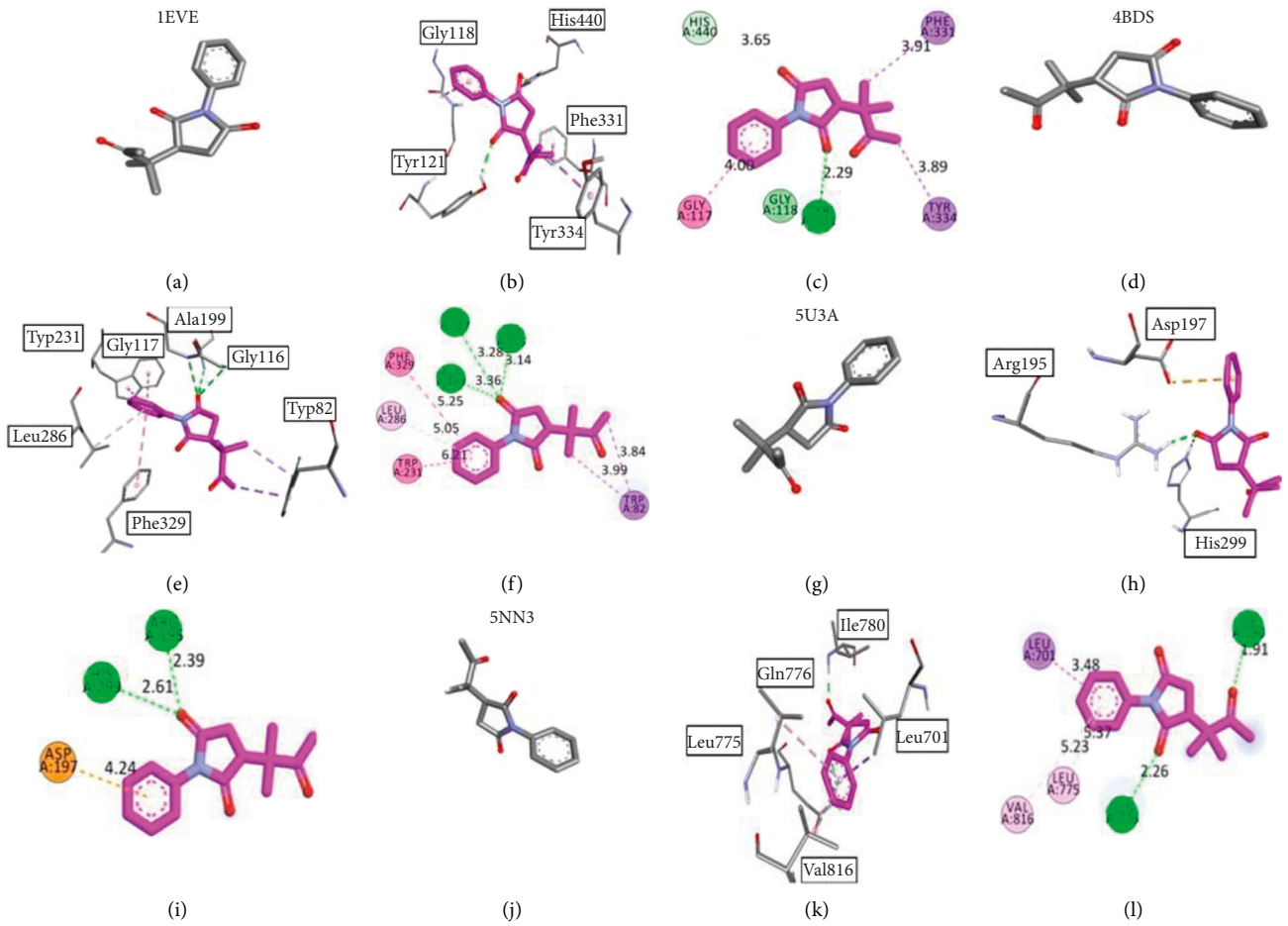

FIGURE 4: Docking 3-dimensional and 2-dimensional poses of ligand **MSJ10** inside the binding pockets of the targeted proteins. (a–c) indicate the best binding postures with acetylcholinesterase, (d–f) with butyrylcholinesterase, (g–i) with α-amylase, and (j–l) with α-glucosidase.

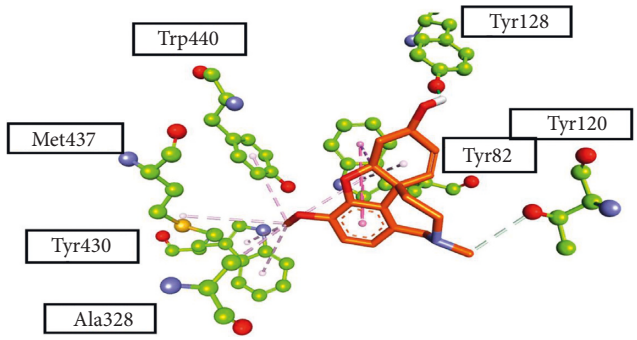

FIGURE 5: Three-dimensional visualization of the standard drug galantamine, inside the active binding site of butyrylcholinesterase PDB ID: 4BDS with amino acid (AA) residues' interaction shown.

then severe tissue damage occurs [43]. Therefore, those drugs with potential free radical scavenging effects are useful in the treatment and prevention of various disorders [44]. Antioxidant substances are identified to possess biochemical effects on different pathways, including hydrogen abstraction for long-term, peroxide breakdown, chain initiation inhibition, radical scavenging, metal ion chelation, and reductive capacity [24, 45]. Therefore, numerous techniques have been suggested for the determination of the anti-oxidant activity. The most commonly used method to measure the scavenging capability of free radicals is the DPPH method [46]. Antioxidants scavenge DPPH radicals by giving hydrogen as a result of decrease in DPPH-H. After reduction, the color changes ultimately from purple to yellow, which is counted by evaluating the absorbance of the compounds at 571 nm wavelength [47]. In the ABTS test, the anti-oxidant capacity of the test sample was used to inhibit the oxidation of ABTS into $ABTS^{++}$ radical cation [48].

The anti-cholinesterase enzyme presents a striking targeting moiety for normal drugs as well as for finding the mechanism's base inhibitors it plays a part in the breakdown of neurotransmitters like acetylcholine. The synthesis of AChE inhibitors presents an efficient approach to diagnose the mental symptoms of AD (Alzheimer disorder) and other promising therapeutic applications in the management of ataxia, senile dementia, and Parkinson's disease [49]. Furthermore, the compounds displayed substantial anti-cholinesterase scavenging activity, approximately halving the substrate breakage via human cholinesterase [50]. All the synthesized compounds include some stage of inhibitory

potential against BChE and AChE. A low IC_{50} of the compounds displayed virtuous enzyme inhibition. **MSJ10, MSJ2,** and **MSJ7** had the final IC_{50} value, representing that they have good inhibition of the enzymes.

The in vitro α-amylase inhibition of the tested compounds was evaluated [51]. However, the enzyme α-amylase is present in pancreatic juice and saliva which can convert larger polysaccharides into smaller particles [52]. Similarly, the enzyme α-glucosidase was present in the small intestine which can convert disaccharides into monosaccharides. The metabolism of carbohydrates was delayed due to the inhibitory action on α-glucosidase and α-amylase, which decreased the postprandial blood glucose level but also has adverse drug reactions (ADRs) like diarrhea and intestinal problems [53, 54]. At present, acarbose was the drug of choice to delay the metabolism of carbohydrates by inhibiting the enzyme and also by decreasing postprandial blood glucose level, but it has ADRs like intestinal disorders and diarrhea [55, 56]. The α-amylase inhibition effect of **MSJ10** shows an IC_{50} value of 16.62 μM and MSJ9 has 27.24 μM. For α-glucosidase, **MSJ10** shows an IC_{50} of 28.04 μM while **MSJ9** exhibited 32 μM. The results are shown in Table 3.

5. Conclusions

In conclusion, we synthesized ketone succinimide derivatives. All these molecules were formed in a single step with excellent isolated produces. The finding of the current research work shows the devastating AChE, BChE, α-amylase, and α-glucosidase potentials of these compounds and reveals their central role in AD and diabetes. Furthermore, these compounds also scavenge ABTS and DPPH free radicals. Due to the background information and present studies of succinimide derivatives, it may be assumed that compound **MSJ10** is a potentially active compound as compared to the other derivatives and could be a significant drug against DM (diabetes mellitus) and AD (Alzheimer's disease), subsequently going through additional screening and evaluations.

Data Availability

The data used to support the findings of the study can be obtained from the corresponding author upon request.

Disclosure

The authors declare that they have no conflicts of interest in this work.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

The spectral data of the synthesized compounds (Figure S1–S10) as well as various pharmacological activities like anti-oxidant (Figure S11, S12), anti-cholinesterase (Figure S13, S14), and anti-diabetic percent inhibition details (Figure S15, S16) are provided in the Supporting Information. (*Supplementary Materials*)

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Retraction

Retracted: Comparative Study on the Clinical Effects of Different Surgical Methods in the Treatment of Gastrointestinal Stromal Tumors

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] J. Wu, B. Mao, T. Jin, X. Xu, X. Xu, and S. Jiang, "Comparative Study on the Clinical Effects of Different Surgical Methods in the Treatment of Gastrointestinal Stromal Tumors," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 1280756, 7 pages, 2022.

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Research Article

Comparative Study on the Clinical Effects of Different Surgical Methods in the Treatment of Gastrointestinal Stromal Tumors

Jinyan Wu,[1] Boneng Mao,[1] Tao Jin,[1] Xinfang Xu,[1] Xiao Xu,[2] and Shengjun Jiang [1]

[1]*Department of Gastroenterology, Yixing People's Hospital, Wuxi 214200, Jiangsu, China*
[2]*Department of Gastrointestinal Surgery, Yixing People's Hospital, Wuxi 214200, Jiangsu, China*

Correspondence should be addressed to Shengjun Jiang; staff1152@yxph.com

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Objective. The objective is to compare the clinical efficacy of laparoscopic resection (LAP), endoscopic full-thickness resection (EFR), and endoscopic submucosal dissection (ESD) in the treatment of gastrointestinal stromal tumors. *Methods*. The clinical data of 105 patients who were treated in our hospital and diagnosed with GIST by pathology after surgery from March 2019 to March 2021 were collected. Patients were divided into the LAP group, EFR group, and ESD group according to different surgical methods. The clinical data, surgical conditions, complications, and postoperative conditions of the patients were recorded retrospectively. Patients were followed up closely after surgery. *Results*. The operation time of the EFR group and ESD group was shorter than that of the LAP group, and the operation time of the EFR group was shorter than that of the ESD group ($P < 0.05$). The amount of intraoperative blood loss in the EFR group and ESD group was lower than that in the LAP group ($P < 0.05$). There was no significant difference in the complete resection rate among the three groups ($P > 0.05$). There was no significant difference in the total incidence of complications among the three groups ($P > 0.05$). The postoperative abdominal pain time, postoperative hospital stay, and total hospitalization costs of the EFR group and ESD group were lower than those of the LAP group ($P < 0.05$). No recurrence or metastasis cases were found in the three groups during the follow-up period, and there were no GIST-related deaths in the three groups. *Conclusion*. LAP, EFR, and ESD have good curative effect, good safety, and good prognosis in the treatment of GIST. But compared with LAP, EFR and ESD have the advantages of less trauma, faster recovery, shorter hospitalization time, and lower hospitalization cost.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common type of gastrointestinal mesenchymal tumors, which are mainly found in middle-aged and elderly people, and the onset age is often >55 years. They originate from the interstitial cells surrounding the muscular plexus in the gastrointestinal wall and are nonepithelial tumors with malignant potential [1]. GISTs account for about 70% of gastrointestinal mesenchymal tumors and account for 1%~2% of all gastrointestinal malignant tumors. GISTs can occur in any part of the digestive tract, and gastric stromal tumors and small intestinal stromal tumors are the most common [2]. Once GISTs occur, patients usually lack typical symptoms, and their main clinical manifestations are gastrointestinal bleeding, abdominal pain, nausea, belching, obstruction, etc. If the GISTs condition worsens, resulting in tumor volume enlargement or ulceration, the patient may have symptoms such as severe abdominal pain, hematemesis, and black stool [3, 4]. At present, surgery is a widely used GIST treatment in clinics. Lymph node metastasis rarely occurs in GISTs, and routine lymph node dissection is not required during surgery. It is precisely because of these biological characteristics that the advantages of minimally invasive surgery such as laparoscopy and endoscopy can be fully reflected in the surgical treatment of GISTs. The advent of laparoscopic-endoscopic-combined techniques has broadened the scope of the application of minimally invasive surgical treatment of GISTs and improved surgical safety. With the continuous development of medical technology,

minimally invasive surgery has attracted attention in the GIST field. The effectiveness and safety of laparoscopic resection (LAP), endoscopic full-thickness resection (EFR), and endoscopic submucosal dissection (ESD) have been confirmed [5]. However, there are few studies comparing LAP, EFR, and ESD methods. Therefore, by observing 105 GIST patients and analyzing the application of different surgical methods, our doctors hope to improve the quality of life of patients and provide theoretical reference for the optimization of clinical medical work.

2. Materials and Methods

2.1. Research Object. The clinical data of 105 patients who were treated in our hospital and diagnosed with GIST by pathology after surgery from March 2019 to March 2021 were collected. Patients were divided into the LAP group ($n = 20$), EFR group ($n = 27$), and ESD group ($n = 58$) according to different surgical methods.

2.1.1. Selection Criteria. Selection criteria are as follows: ① tumor diameter ≤6 cm; ② before surgery, gastroscopy, ultrasonic gastroscopy, abdominal CT, and other examinations have been completed; and ③ patients with nonmetastatic tumor or recurrent GIST.

2.1.2. Exclusion Criteria. Exclusion criteria are as follows: ① patients with contraindications of routine endoscopic and surgical treatment; ② patients with other malignant tumors; ③ patients with severe heart, lung, and brain dysfunction; ④ patients with coagulation dysfunction; and ⑤ all patients signed the operation consent before operation.

2.2. Methods

2.2.1. Preoperative Preparation. Preoperative endoscopic ultrasonography was improved to understand the size and depth of the lesion. A CT scan of the upper abdomen was performed to find out the growth inside and outside the tumor cavity and whether there was metastasis or not. All patients fasted for 8 hours before surgery and underwent the surgery under tracheal intubation and general anesthesia. The vital signs of patients were monitored during the surgery.

2.2.2. LAP Surgery. Laparoscopic abdominal examination was performed before surgery to determine the location and size of the tumor and to exclude the spread and metastasis of the tumor. Different approaches were chosen according to the size and location of the tumor. For tumors in the anterior or posterior wall of the stomach, wedge resection can be performed using a laparoscopic stapler. To prevent stenosis after partial resection, proximal or distal gastrectomy is often used for proximal or pyloric tumors.

2.2.3. EFR Surgery. ① Patients were placed in the left lateral position, a gastroscope was inserted routinely, and the gastroduodenal cavity was flushed; ② the location of the lesion was determined, and the mixed solution of indigo carmine, epinephrine, and normal saline was injected under the mucosa of the lesion to make the mucosa bulge; ③ a dual knife was used to cut the mucosa horizontally and to strip the submucosa; ④ combined with a second generation IT knife, full-thickness resection of the lesion was performed to keep the capsule of the tumor intact and prevent the tumor from falling into the abdominal cavity. The tumor was taken out of the body with a stone-taking net basket, and blood oxygen saturation and pneumatosis in the abdominal cavity were observed. The abdominal cavity was punctured and exhausted using a 20ml empty needle at Macbeth's point in the right lower abdomen; ⑤ hot hemostatic forceps electrocoagulation was performed to expose blood vessels at the bleeding level. After no bleeding was observed, the perforation and the whole wound were closed, and no air leakage was observed in the closed wound. All patients were left with a nasogastric tube and the surgery was finished; and ⑥ the size of the tumor was measured and surgical specimens for pathological and immunohistochemical diagnoses were sent.

2.3. ESD Surgery. ① Patients were placed in the left lateral position, a gastroscope was inserted routinely, and the gastroduodenal cavity was flushed; ② the location of the lesion was determined and the mixed solution of indigo carmine, epinephrine, and normal saline was inserted under the mucosa of the lesion to make the mucosa bulge; ③ a dual knife was used to cut the mucosa horizontally and strip the submucosa; ④ the muscularis propria tumor was exposed and peeled off along the periphery and basement of the tumor; the tumor was completely removed and taken out of the body using a stone-taking net basket; ⑤ hot hemostatic forceps electrocoagulation was used to expose blood vessels at the bleeding level, the presence of a perforation was observed and the whole wound was sutured and closed; some patients were left with a nasogastric tube to finish the surgery; and ⑥ the size of the tumor was measured and surgical specimens for pathological and immunohistochemical diagnoses were sent.

2.4. Observation Indicators. The clinical data, surgical conditions, complications, and postoperative conditions of the patients were recorded retrospectively. After surgery, specimens were sectioned continuously, and full-thickness pathological examination and immunohistochemistry were performed. The NIH risk grading standard was used to evaluate the risk of GIST after surgery [6]. Patients were followed up closely after surgery. Gastroscopy and abdominal CT were reexamined at 3, 6, and 12 months after surgery and then followed up once a year. Follow-up includes the survival of patients and whether there is tumor recurrence or tumor metastasis.

2.5. Statistical Methods. SPSS 22.0 software was used for analysis, measurement data were expressed as $\overline{x} \pm s$, and the F-test was used to analyze the comparison. Count data were

expressed as ratios, and the χ^2-test was used to analyze the comparison. $P < 0.05$ was statistically significant.

3. Results

3.1. Comparison of Clinical Data of the Three Groups. There was a significant difference in tumor diameter and risk degree classification among the three groups ($P < 0.05$). There was no significant difference in age, sex, tumor location, and mitosis among the three groups ($P > 0.05$), as shown in Table 1.

3.2. Comparison of Surgical Conditions among the Three Groups. The operation time of the EFR group and ESD group was shorter than that of the LAP group, and the operation time of the EFR group was shorter than that of the ESD group ($P < 0.05$). The amount of intraoperative blood loss in the EFR group and ESD group was lower than that in the LAP group ($P < 0.05$). There was no significant difference in the complete resection rate among the three groups ($P > 0.05$) as shown in Figure 1.

3.3. Comparison of Complications among the Three Groups. There was no significant difference in the total incidence of complications among the three groups ($P > 0.05$), as shown in Table 2.

3.4. Comparison of Postoperative Conditions among the Three Groups. The postoperative abdominal pain time, postoperative hospital stay, and total hospitalization costs of the EFR group and ESD group were lower than those of the LAP group ($P < 0.05$), as shown in Table 2.

3.5. Comparison of Follow-Up among the Three Groups. In the LAP group, 17 cases were followed up by endoscopy, 2 cases were followed up by CT, and 1 case was lost to follow-up; the median follow-up time was 7 (3~12) months. In the EFR group, 22 cases were followed up by endoscopy and 5 cases were lost to follow-up; the median follow-up time was 7 (3~11) months. In the ESD group, 49 cases were followed up by endoscopy, 3 cases were followed up by CT, and 6 cases were lost follow-up; the median follow-up time was 8 (4~12) months. No recurrence or metastasis cases were found in the three groups during the follow-up period, and there were no GIST-related deaths in the three groups.

4. Discussion

At present, GIST patients are mainly treated by surgery. Due to the continuous improvement of minimally invasive technology and the continuous update of medical instruments, LAP, EFR, and ESD have played a key role in the treatment of GISTs [7]. The purpose of this study was to retrospectively analyze the medical records of GIST patients and compare the clinical therapeutic effects of three surgical methods.

LAP surgery is usually recommended for the treatment of GISTs with a diameter of ≤5 cm, and it is often applied to the sites that are easy to operate under laparoscopy, such as the big curved side of the stomach and the front wall of the gastric fundus [8]. Florin et al.'s research show that LAP surgery has high feasibility in GIST patients with tumor diameter ≤5 cm. Compared with open surgery, the complication rate of LAP surgery is lower (33.33% vs. 43.75%) and the patients' survival is good. Yang et al. summarized 10 reports of 485 patients with GIST and found that LAP surgery had less blood loss, shorter hospitalization time, patients could eat earlier, and it was safe, which was beneficial to the early recovery of GIST patients [9]. However, for some small endogenous GIST, it is difficult to locate via LAP surgery. At the same time, LAP surgery is inconvenient and difficult to expose the lesions of the cardia or the upper part of the stomach near the gastric fundus [10], this limits the clinical application of LAP surgery. Yin et al. believe that the surgery time of LAP is longer than that of ESD, and the intraoperative blood loss is more than that of ESD [11]. In this study, compared with the EFR group and ESD group, the LAP group has a longer surgery time and a larger amount of intraoperative blood loss, and the postoperative abdominal pain time, postoperative hospital stay, and total hospitalization costs are all greater than those of the EFR group and ESD group. This is roughly consistent with previous research results [12, 13].

Open surgery and laparoscopic surgery mostly use partial gastric resection, wedge resection, proximal or distal large gastric resection, and total gastrectomy, and there is no obvious difference in the surgical effect between the two. Compared with surgical open surgery, laparoscopic surgery has the advantages of small trauma and fast recovery, and its clinical application is becoming more and more extensive, but laparoscopic surgery is only suitable for gastric stromal tumors with a diameter of 5 cm, a clear boundary of the tumor body, and no metastases [14]. Also, it is often difficult to locate endophytic, small, or stromal tumors located in the posterior wall of the stomach in laparoscopic surgery. Endoscopic surgery has the advantages of small trauma and fast recovery, but the operation is difficult and the technical level of endoscopists and endoscopic instruments and equipment are very high; it is prone to complications such as bleeding and abdominal infection.

ASGE guidelines report that EFR has become a treatment option for the treatment of subcutaneous tumors and epithelioma with significant fibrosis, which is worthy of wide clinical application [15]. Ye et al. treated 726 patients with submucosal tumors of the upper digestive tract from the MP layer. The results showed that EFR was effective and safe, with a total resection rate of 97.1%, and no residual or recurrence of lesions was found during the follow-up period [16]. In addition, compared with the LAP group, ESD surgery can not only quickly find lesions and intuitively understand the size, texture, and boundary of tumors, but also treat cardia lesions that are difficult to treat under laparoscopy [17, 18]. Jiao et al. retrospectively analyzed the clinical data of GIST patients who received ESD. 98.7% of the patients had their lesions completely removed, 64.0% of

Table 1: Comparison of clinical data of three groups (n, %, $\overline{x} \pm s$).

Clinical data	LAP group ($n = 20$)	EFR group ($n = 27$)	ESD group ($n = 58$)	F/χ^2 value	P value
Age	59.61 ± 5.17	60.08 ± 4.94	58.93 ± 5.20	0.493	0.611
Gender				0.309	0.857
Male	8 (40.00%)	13 (48.15%)	26 (44.83%)		
Female	12 (60.00%)	14 (51.85%)	32 (55.17%)		
Tumor diameter (cm)	3.42 ± 0.81	1.97 ± 0.54	1.60 ± 0.36	91.923	<0.001
Tumor location				5.476	0.706
Fundus of the stomach	9 (45.00%)	13 (48.15%)	32 (55.17%)		
Gastric body	5 (25.00%)	6 (22.22%)	14 (24.14%)		
Gastric antrum	1 (5.00%)	2 (7.41%)	6 (10.34%)		
Junction of the fundus of stomach and gastric body	3 (15.00%)	2 (7.41%)	4 (6.90%)		
Cardia	2 (10.00%)	4 (14.81%)	2 (3.45%)		
Mitosis				0.589	0.745
≤5/50 HPF	18 (90.00%)	25 (92.59%)	55 (94.83%)		
>5/50 HPF	2 (10.00%)	2 (7.41%)	3 (5.17%)		
Risk degree classification				19.612	0.003
Very low danger	2 (10.00%)	16 (59.26%)	36 (62.07%)		
Low danger	11 (55.00%)	8 (29.63%)	16 (27.59%)		
Moderate danger	6 (30.00%)	2 (7.41%)	6 (10.34%)		
High danger	1 (5.00%)	1 (3.70%)	0 (0.00%)		

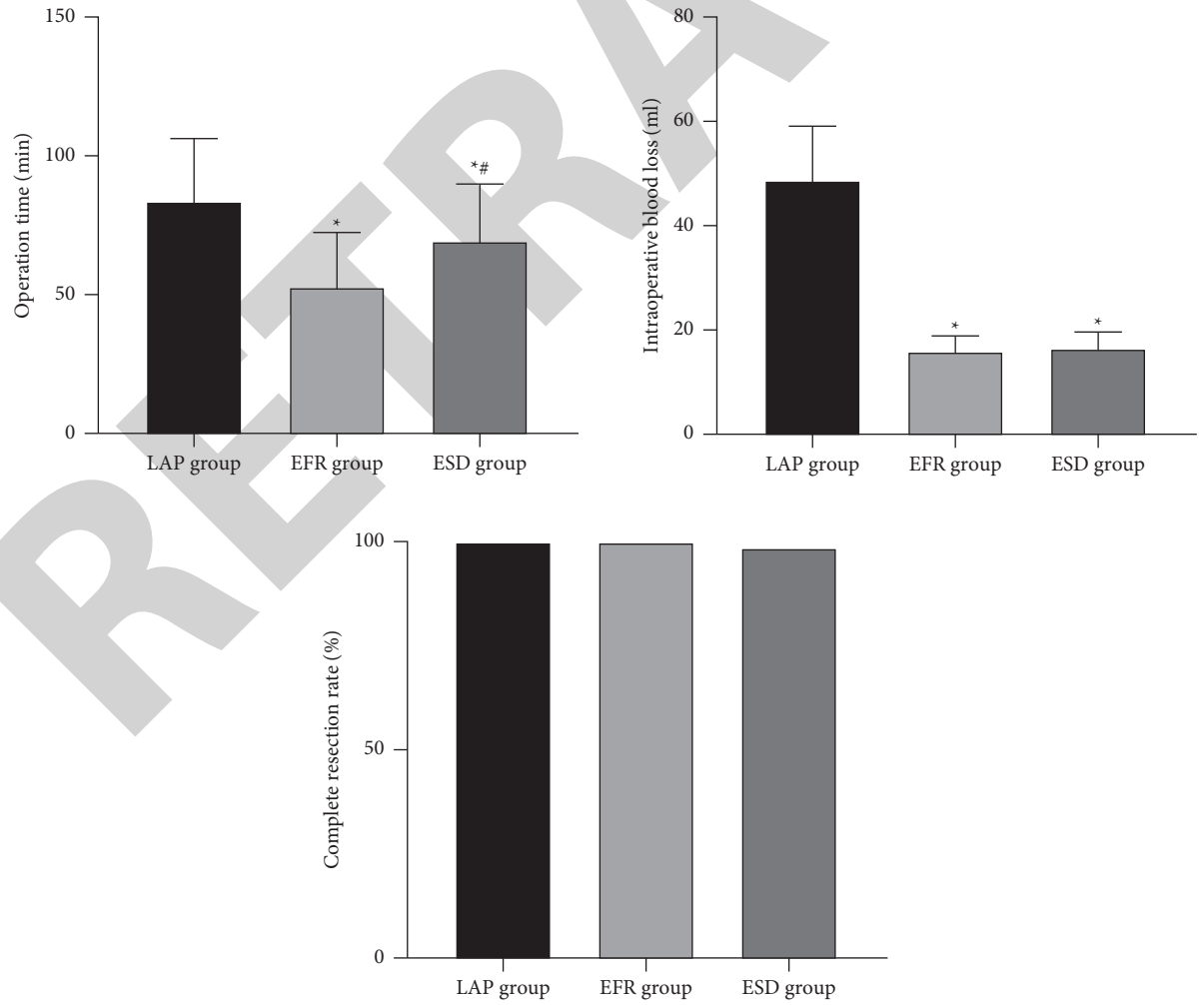

Figure 1: Comparison of surgical conditions among the three groups. Note: compared with the LAP group, $^{*}P < 0.05$; compared with the EFR group, $^{\#}P < 0.05$.

Table 2: Comparison of complications among the three groups (n, %).

Complication	LAP group ($n = 20$)	EFR group ($n = 27$)	ESD group ($n = 58$)	χ^2 value	P value
Delayed hemorrhage	1 (5.00%)	2 (7.41%)	2 (3.45%)		
Delayed perforation	0 (0.00%)	0 (0.00%)	2 (3.45%)		
Postoperative infection	0 (0.00%)	1 (3.70%)	1 (1.72%)		
Postoperative fever	1 (5.00%)	2 (7.41%)	3 (5.17%)		
Fistula	1 (5.00%)	0 (0.00%)	0 (0.00%)		
Total incidence rate	3 (15.00%)	5 (18.52%)	8 (13.79%)	0.320	0.852

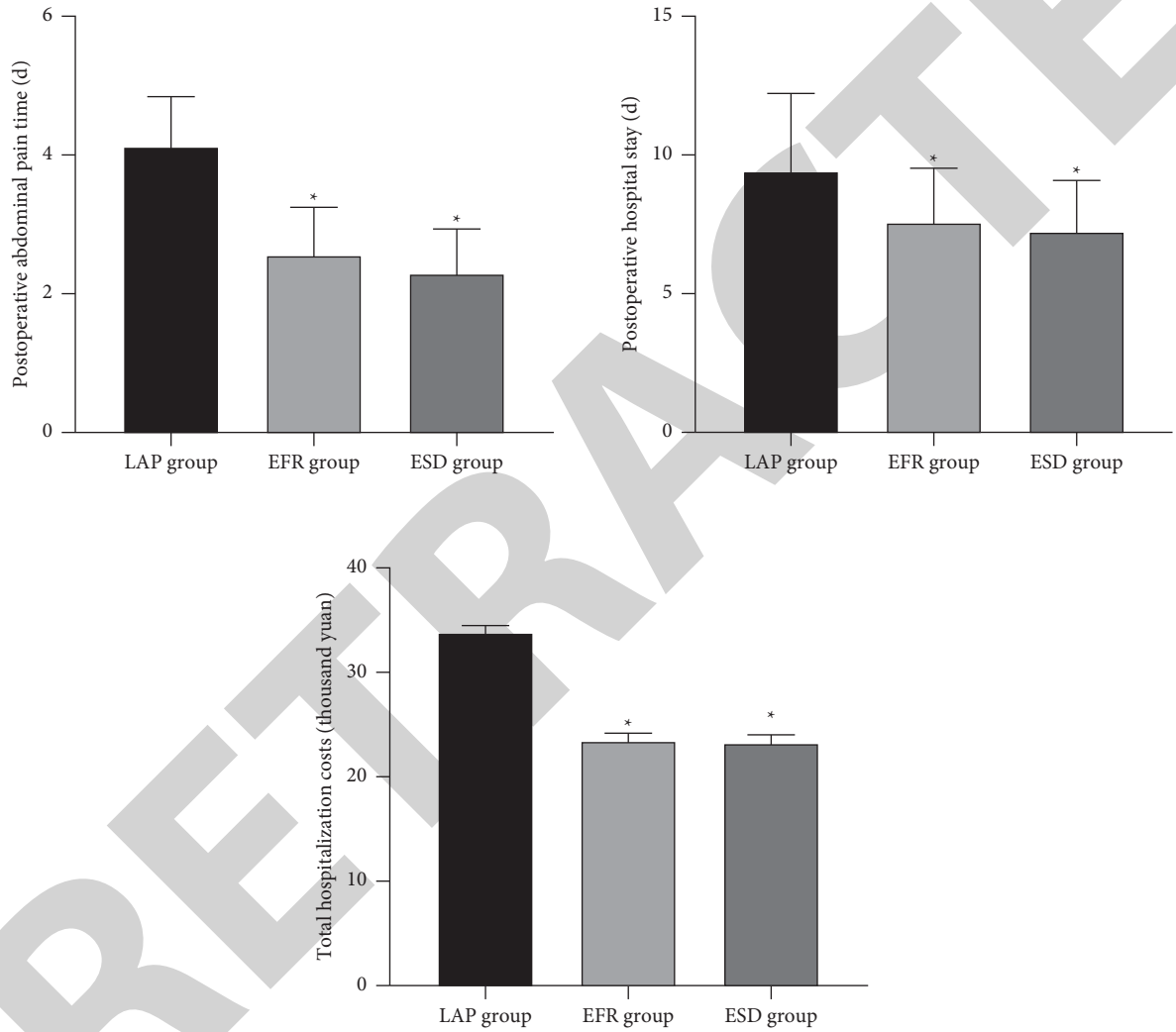

Figure 2: Comparison of postoperative conditions among the three groups. Note: compared with the LAP group, $^*P < 0.05$.

them had very low risk, 25.3% had low risk, 6.7% had medium risk, and 4.0% had high risk [19]. Meng et al. reported that the clinical efficacy of the ESD group and LAP group in treating GISTs was similar, and there was no difference in the complication rate, recurrence rate, and survival condition between them, but the ESD group had obvious advantages in surgery time, estimated blood loss, and hospitalization time [20]. There were no significant differences in complete resection rate, total complication rate, and postoperative follow-up (survival rate, tumor recurrence, or metastasis) between the three groups in this study. The results showed that LAP, EFR, and ESD had good curative effect, good safety, and good prognosis in the treatment of GISTs. However, compared with LAP, EFR and ESD have the advantages of less trauma, faster recovery, shorter hospitalization time, and lower hospitalization cost.

Clinically, it is generally believed that bleeding and perforation are the most common complications of EFR and ESD in treating GISTs, and they are also important factors limiting endoscopic treatment [21]. In this study, there was no significant difference in the total incidence of complications among the LAP, EFR, and ESD groups. The total

incidence of bleeding and perforation was 7.41% in the EFR group and 6.90% in the ESD group. All patients with bleeding had mild bleeding, and all patients were successfully stopped from bleeding by electrocoagulation during surgery. The perforations in all patients were successfully closed. The incidence of complications in the cases included in this study is less, which may be due to the small diameter of the tumor and the fact that the tumor is mostly located in the fundus and body of the stomach and other factors. During the development of endoscopy, timely and accurate surgical hemostasis, the application of CO^2 air pumps, the absorption of gastric juice, postoperative fasting, gastrointestinal decompression, and other measures can effectively reduce the incidence of complications and improve patient comfort. It is worth noting that some scholars have reported that EFR is suitable for GIST patients whose tumors are located in the deep layer of the intrinsic muscle, especially those growing outside the stomach wall, and ESD is suitable for GIST patients whose tumors are located in the shallow layer of the intrinsic muscle [22, 23]. Based on the summary of the clinical experience, our physician thinks that the choice of GIST treatment should be considered according to the comprehensive factors such as tumor size, tumor location, tumor growth mode, surgery experience, and patient's wishes.

5. Conclusion

To sum up, LAP, EFR, and ESD have good curative effect, good safety, and good prognosis in the treatment of GIST. However, compared with LAP, EFR and ESD have the advantages of less trauma, faster recovery, shorter hospitalization time, and lower hospitalization costs. This study is only a single-center retrospective study, and the number of cases included is small; therefore, the research plan needs to be further improved in the future.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Retraction

Retracted: Influencing Factors of Physical Activity in Patients with Lung Cancer Surgery and Its Correlation with Exercise Self-Efficacy and Perceived Social Support

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] N. Zhang, X. He, H. Zhang, Y. Zhu, and Y. Liu, "Influencing Factors of Physical Activity in Patients with Lung Cancer Surgery and Its Correlation with Exercise Self-Efficacy and Perceived Social Support," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7572530, 7 pages, 2022.

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Research Article

Influencing Factors of Physical Activity in Patients with Lung Cancer Surgery and Its Correlation with Exercise Self-Efficacy and Perceived Social Support

Na Zhang, Xin He, Huanhuan Zhang, Yajing Zhu, and Yan Liu

Department of Thoracic Surgery, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Chaoyang District, Beijing 100021, China

Correspondence should be addressed to Yan Liu; 15201119199@139.com

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Purpose. The aim of the study is to understand the current status of physical activity in patients with lung cancer surgery, explore its influencing factors, and analyze the correlation between physical activity and exercise self-efficacy and perception of social support. *Methods*. The General Information Questionnaire was designed for 145 patients, Chinese version of EPIC-PAQ physical activity scale for lung cancer patients. The Exercise Self-Efficacy Scale (SEE) is used to evaluate the ability of people to organize and execute motor behaviors in various difficult situations. The Perceived Social Support Scale (PSSS) was used to emphasize individual self-understanding and self-feeling. *Results*. The median and quartile of total physical activity scores in lung cancer surgery patients were 73.0 (34.8, 129.7) points; univariate analysis showed that there were statistically significant differences in physical activity levels among lung cancer surgery patients with different ages, work status before hospitalization, and perceived disease severity. The results of multivariate analysis showed that age, perceived disease severity, exercise self-efficacy, and total score of perceived social support affected the physical activity level of patients ($P < 0.05$). Efficacy were positively correlated with perceived social support ($P < 0.01$). *Conclusion*. The level of physical activity of patients undergoing lung cancer surgery needs to be further improved. Physical activity is affected by patient age, perceived disease severity, exercise self-efficacy, and perceived social support and is positively correlated with exercise self-efficacy and perceived social support. Medical staff should provide targeted activity guidance according to the age and other characteristics of patients undergoing lung cancer surgery, enhance patients' exercise self-efficacy and comprehend social support, and improve their physical activity level, thereby promoting patients' early recovery.

1. Introduction

Lung cancer is the most common malignant tumor in the world. According to the latest data from the National Cancer Center, lung cancer is the malignant tumor with the largest number of morbidities and deaths in my country [1]. Surgery is one of the main treatments for lung cancer patients. Physical activity (PA) refers to any physical activity that results in energy expenditure due to skeletal muscle movement [2]. The American College of Sports Medicine (ACSM) and the American Cancer Society have recommended physical activity as an intervention to help cancer survivors cope with pain, improve quality of life, and potentially prolong survival [3]. Research evidence shows [4–8] that regular and appropriate physical activity has a good effect on the primary prevention of cancer patients, prolonging survival time, and improving quality of life. Physical activity can improve cardiopulmonary function, improve body composition, reduce fatigue, relieve anxiety and depression, and improve the quality of life of cancer survivors. Although physical activity has many benefits for cancer patients, studies have shown [9] that nearly 2/3 of cancer patients do not meet the recommended amount of physical activity. Strategies to increase physical activity in cancer patients include encouraging physical activity practice, changing patient self-efficacy, and encouraging social

support [10, 11]. The purpose of this study is to understand the current status of physical activity, exercise self-efficacy and perception of social support in patients with lung cancer surgery, and to explore the influencing factors of physical activity and the relationship between the three, so as to provide medical staff with more targeted activities and health care for patients with lung cancer surgery. Guidance provides the basis for enhancing the patient's exercise self-efficacy and social support, improving their physical activity level, and promoting the patient's early recovery.

2. Materials and Methods

2.1. Research Subjects. Patients with lung cancer who were hospitalized in the Department of Thoracic Surgery of our hospital for surgical treatment from February to April 2022 were selected as the research subjects. Inclusion criteria were as follows: ① those who met the diagnostic criteria for lung cancer in the "Chinese Standards for the Diagnosis and Treatment of Primary Lung Cancer (2015 Edition)", and be diagnosed by pathological examination; ② aged 18–75 years old; ③ clear consciousness, no cognitive function, and communication impairment; ④ know their condition and diagnosis; and ⑤ those who submitted informed consent and are willing to participate in this study. Exclusion criteria were as follows: ① has metastasized to other parts, affecting systemic function; ② has a severe mental disorder, language communication disorder, and cognitive impairment; and ③ voluntarily withdrawn from the researcher.

2.2. Methods

2.2.1. Survey Tools

(1) General Information Questionnaire. General Information Questionnaire was designed for 145 patients including general demographic information such as age, gender, occupation, education level, and per capita monthly income of the family, and disease-related information such as disease course, lesion size, and surgical method.

(2) Chinese version of EPIC-PAQ physical activity scale for cancer patients. It was obtained by Shujin et al. [12] Chinese translation of the EPIC Physical Activity Questionnaire (EPIC-PAQ) developed by the European Nutrition and Cancer Prospective Cohort Research Organization. The test-retest reliability of the Chinese version of the Physical Activity Scale for Cancer Patients was 0.818, the content validity index was 0.900, and the criterion validity was 0.417. The Physical Activity Scale for Cancer Patients includes 3 dimensions and 4 questions of occupational physical activity, housework physical activity, and leisure time physical activity. There are 6 kinds of physical activities in the second question, so there are 9 items in the whole questionnaire. EPIC assigns metabolic equivalents (METs) to each physical activity. We divide the population into 4 categories based on work status and leisure time physical activity time: Insufficient physical activity-sedentary work, no recreational activities; mild insufficiency of physical activity-sedentary work with less than 0.5 hours of recreational activity per day or standing work with no recreational activity. Moderate physical activity-sedentary work with 0.5 to 1 hour of recreational activity per day or standing work with 0.5 hour of recreational activity per day or physical work with no recreational activity; physically active-sedentary work with more than 1 hour of recreational activity per day or standing work with >0.5 hours of recreational activity per day or physical work or heavy manual work with at least some recreational activity [13].

(3) Exercise Self-Efficacy Scale (SEE). The SEE developed by Bandura, translated, and revised by Taiwan scholar Lee et al. [14] is used to evaluate the ability of people to organize and execute motor behaviors in various difficult situations. The scale contains 18 items, each graded on a scale of 0 to 100, with 100 representing full confidence, 50 representing half confidence, and 0 representing no confidence at all. The exercise self-efficacy score is the sum of the scores for each assessment item and then divided by the total number of items. A higher score indicates a higher level of exercise self-efficacy. The reliability of the scale is between 0.82 and 0.96.

(4) Perceived Social Support Scale (PSSS). This scale is a social support scale that emphasizes individual self-understanding and self-feeling. For the degree of support from friends and others, Cronbach's alpha coefficient is 0.922, using a scale of 1 to 7, and the total score reflects the overall degree of social support felt by individuals [15].

2.2.2. Survey Methods. This questionnaire is distributed when patients with lung cancer surgery are discharged from the hospital. Before distributing the questionnaires, the distribution personnel will be trained uniformly through group meetings to make them understand the content of the questionnaires. According to the inclusion and exclusion criteria, the questionnaire star QR code was issued to the lung cancer patients who met the requirements, and the patients scanned the code to fill in the questionnaire by themselves. In the process of distributing the questionnaire, it is necessary to obtain the informed consent of the patients, use a unified guide language to explain the purpose and significance of this research to the patients, fill in anonymously, and explain the filling requirements on the first page of the questionnaire. For patients who are unable to complete the questionnaire, their immediate family members will fill it out on their behalf. A time limit was set for answering questions on WeChat, and you can submit it only after filling in no missing items.

2.3. Statistical Analysis. SPSS 24.0 statistical software was used for statistical analysis. The enumeration data were expressed as the number of cases and the composition ratio (%). The measurement data conforming to the normal distribution are expressed as the mean ± standard deviation, the nonnormally distributed data are expressed as the median (quartile) (M (P25, P75)), and the chi-square test and rank sums are used for comparison between groups.

Unordered multiclass logistic regression analysis was used to explore the main influencing factors of physical activity in patients with lung cancer surgery. The relationship between physical activity and exercise self-efficacy and perceived social support was analyzed by the Pearson correlation. $P < 0.05$ was considered to be statistically significant.

2.4. Ethical Review. This study has been approved by the Ethics Committee of the National Cancer Center/Peking Union Medical College Cancer Hospital, Chinese Academy of Medical Sciences (approval number: 21/018–2689).

3. Results

3.1. Physical Activity of Patients with Lung Cancer Surgery. The results showed that the total physical activity score of patients after lung cancer surgery was 9.0–310.0 points, and the median and quartile were 73.0 (34.8, 129.7) points. There were 43 cases of insufficient/mild insufficiency of physical activity, accounting for 29.7%; physical activity was moderate in 58 cases, accounting for 40.0%. Physical activity was active in 44 cases, accounting for 30.3%.

3.2. Scores of Exercise Self-Efficacy and Perceived Social Support in Patients with Lung Cancer Surgery. The results showed that after lung cancer surgery, the median and quartile of exercise self-efficacy were 90.0 (45.5, 155.0) points and the median and quartile of perceived social support were 64.0 (48.5, 74.5) points.

3.3. Univariate Analysis of Physical Activity Levels in Patients with Different Characteristics of Lung Cancer Surgery. A total of 146 questionnaires were distributed, of which 145 were collected and collated. The results showed that there were statistically significant differences in physical activity levels among lung cancer patients with different ages, work status before hospitalization, and perceived disease severity ($P < 0.05$), as shown in Table 1.

3.4. Unordered Multiclass Logistic Regression Analysis of Influencing Factors of Physical Activity in Patients with Lung Cancer Surgery. With physical activity level as the dependent variable, age, prehospital work status, perceived disease severity, exercise self-efficacy, and perceived social support total score as independent variables, unordered multi-category logistic regression analysis was performed. The results showed that age, perceived disease severity, exercise self-efficacy, and perceived social support total score affected the level of physical activity in patients with lung cancer surgery ($P < 0.05$). See Tables 2-3.

3.5. Correlation Analysis of Physical Activity Level with Sport Self-Efficacy and Understanding Social Support in Patients with Lung Cancer Surgery. The results showed that physical activity was positively correlated with exercise self-efficacy and perceived social support in patients with lung cancer surgery ($P < 0.01$), as shown in Table 4 and Figures 1–2.

4. Discussion

It can be seen that the exercise level of lung cancer patients is not optimistic, which is consistent with the results of many studies. The study of Williams et al. [16] showed that the physical activity of lung cancer patients is lower than that of ordinary people, and the physical activity is less after diagnosis, and more is just sitting. Feng Liyan et al. [17] surveyed 191 lung cancer patients during chemotherapy and showed that only 6.81% of the patients reached the recommended amount of exercise and 67.02% of the patients were at a low level of exercise; A longitudinal study by Lin et al. [18] showed that 36% of lung cancer patients reported reduced or stopped walking exercise in the past 6 months. The reasons for the analysis are related to many factors such as the patient's physiology, psychology, and social culture, including the patient's physical condition, living habits, psychological condition, medical staff guidance, time factors, and environmental factors [19]. Studies have shown that physical activity can produce a series of benefits for lung cancer patients, which can improve the cardiopulmonary and fatigue status of lung cancer patients, and improve the survival rate [20, 21]. We reduce physical and mental fatigue, reduce anxiety, increase cognitive function, improve self-esteem, increase muscle tone and balance, help weight control, enhance immune system, improve sleep, improve quality of life, etc. [22–24]. The American College of Sports Medicine (ACSM) recommends that cancer patients do at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity exercise per week [25]. In view of the fact that the level of physical activity of patients undergoing lung cancer surgery needs to be improved, medical staff and patients should pay more attention to physical activity and formulate a reasonable exercise program according to the specific situation of the patient to improve the physical activity level of the patient.

Young and middle-aged patients are more likely to suffer from insufficient physical activity, and patients with less severe disease are more active in physical activity. The reasons for this analysis may be that the incidence of lung cancer tends to be younger and today's social life is under great pressure, and young and middle-aged patients have heavy work and family tasks, resulting in physical and mental exhaustion and lower physical activity levels [26]. Patients with perceived high disease severity had lower levels of physical activity. The reason is that a considerable number of patients believe that their condition is poor and increasing their activity will lead to relapse or aggravation of the disease, so they choose to sit still for recuperation [27].

Patients with high exercise self-efficacy were more physically active. On the contrary, patients with low exercise self-efficacy are more likely to suffer from insufficient physical activity, which is consistent with the findings of Qiu Pingping et al. [28]. Self-efficacy (Self-efficacy) refers to people's judgment on the organization and execution ability of the action process required to complete their own behavioral goals [29]. Sports self-efficacy is the embodiment of positive psychology applied to the field of sports. Many physical and mental problems are caused by the disease and treatment of lung

Table 1: Univariate analysis of physical activity levels in lung cancer surgery patients with different characteristics ($n = 145$).

Indexes	Number of cases	Physical activity level			X^2/z score	P score
		Insufficient/mildly deficient	Moderate	Active		
Gender					−0.358	0.721
Male	57	19(33.3%)	17(29.8%)	21(36.8%)		
Female	88	24(27.3%)	41(46.4%)	23(26.1%)		
Body mass index					0.657	0.720
20-25	73	21(28.8%)	29(39.7%)	23(31.5%)		
< 20	11	4(36.4%)	5(45.5%)	2(18.2%)		
> 25	61	18(29.5%)	24(39.3%)	19(31.1%)		
Age					7.606	**0.022**
< 40 year	11	7(63.6%)	3(27.3%)	1(9.1%)		
40-60 year	86	28(32.6%)	31(36.0%)	27(31.4%)		
> 60 year	48	8(16.7%)	24(50.0%)	16(33.3%)		
Smoking					−1.049	0.294
No	118	36(30.5%)	49(41.5%)	33(28.0%)		
Yes	27	7(25.9%)	9(33.3%)	11(40.7%)		
Marriage						
Yes	138	40(29.9%)	55(39.9%)	43(31.2%)	−1.021	0.307
No or others	7	3(42.9%)	3(42.9%)	1(14.3%)		
Having children					−1.646	0.100
No	11	5(45.5%)	5(45.5%)	1(9.1%)		
Yes	134	38(28.4%)	53(39.6%)	43(32.1%)		
Education					0.344	0.842
Graduate and above	12	3(25.0%)	5(41.7%)	4(33.3%)		
Undergraduate and college	51	18(35.3%)	13(25.5%)	20(39.2%)		
High school and below	82	22(26.8%)	40(48.8%)	20(24.4%)		
Work status before hospitalization					8.611	0.013
Full-time work	56	25(44.6%)	19(33.9%)	12(21.4%)		
Part-time work	18	5(27.8%)	5(27.8%)	8(44.4%)		
Does not work	71	13(18.3%)	34(47.9%)	24(33.8%)		
Payment of medical expenses					3.615	0.306
Self-pay	3	2(66.7%)	1(33.3%)	0(0.0%)		
Reimbursed	6	4(66.7%)	0(0.0%)	2(33.3%)		
Medical Insurance/Commercial Insurance	125	35(28.0%)	50(40.0%)	40(32.0%)		
New rural cooperative medical system	11	2(18.2%)	7(63.6%)	2(18.2%)		
Per capita monthly household income					3.473	0.324
¥ 0-2999	16	6(37.5%)	9(56.3%)	1(6.3%)		
¥ 3000-4999	63	16(25.4%)	28(44.4%)	19(30.2%)		
¥ 5000-9999	48	15(31.3%)	14(29.2%)	19(39.6%)		
≥ ¥ 10000	18	6(33.3%)	7(38.9%)	5(27.8%)		
Economic Burden of Disease					2.583	0.275
Light	20	5(25.0%)	6(30.0%)	9(45.0%)		
Moderate	103	32(31.1%)	45(43.7%)	26(25.2%)		
Heavy	22	6(27.2%)	7(31.8%)	9(40.9%)		
Primary carrier					0.211	0.900
Spouse	101	31(30.7%)	40(39.6%)	30(29.7%)		
Sons and daughters	32	8(25.0%)	14(43.8%)	10(31.3%)		
Others	12	4(33.3%)	4(33.3%)	4(33.3%)		
Degree of understanding of the disease					0.6673	0.716
Very understanding	33	11(33.3%)	11(33.3%)	11(33.3%)		
General understanding	102	30(29.4%)	43(42.2%)	29(28.4%)		
Poor understanding	10	2(20.0%)	4(40.0%)	4(40.0%)		
Degree of understanding of disease prognosis					5.187	0.075
Very understanding	27	7(25.9%)	8(29.6%)	12(44.4%)		
General understanding	100	32(32.0%)	45(45.0%)	23(23.0%)		
Poor understanding	18	4(22.2%)	5(27.8%)	9(50.0%)		

Table 1: Continued.

Indexes	Number of cases	Physical activity level			X^2/z score	P score
		Insufficient/mildly deficient	Moderate	Active		
Perceived severity of illness					37.982	<0.001
Very serious	29	17(58.6%)	12(41.4%)	0(0.0%)		
Generally serious	85	24(28.2%)	39(45.9%)	22(25.9%)		
Not severe	31	2(6.5%)	7(22.6%)	22(71.0%)		
Number of lesions					−0.742	0.458
Single	91	24(26.4%)	39(42.9%)	28(30.8%)		
Multiple	54	19(35.2%)	19(35.2%)	16(29.6%)		
Underlying disease					−0.765	0.444
No	64	17(26.6%)	26(40.6%)	21(32.8%)		
Yes	81	26(32.1%)	32(39.5%)	23(28.4%)		

Table 2: Assignment table for unordered multiclass logistic regression analysis.

Factors	Variables	Assignment
Total exercise self-efficacy score	X1	Continuous variable
Comprehend social support total score	X2	Continuous variable
Age	X3	Continuous variable
Work status before hospitalization	X4	Works fine = 0, not working = 1
Perceived severity of illness	X5	Not serious = 0, very serious = 1

Table 3: Unordered multiclass logistic regression analysis of physical activity in patients with lung cancer surgery.

Indexes	Physically active			Physical inactivity/mild insufficiency		
	p	OR	95% CI	P	OR	95% CI
Total exercise self-efficacy score	<0.001	1.034	1.017~1.052	<0.001	0.950	0.927~0.974
Comprehend social support total score	0.760	1.009	0.953~1.068	0.025	0.940	0.890~0.992
Age	0.402	1.036	0.954~1.126	0.023	0.916	0.850~0.988
Work status before hospitalization						
Works fine	0.300	0.319	0.037~2.768	0.805	0.776	0.103~5.839
Not working	0.746	0.720	0.098~5.288	0.436	0.437	0.064~3.507
Perceived severity of illness						
Very serious		—	—	0.967	1.030	0.249~4.271
Not severe	0.009	6.108	1.567~23.803	0.798	0.727	0.063~8.349

The independent variable work status before hospitalization and the perceived severity of the disease are taken as reference levels for taking part in work and general severity, respectively; the reference level of the dependent variable is moderate physical activity (patients who are not physically active in the perceived very severity of their disease, so no relevant value is discussed.).

Table 4: Physical activity level and sport self-efficacy, understanding social support in patients with lung cancer surgery Pearson correlation analysis ($n = 145$).

Indexes	Physical activity level	
	R	P
Sport self-efficacy	0.794	<0.001
Understanding social support	0.637	<0.001

cancer patients, as well as the influence of the traditional thinking of "more rest when sick" may lead to lung cancer patients being not fully aware of the benefits of exercise, or even knowing that exercise is beneficial, but due to the impact on their physical and mental conditions. Worry and lack of confidence in exercise ability, i.e., low exercise self-efficacy, both prevent lung cancer patients from benefiting from exercise. As a behavioral predictor, exercise self-efficacy is closely related to the exercise level and compliance of cancer patients, suggesting that the lack of exercise in lung cancer patients can be improved by improving the self-efficacy level of lung cancer patients [30].

Patients with a low perception of social support are more likely to suffer from insufficient physical activity, which is consistent with the findings of Yu Xiaomei et al. [27]. Social support is an important variable in promoting patient participation in physical activity. [31, 32]. Patients have close relationships with family members, and support and encouragement from family members, especially spouses, play a very important role.

The higher the patient's exercise self-efficacy and perceived social support scores, the higher the level of physical activity. Exercise self-efficacy is a good predictor of exercise behavior. Studies have shown [33] that exercise self-efficacy is related to individual exercise plan commitment and exercise persistence. Individuals with high exercise self-efficacy are more inclined to take the initiative to formulate and abide by exercise plans. Even if you encounter difficulties, you will try your best to overcome the obstacles and continue to exercise [34]. The more

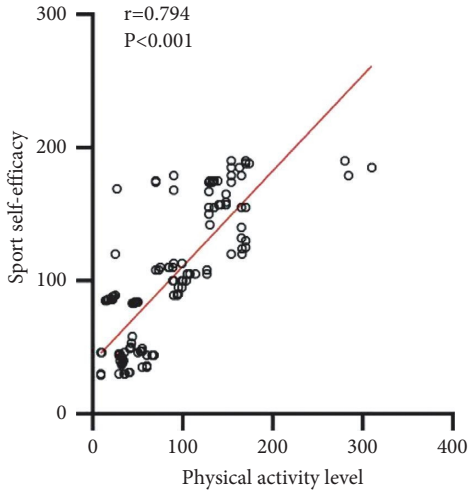

Figure 1: Correlation scatter diagram of the physical activity level and sport self-efficacy.

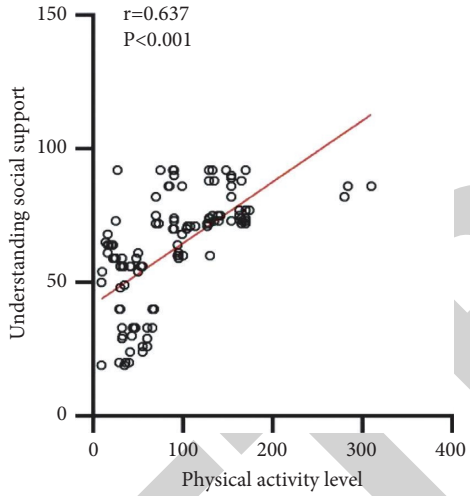

Figure 2: Correlation scatter diagram of the physical activity level and understanding social support.

support a patient feels from relatives, friends, colleagues, and patients, the more secure the timing, intensity, and persistence of physical activity. It is recommended that medical staff start from enhancing the patient's sense of self-efficacy in sports and understanding of social support and taking relevant measures, such as explaining the benefits and safety of physical activity in detail, enhancing patients' exercise confidence, encouraging family members to participate in the patient's rehabilitation plan, and holding regular patient friendship meetings, and other activities to improve the physical activity level of lung cancer surgery patients.

5. Conclusions

The level of physical activity of patients undergoing lung cancer surgery needs to be further improved, and age, perceived disease severity, exercise self-efficacy, and perceived social support are the influencing factors. Physical activity levels were positively correlated with exercise self-efficacy and perceived social support. According to the age and characteristics of lung cancer surgery patients, medical staff can target young and middle-aged patients and patients who believe that they have a serious condition and enhance the sense of sports self-efficacy and social support for lung cancer surgery patients. This study also has certain limitations, such as studying patients from a single medical institution and having a limited sample size. In the future, multicenter and large-sample studies can be carried out to further explore the related factors of physical activity in patients with lung cancer surgery.

Data Availability

The data can be obtained from the author upon reasonable request.

Disclosure

Na Zhang and Xin He are co-first authors.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Retraction

Retracted: Influence of Adenoid Hypertrophy on Malocclusion and Maxillofacial Development in Children

Evidence-Based Complementary and Alternative Medicine

Received 26 September 2023; Accepted 26 September 2023; Published 27 September 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] L. Zhang and H. Liu, "Influence of Adenoid Hypertrophy on Malocclusion and Maxillofacial Development in Children," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2052359, 6 pages, 2022.

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Research Article

Influence of Adenoid Hypertrophy on Malocclusion and Maxillofacial Development in Children

Liping Zhang[1] and Hui Liu[2]

[1]*Department of Stomatology, Zhuji People's Hospital, Zhuji 311800, Zhejiang Province, China*
[2]*Operating Room, The First Affiliated Hospital of Hunan Traditional Chinese Medical College, Zhuzhou 412000, Hunan Province, China*

Correspondence should be addressed to Hui Liu; liuhui13973331485@163.com

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Objective. To investigate the effect of adenoid hypertrophy on malocclusion and maxillofacial development in children. *Methods*. Total of 102 children with malocclusion or maxillofacial dysplasia admitted to our hospital from March 2017 to June 2020 were selected as the research subjects. All children were divided into a control group (50 cases with adenoid hypertrophy) and an observation group (52 cases without adenoid hypertrophy) according to the presence or absence of adenoid hypertrophy. The incidence of malocclusion was compared between the two groups, and lateral cranial radiographs were taken in both groups to measure and compare the malocclusion angle, jaw angle, and jaw length indexes between the two groups. *Results*. The incidence of malocclusion in the observation group (71.15%) was higher than that in the control group (42.00%), and the difference was statistically significant ($P < 0.05$). The angle between the long axis of the upper central incisor and the nasal root point and the upper alveolar base point (U1-NA), the angle between the long axis of the lower central incisor and the nasal root point and the lower alveolar base point (L1-NB), the angle between mandibular plane and anterior cranial base plane (MP-SN), the angle between the long axis of upper central incisor and anterior cranial base plane (U1-SN), the angle between the long axis of lower central incisor and mandibular plane (L1-MP), the angle of *Y* axis, the overall height (N-Me), lower height (ANS-Me), overall height/back height (N-Me/S-Go), and lower height/overall height (ANS-Me/N-Me) values in the observation group were higher than those in the control group, while the mandibular length (Go-Gn) values in the observation group were lower than those in the control group ($P < 0.05$). *Conclusion*. Adenoid hypertrophy can increase the incidence of malocclusion in children and can also increase the steepness and overall height and lower height of the mandible, resulting in the lengthening of the facial shape and the development of the maxillofacial deformity.

1. Introduction

The dental and maxillofacial growth and development of children is a complex but coordinated and continuous process with great growth potential in the upper and lower jaws, which is influenced by a combination of genetic factors, behavioral patterns, and environmental factors [1, 2]. The adenoids, also known as pharyngeal tonsils, are also an important part of the pharyngeal lymphatic ring (Waldeyer's ring) and play an important immune-inducing role as a physiological defense mechanism of the body, against inhaled allergens and microorganisms [3, 4]. The adenoids are located at the top of the nasopharynx and the posterior pharyngeal wall, and when the adenoids or their surrounding lymphatic tissues are repeatedly stimulated by inflammation, this can lead to pathological hyperplasia of the adenoids, resulting in adenoid hypertrophy [5, 6]. When pathological hyperplasia of adenoids occurs, it is highly likely to cause a variety of diseases such as otitis media, inflammation of the lower respiratory tract, and even sleep apnea [7, 8].

Adenoid hypertrophy can lead to blockage of the already narrow nasopharynx in children affecting breathing, when the child's nasal airway is blocked and ventilation is reduced,

causing a physiological neuromuscular feedback effect and passive stretching of the head and neck muscles, and then, open-mouth breathing occurs [9, 10]. Long-term open-mouth breathing often tends to trigger abnormal neuromuscular activity, causing relative body position changes in the maxillofacial muscles, resulting in abnormal development of the upper and lower jaws, which affects the normal development of the child's maxillofacial structures and eventually leads to imbalance or even deformed development of the maxillofacial morphology [11, 12]. Bandyopadhyay and Slaven [13] found that abnormalities in the anatomical structures adjacent to the upper airway or multiple lesions can cause open-mouth breathing, such as tonsillar hypertrophy, adenoid hypertrophy, allergic rhinitis, nasal septal deviation, and turbinate hypertrophy nasal stenosis, but it is now generally accepted that adenoid and tonsillar hypertrophy are the most important causes of open-mouth breathing in childhood. The aim of this study was to investigate the effects of adenoid hypertrophy on malformation and maxillofacial development in children. The details are reported in this study.

2. Information and Methods

2.1. General Information. One hundred and two children with malocclusion or maxillofacial developmental abnormalities admitted to our hospital from March 2017 to June 2020 were selected for the study, including 55 males and 47 females, aged 3–12 years, with an average age of (8.01 ± 2.09) years. Inclusion criteria were as follows: all lateral cephalometric films were performed, no history of orthodontic treatment, and no other congenital diseases. Exclusion criteria were as follows: history of adenoidectomy; history of ear, nose, and throat related diseases; and those with upper respiratory tract infections.

All children were grouped according to the presence or absence of adenoid hypertrophy: control group (50 cases): no adenoid hypertrophy, maximum adenoid thickness (A)/nasopharyngeal cavity width (N) value <0.71; observation group (52 cases): with adenoid hypertrophy, A/N value ≥0.71. There were 26 boys and 24 girls in the control group, aged 3–12 (7.86 ± 2.04) years. In the observation group, there were 29 boys and 23 girls, aged 5–12 (8.15 ± 1.96) years. The general data of the children in the two groups were compared, and the differences were not statistically significant ($P > 0.05$). The study was approved by the ethics committee of our hospital, and the families of the children gave their informed consent and signed the informed consent form.

3. Research Methodology

Referring to the literature [9], all children were classified into normal, An I, II, and III malocclusions, and the incidence of jaw deformity was counted. All children had lateral cephalometric films taken by the same physician using the Planmeca Proline XC system (Planmeca, Finland), with the child in a natural head position, no deflection, upper and lower lips closed naturally, no swallowing, and relaxed facial muscles. The measured images were transferred to the WinCeph 8.0 software, and all indicators were measured by the same physician, and each indicator was measured three times, and the final average was taken as the study data. Measurements include the angle between the NPo of the face plane and the SN of the anterior cranial base plane (NPo-SN), angle (U1-NA) between the long axis U1 of the upper central incisor and the line connecting the nasal root point and the seat point of the upper tooth groove, angle between the long axis of the lower central incisor L1 and the line connecting the nasal root point and the seat point of the lower tooth groove (L1-NB), angle between the long axis L1 of the lower central incisor and the Gn-Me angle in the mandibular plane (IMPA), subspinale plane angle (SNA), supramental plane angle (SNB), AB plane angle (ANB), angle between the mandibular plane MP and the anterior skull base plane SN (MP-SN), angle between the long axis of the upper central incisor U1 and the anterior cranial base plane SN (U1-SN), angle between the long axis of the lower central incisor L1 and the mandibular plane MP (L1-MP), angle between the line connecting the butterfly saddle point and the chin vertex and the orbital ear plane (*Y*-axis angle, SGn-FH), vertical distance between nasal root point and subchin point (N-Me), distance from the anterior nasal spine to the point under the chin (ANS-Me), vertical distance between the point of the butterfly saddle and the point of the mandibular angle (S-Go), N-Me/S-Go, ANS-Me/N-Me, and length of the corpora mandibulae (Go-Gn). Figure 1 shows the details.

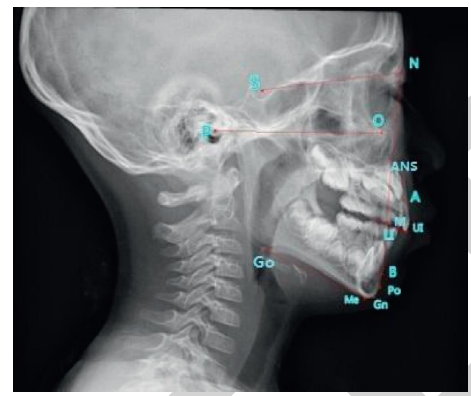

Figure 1: Schematic diagram of imaging marker point measurement.

3.1. Statistical Methods. SPSS 22.0 software was applied for processing, and the experimental data measurement data were expressed as mean ± standard deviation ($\overline{x} \pm s$), and the *t*-test was used for two-comparison analysis. Count data were expressed as (%), and the χ^2 test was used. The test level was $\alpha = 0.05$, and $P < 0.05$ was considered a statistically significant difference.

4. Results

4.1. Comparison of the Prevalence of Malocclusion between the Two Groups. In the control group, there were 10 cases of angle class I, 7 cases of angle class II, and 4 cases of angle

Table 1: Comparison of prevalence of malocclusion between two groups (n, %).

Group	Class I	Class II	Class III	Total
Control group ($n = 50$)	10 (20.00%)	7 (14.00%)	4 (8.00%)	21 (42.00%)
Observation group ($n = 52$)	18 (34.62%)	11 (21.15%)	8 (15.38%)	37 (71.15%)
χ^2 value				8.833
P value				0.003

class III, with a total of 21 cases of malformation, and the total incidence was 42.00% (21/50). In the observation group, there were 18 cases of angle class I, 11 cases of angle class II, and 8 cases of angle class III, totaling 37 cases of malformation, with a total incidence of 71.15% (37/52). The incidence of malformation in the observation group was higher than that in the control group ($P < 0.05$), as given in Table 1.

4.2. Comparison of Misshapen Angle Indexes between the Two Groups. He U1-NA and L1-NB values in the observation group were significantly higher than those in the control group (all $P < 0.05$); the differences in NPo-SN and IMPA between the two groups were not statistically significant (all $P > 0.05$), as shown in Figure 2.

4.3. Comparison of Jaw Angle Indexes between the Two Groups. The MP-SN, U1-SN, L1-MP, and Y-axis angle values were higher in the observation group than in the control group (all $P < 0.05$). There was no statistically significant difference in the comparison of SNA, SNB, and ANB between the two groups (all $P > 0.05$), as shown in Figure 3.

4.4. Comparison of Jaw Bone Length Indexes between the Two Groups. The N-Me, ANS-Me, N-Me/S-Go, and ANS-Me/N-Me values in the observation group were higher than those in the control group, and the Go-Gn values were lower than those in the control group (all $P < 0.05$); the difference between the S-Go values of the two groups was not statistically significant ($P > 0.05$), as shown in Figure 4.

5. Discussion

Maxillofacial growth and development in children are determined by a combination of genetic and environmental factors, with genetic factors playing an important role and environmental factors not being neglected. Maxillofacial growth occurs mainly during childhood and shows two growth spurts, the first between 5 and 10 years of age (the period of change from milk teeth to permanent teeth) and the second between 10 and 15 years of age [14], the first peak being also the age of high prevalence of physiological and pathological hypertrophy of the adenoids and/or tonsils. The adenoids are important immune organs in the nasopharynx, and inflammatory stimulation can lead to pathological hypertrophy and subsequent nasal congestion and nasosinusitis [15–17]. Adenoid hypertrophy occurs mostly in children and is the main cause of open-mouth breathing; adenoid hypertrophy can obstruct the upper airway in children, causing narrowing of the airway and respiratory distress; in order to better ventilate and enhance the respiratory effect, the body position of the bones and soft tissues of the maxillofacial region undergoes adaptive changes; this continuous change in body position can lead to an imbalance in the forces on the teeth and bones, resulting in abnormal development of the maxillofacial region [18]. As children are in the growth and development stage, their maxillofacial skeleton is not yet fully developed and is highly susceptible to breathing habits. Long-term open-mouth breathing can cause malfunction of the perioral muscles and soft tissues in children, which in turn affects the normal development of the child's maxillofacial skeleton and is more likely to form malformations [19, 20].

The results of this study showed that the incidence of malocclusion was higher in the observation group than in the control group, indicating that adenoid hypertrophy can significantly increase the incidence of malocclusion in children. Analysis of the reasons for this is that the airway of children with adenoid hypertrophy is blocked, the breathing pattern changes, long-term open-mouth breathing will cause the palate to lift up, and the palate high arch phenomenon occurs after the impact of airflow; it will also cause changes in oral muscle activity; the function of the closed-lip muscle decreases, causing children to open their lips and expose their teeth, which breaks the balance between oral muscles and jawbone, leading to passive movement of teeth and protrusion of upper incisors, affecting the normal development of the jawbone, thus causing malocclusion [21]. Moreover, the results of this study showed that the U1-NA and L1-NB values in the observation group were higher than those in the control group, further indicating that adenoid hypertrophy promotes the occurrence of malocclusion in children.

The results of this study showed that the MP-SN, U1-SN, L1-MP, and Y-axis angle values were higher in the observation group than in the control group, indicating that the mandibles of children with adenoid hypertrophy underwent posterior rotation and the mandibles grew posteriorly, which is partially consistent with the results of previous studies [22, 23]. The results of this study showed that the N-Me, ANS-Me, N-Me/S-Go, and ANS-Me/N-Me values were higher in the observation group than in the control group, and the Go-Gn values were lower than in the control group, indicating increased mandibular steepness in children with adenoid hypertrophy. The reasons for this are that adenoid hypertrophy causes airway obstruction and narrowing of the upper airway in children, and at this time, the lower jaw needs to be extended forward to keep the airway open, plus open-mouth breathing causes the

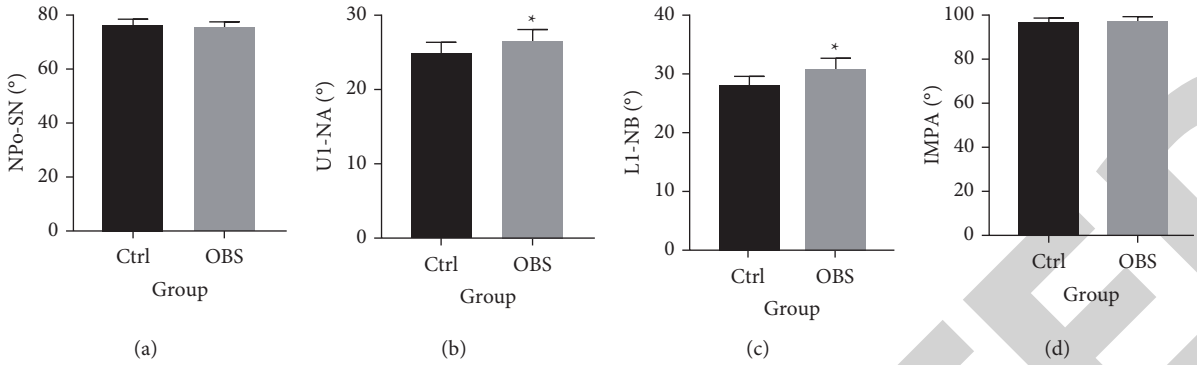

Figure 2: Comparison of misshapen angle indexes between the two groups. (a) NPo-SN. (b) UI-NA. (c) LI-NB. (d) IMPA. Compared with the control group, $^{*}P < 0.05$.

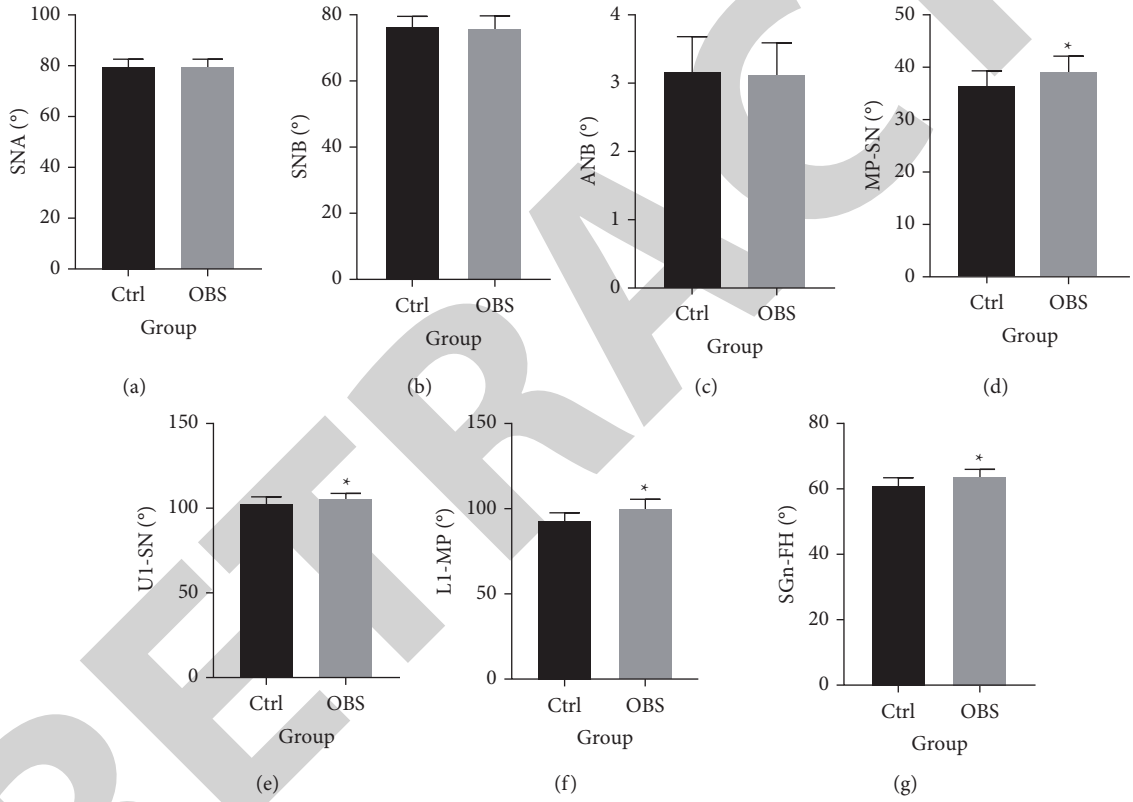

Figure 3: Comparison of jaw angle indexes between the two groups. (a) SNA. (b) SNB. (c) ANB. (d) MO-NS. (e) UI-SN. (f) LI-MP. (g) S-Go-FH. Compared with the control group, $^{*}P < 0.05$.

child's lower jaw to rotate back clockwise, increasing the steepness of the lower jaw and contributing to excessive vertical growth and development of the lower jaw, resulting in an elongated face and increased N-Me and ANS-Me [24, 25].

In conclusion, adenoid hypertrophy can increase the incidence of malocclusion in children and also increase jaw steepness, N-Me and ANS-Me, leading to an elongated facial shape and causing malformations in jaw and facial development. Therefore, we should pay more attention to adenoid hypertrophy in children and actively prevent adenoid hypertrophy from causing poor jaw and facial development. In this experiment, it was difficult to collect children without malocclusion or abnormal maxillofacial development and their guardians who were unwilling to receive X-ray radiation, so normal children were not selected as a control group in this study, and the number of study subjects in this experiment was small and the conclusions were less convincing. In the long term, when the number of cases is sufficient, the results of this experiment will be demonstrated and the effects of different degrees of hypertrophy, duration, and age on maxillofacial growth and malocclusion in normal children and children with adenoidal hypertrophy will be further studied.

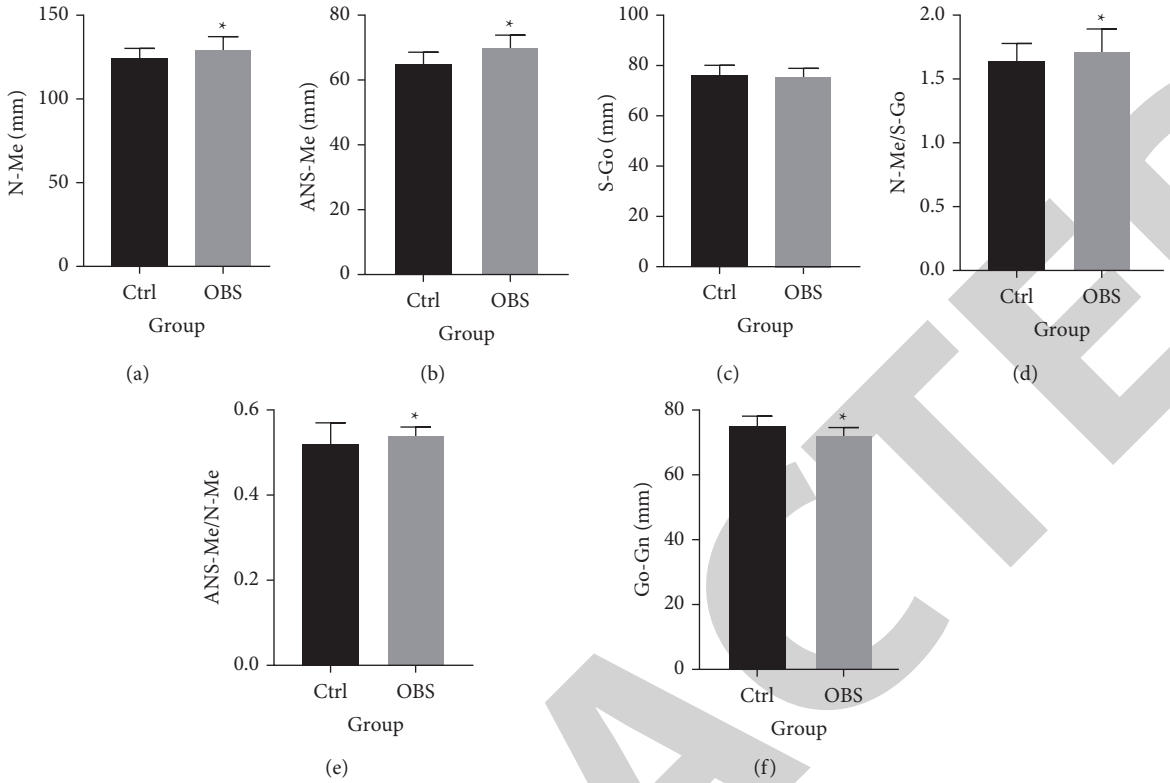

Figure 4: Comparison of jaw angle indexes between the two groups. (a) N-Me. (b) ANS-Me. (c) S-Go. (d) N-Me/S-Go. (e) ANS-Me/N-Me. (f) Go-Gn. Compared with the control group, $^{*}P < 0.05$.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study was approved by the Ethics Committee of Zhuji People's Hospital.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Research Article

Observation of Wound Healing Effect and Aesthetic Satisfaction of Patient with Second Degree Burn Wounds Treated by Kangfuxin Solution

Changhai Liu, Yuren Zhong, Cuie Wei, Fanjun Meng, Yongdong Pei, and Xiangsheng Ding

Department of Burn and Plastic Surgery, The First People's Hospital of Lianyungang, The Affiliated Lianyungang Hospital of Xuzhou Medical University, Lianyungang 222000, Jiangsu, China

Correspondence should be addressed to Yongdong Pei; peiyongdong@163.com and Xiangsheng Ding; dingxiangsheng2021@163.com

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Objective. To study the effect of wound healing and aesthetic satisfaction of patient with second degree burn wounds treated by Kangfuxin solution. *Methods*. 84 cases of burn plastic surgery in our hospital from October 2020 to October 2021 were included. All patients were randomly divided into observation group and control group with 42 cases in each group. Patients in both groups received basic treatment after admission, and patients in the control group received conventional treatment. Patients in the observation group were treated with Kangfuxin solution after admission. The clinical efficacy, wound healing time, secretion disappearance time, infection rate, and scar formation rate after treatment were compared between the two groups. The scores of patients and observer scar assessment scale (POSAS) before and after treatment were compared between the two groups, and the occurrence of adverse reactions during treatment was also compared between the two groups. *Results*. The total effective rate of the observation group was 92.86%, which was significantly higher than that of the control group (61.90%) ($P < 0.05$).The time of wound healing and secretion disappearance in the observation group was significantly shorter than that in the control group ($P < 0.05$); the infection rate and scar formation rate in the observation group were significantly lower than those in the control group ($P < 0.05$).The scores of PSAs and OSAS in the observation group were significantly lower than those before treatment and after treatment in the control group ($P < 0.05$). There was no significant difference in the total incidence of adverse reactions between the observation group (7.14%) and the control group (9.52%) ($P > 0.05$). *Conclusion*. The Kangfuxin solution has the advantages of fast wound healing, high patient satisfaction, better therapeutic effect, and high safety, which is worth clinical application.

1. Introduction

Burns are caused by various reasons, such as fire, electricity, and chemicals. Various injuries induce the damage of skin and mucosa, which affect the defense function of the skin, causing damage to the body's tissues and organs. Burns are a common injury in everyday life and work [1,2]. Burned tissue may become necrotic. In tissue burns, fluid leaks from the blood vessels causing tissue edema. In large burns, abnormal vascular permeability, loss of large amounts of fluid, and possible shock occur. Effective treatment for the patients with burns admitted to the hospital in time will avoid the adverse consequences. If the treatment is not timely or improper, severe consequences would occur, for instance infection. Severe burns can even lead to the death of the patient.

Therefore, what are the effective ways to promote the healing of patient wounds and to improve the patient's prognosis have become a key topic of physicians in burn department. The Kangfuxin solution is an ethanol extract of the dried insect body of the American cockroach, which is widely internally and externally used for anti-inflammatory

and regulatory immunity. Kangfuxin liquid is a light brown liquid with a slightly fishy smell and a sweet taste. The main component is the extract of dried American cockroaches, which contains various polyols, epidermal growth factor, amino acids, mucoglycosine, and other amino acids and other activities. Substances have the functions of anti-inflammatory, reducing swelling, promoting cell proliferation and growth of new granulation tissue, accelerating the repair of damaged parts, accelerating the shedding of necrotic tissue, and improving the body's immunity. Generally, there are two ways to use the new rehabilitation solution: internal use and external use. Oral administration is mainly for the treatment of digestive system ulcer-related diseases, such as gastric ulcer and duodenal ulcer, as well as the adjuvant treatment of pulmonary tuberculosis and hemoptysis. External application is mainly used for adjuvant treatment of wounds, with anti-inflammatory, detumescence, promoting cell proliferation and growth of new granulation tissue, accelerating the repair of damaged tissue, accelerating the shedding of necrotic tissue, and improving the immune function of the body [3,4]. Therefore, We studied the effect of Kangfuxin solution in the treatment of burn wound, and the satisfactory effect was obtained.

2. Materials and Methods

2.1. Basic Data. A total of 84 burn patients admitted to the Department of Burn and Plastic Surgery in our hospital from October 2020 to October 2021 were selected and included in the study. All patients were divided into an observation group and a control group by random number table method, with 42 cases in each group. Among the observation groups, there were 22 males and 20 females, aged 32 to 56 years old, with an average of (44.72 ± 10.64) years old; burn sites: 15 cases of face, 23 cases of limbs, and 4 cases of others; cause of burns: 15 cases of hot liquid scald, 12 cases of hot metal scald, and 15 cases of flame burns; control group: 21 males and 21 females, aged 32–56 years, mean (44.50 ± 10.42) years old; burn sites: 16 cases of face, 21 cases of limbs, and 5 other cases; reasons for burns: 16 cases of hydrothermal scald, 10 cases of hot metal scald, and 16 cases of flame burn; There was no significant difference in basic data between the two groups ($P > 0.05$), which was comparable.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria. ① All patients were diagnosed with three degrees of four-degree standards, and they were shallowed by skin II; ② they were 18 to 65 years old; ③ patients and family understood this research purpose and the method, agreed to participate, and signed an informed consent.

2.2.2. Exclusion Criteria. ① Allergic to the study drug; ② immunization and blood disease exist; ③ accompanied by severe cardiovascular disease or malignant tumors; ④ burn until admission time >24 h.

2.3. Methods. ① Basic treatment: after admission, both groups received anti-infection, wound treatment, supplemented blood volume, and corrected acid-base and water-electrolyte imbalance. ② The patients in the control group were given routine treatment after admission: gauze was soaked with iodophor (code number approved by SFDA: H65020365, batch number: 20030531, production unit: Urumqi Iodophor Disinfectant Co., Ltd.) and then applied to the wound surface, covered with oil gauze and then bandaged, dressing changed once a day, and reexamination was performed every 2 days during the treatment period, until the patient's wound healed. ③ After admission, the patients in the observation group were treated with Kangfuxin solution: the gauze was soaked with Kangfuxin solution (Z51021834, production batch number: 20150408, production unit: Sichuan Good Doctor Panxi Pharmaceutical Co., Ltd.) and then applied to the wound. Oil gauze was covered with bandages, and the dressing change time, reexamination time, and medication time were the same as those of the control group.

2.4. Observation Indicators. ① Comparing the clinical efficacy of the two groups, the two groups were evaluated at 7 days after treatment, and the clinical efficacy was markedly effective: the burn wound was completely healed, with no scar hyperplasia and no infection; scar hyperplasia was without infection; ineffective: no healing of the burn wound, and even infection. ② The wound healing time, secretion disappearance time, infection rate, and scar formation rate were compared between the two groups after treatment, and the wound healing time, time of secretion disappearing, infection rate, and scar formation rate were counted during the treatment period of the two groups of patients, respectively. ③ The patient and observer scar assessment scale (POSAS) [5] scores were compared between the two groups before and after treatment, and the two groups were evaluated at admission and 1 month after treatment, respectively. POSAS scores included patient evaluations scale (patient scar assessment scale, PSAS) and observer scar assessment scale (OSAS), PSAS is evaluated from 6 directions of scar pain, itching, color, thickness, flexibility, regularity, score ranges from 6 to 60 points, the higher the score, the more severe the scar. OSAS evaluates from 5 directions of pigmentation, color, thickness, concavity and convexity, and softness. The score ranges from 5 to 50 points. Evaluation was performed by 5 professional physicians. The higher score indicates the worse scar appearance. ④ Comparing the occurrence of adverse reactions in the two groups during treatment, and counting the incidence of adverse reactions in the two groups during treatment.

2.5. Statistical Method. SPSS19.0 statistical software was used to process the data, measurement data were expressed as $(\overline{x} \pm s)$, and t-test was used for comparison between groups; count data were expressed as (%), and X^2 test was used for comparison between groups, and $P < 0.05$ was considered a statistically significant difference.

3. Results

3.1. Comparison of Clinical Efficacy between the Two Groups. After treatment, the total effective rate of clinical efficacy in the observation group was 92.86%, which was significantly higher than that in the control group (61.90%), and the difference was statistically significant ($P < 0.05$), as shown in Table 1.

3.2. Comparison of Relevant Clinical Indicators between the Two Groups after Treatment. After treatment, the wound healing time and the disappearance time of secretions in the observation group were significantly shorter than those in the control group, and the difference was statistically significant ($P < 0.05$); the infection rate and scar formation rate in the observation group after treatment were significantly lower than those in the control group, and the difference was statistically significant ($P < 0.05$), as shown in Table 2.

3.3. Comparison of POSAS Scores between the Two Groups before and after Treatment. The PSAS and OSAS scores of the two groups after treatment were significantly lower than those before treatment ($P < 0.05$). The PSAS and OSAS scores of the observation group after treatment were significantly lower than those of the control group after treatment, and the differences were statistically significant ($P < 0.05$), as shown in Table 3.

3.4. Comparison of Adverse Reactions between the Two Groups during Treatment. There was no significant difference in the total incidence of adverse reactions in the observation group (7.14%) and the control group (9.52%) during treatment ($P < 0.05$), as shown in Table 4. The adverse reactions of the two groups of patients disappeared with the extension of time and the corresponding nursing care.

4. Discussion

There are many reasons for the formation of burns. Different patients have different burn areas, locations, and burn degrees. At the same time, affected by factors such as age and personal constitution, the clinical symptoms of patients are also different. In the past treatment, anti-infection, semi-exposure, and other methods were mostly chosen to make it heal naturally. However, the new skin formed after natural healing after injury is thin and inflexible, and it is very easy to tear and fall off, causing the patient to repeat the disease and easy to appear. Bacterial infection and scarring not only affect the clinical treatment effect but also affect the aesthetics of the skin [6, 7]. The main purpose of clinical treatment of burns is to promote wound healing, prevent infection and scar hyperplasia, and restore the normal function of the wound. In this study, Kangfuxin solution was applied externally to the wound in the treatment of burn wounds, and its clinical treatment effect and the aesthetics of wound recovery were observed to provide help for the treatment of burn wounds.

The results of this study showed that the total effective rate of clinical efficacy in the observation group after treatment was 92.86%, which was significantly higher than that in the control group, which was 61.90%, indicating that the use of Kangfuxin solution to treat burn wounds could achieve better therapeutic effects. Iodophor is one of the commonly used drugs for clinical treatment of burn wounds. It has antitoxic effect and can be used for disinfection of skin and mucous membranes. Many scholars have reported [8,9]. Kangfuxin solution is composed of a variety of amino acids, polyols, peptides and other ingredients. It has the effect of inhibiting protein and RNA synthesis and can play an anti-infective effect. At the same time, Kangfuxin solution also has the effect of improving blood circulation and promoting granulation growth. The author analyzed the specific mechanism of Kangfuxin solution in the treatment of burn wounds as follows: Kangfuxin solution can chemotaxis into fibroblast aggregation when cells proliferate, promoting the growth of granulation tissue and the formation of new blood vessels [10]; in the process of repair and reconstruction, Kangfuxin solution can strengthen the healing of wounds and promote the recovery of skin structure and function. At the same time, Kangfuxin solution also has the effect of regulating immunity, which can enhance the phagocytic ability of phagocytes and the hemolysin activity of lymphocytes. The physiological balance of the body is of great significance and is beneficial to the healing of burn wounds [11]. In this study, the higher total effective rate of the observation group may be due to the fact that Kangfuxin solution promotes the growth of granulation and regulates the body's immunity while anti-inflammatory, which improves the clinical therapeutic effect. Zhang. et al. pointed out Kangfuxin solution has anti-inflammatory, immune-regulating, and granulation-tissue-promoting effects and is fast and effective in the treatment of in vitro wounds, which is consistent with the results of this study [12].

The wound healing time and the disappearance time of secretions in the observation group after treatment were significantly shorter than those in the control group, and the infection rate and scar formation rate in the observation group after treatment were significantly lower than those in the control group, suggesting that the use of Kangfuxin solution to treat burn wounds can reduce the incidence of infection and scarring. Kangfuxin solution can be taken orally and externally and play an anti-inflammatory role and promote granulation growth effect and can also affect various cytokines such as growth factors, fibroblasts, trace elements, and epidermal cells and promote wound recovery, thereby shortening wound healing and secretion disappearance time. As for the infection rate and scar formation rate of the observation group after treatment, the author analyzed that it may be that the anti-inflammatory and anti-infective effects of Kangfuxin solution reduce the incidence of infection, while Kangfuxin solution promotes angiogenesis and accelerates the shedding of necrotic tissue. Wang et al. pointed out in an animal experiment that rehabilitation lotion has a significant effect on promoting wound healing and can shorten the healing time of wounds, which is consistent with the results of our study [13].

Table 1: Comparison of clinical efficacy between the two groups (n, (%)).

Group	Significant effect	Curative	Invalid	Total efficiency
Observation group ($n = 42$)	22 (52.38)	17 (40.48)	3 (7.14)	39 (92.86)
Control group ($n = 42$)	18 (42.86)	8 (19.05)	16 (38.10)	26 (61.90)
X^2				11.495
P				0.001

Table 2: Comparison of related clinical indicators between the two groups after treatment (n, ($\overline{x} \pm s$)).

Group	Wound healing time (d)	Time of secretion disappearing (d)	Rate of infection (%)	Scarring rate (%)
Observation group ($n = 42$)	8.24 ± 2.43	5.33 ± 1.09	1 (2.38)	2 (4.76)
Control group ($n = 42$)	13.27 ± 4.54	10.70 ± 3.75	9 (21.43)	16 (38.10)
X^2/t	6.330	8.912	5.742*	13.859
P	<0.001	<0.001	<0.001	<0.001

Note. *Continuous correction.

Table 3: Comparison of POSAS scores between the two groups before and after treatment (points, ($\overline{x} \pm s$)).

Group	POSAS			
	PSAS		OSAS	
	After treatment	Before treatment	After treatment	Before treatment
Observation group ($n = 42$)	18.20 ± 5.45	$7.44 \pm 2.78$①	15.11 ± 4.13	$8.45 \pm 2.22$①
Control group ($n = 42$)	18.24 ± 5.49	$10.46 \pm 4.21$①	15.08 ± 4.10	$11.27 \pm 3.45$①
t	0.034	3.879	0.033	4.455
P	0.973	<0.001	0.973	0.000

Note. Compared with before treatment, ① $P < 0.05$.

Table 4: Comparison of adverse reactions between the two groups during treatment (n, (%)].

Group	Vomiting	Diarrhea	Bloating	Fever	Headache	Total incidence
Observation group (n = 42)	0 (0.00)	1 (2.38)	1 (2.38)	0 (0.00)	1 (2.38)	3 (7.14)
Control group (n = 42)	1 (2.38)	0 (0.00)	1 (2.38)	1 (2.38)	1 (2.38)	4 (9.52)
X^2/t						0.000*
P						1.000

Note. *Continuous correction.

The PSAS and OSAS scores in the observation group after treatment were significantly lower than those before treatment and after treatment in the control group, indicating that Kangfuxin solution treatment of burn wounds can reduce the incidence of scar formation, the wounds recovered well after treatment, and the patients were highly satisfied. The author believes that this is closely related to Kangfuxin solution accelerating the formation of new blood vessels, promoting the production of granulation tissue, and accelerating the shedding of necrotic tissue, which can effectively reduce the probability of scarring and improve the satisfaction of wound healing. In terms of safety, the total incidence of adverse reactions in the observation group was 7.14% and the control group was 7.14%, and there was no significant difference. It can be seen that the use of Kangfuxin solution to treat burns does not increase adverse reactions and has high safety. This is consistent with the results reported by Heuch and Streak Gomersall [14].

In summary, the Kangfuxin solution treatment of burn wound is fast, and the infection rate of the treatment is high, the scar formation rate is low, the clinical treatment is improved, and the patient satisfaction after treatment is high, the drug is safe, and it has a high clinical application value.

Data Availability

The data can be obtained from the corresponding author upon reasonable request.

Ethical Approval

The study has been approved by the medical ethics committee of the hospital.

Disclosure

Changhai Liu and Yuren Zhong are co-first authors.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Retraction

Retracted: Hyal1 Expression in Colorectal Carcinoma Cell Migration and Invasiveness: Significance and Mechanism

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] S. Zhao, J. Zhao, and N. Zhang, "Hyal1 Expression in Colorectal Carcinoma Cell Migration and Invasiveness: Significance and Mechanism," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4418300, 5 pages, 2022.

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Research Article

Hyal1 Expression in Colorectal Carcinoma Cell Migration and Invasiveness: Significance and Mechanism

Shuangshuang Zhao,[1] Junhui Zhao,[2] and Ni Zhang [1]

[1]*Department of Radiation Oncology, Hangzhou Cancer Hospital, Hangzhou, Zhejiang 310002, China*
[2]*College of Basic Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310002, China*

Correspondence should be addressed to Ni Zhang; zhangni7575@sina.com

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Objective. To clarify the significance of hyaluronidsase 1 (Hyal1) expression in colorectal carcinoma (CRC) and its impact on tumor cell migration and invasiveness. *Methods*. Human CRC cell lines SW480, HCT116, and SW620 were purchased, ELISA and western blot were used to detect the expression of Hyal1 in cells, CCK-8 assay to detect cell proliferation ability, cell scratch assay to check cell migration rate, and cell invasion was detected by the transwell assay. The correlation of Hyal1 with CRC cell migration and invasiveness capacities was analyzed. *Result*. ELISA results showed that supernatant Hyal1 level was the lowest in SW480, highest in HCT116, with the level in SW620 in between ($P < 0.05$). No evident difference was identified by western blot in Hyal1 protein expression among the three cells ($P > 0.05$). The cell scratch assay and transwell assay showed that the migration and invasion ability of HCT116 cells was higher than that of SW620 ($P < 0.05$). In vitro, Hyal1 had a synergistic relationship with the invasiveness and migration capacities of CRC cells ($P < 0.05$). *Conclusion*. Hyal1 is elevated in CRC and is consistent with the invasiveness and metastasis abilities of CRC cells. It is hoped that this research can provide reference for future prevention and treatment of CRC.

1. Introduction

Colorectal carcinoma (CRC) is one of the most common malignant neoplastic diseases, second only to lung and gastric carcinomas. Statistics show that in 2018, there were over 1.8 million new CRC cases around the world, with the majority of them aged over 40 [1]. Recent years have witnessed the growing incidence of CRC, and it is expected that by 2030, CRC will become the malignancy with the highest incidence [2]. At present, the pathogenesis of CRC has not yet been fully clarified, but it is believed to be strongly linked to environment, diet, genetics, and other factors in clinical practice [3]. The disease usually has strong concealment in the early stage of illness, which may only be manifested as diarrhea, constipation, and other changes in defecation habits, and as the disease progresses, bloody stools and fatigue begin to appear [4]. This also directly leads to the fact that most CRC patients have reached the middle and late stage at the time of diagnosis when CRC has a high possibility of metastasis and invasiveness, which seriously increases the difficulty of treatment and leads to a bleak prognosis of patients [5]. According to the survey, the 5-year mortality rate of advanced CRC patients is as high as 60–80%, with approximately 900,000 deaths each year due to CRC [6]. Due to the high morbidity and mortality of the disease, clinical work in recent years has been focused on finding new diagnostic and treatment options for CRC, with a focus on molecular pathogenesis.

In 2016, a phase IB clinical study on PEGylation of recombinant human hyaluronidase PH20 (PEGPH20) in the treatment of pancreatic carcinoma found that via removing hyaluronic acid from the extracellular matrix, PEGPH20 can dilate pancreatic carcinoma blood vessels, and increase the gap between tumor vascular endothelial cells and fenestrations to achieve chemosensitization

effects [7], which has aroused people's attention to hyaluronidases (Hyals) in neoplastic diseases. Hyaluronidase 1 (Hyal1), a vital member of the five Hyals, has been shown to promote cell proliferation and motility by accelerating vesicle motility [8], but its relationship with CRC is still unclear. In previous studies, we found that Hyal1 is the only Hyals that can be detected in plasma, and its expression level is closely related to the disease changes of CRC [9]. A large number of basic studies and clinical trials have shown that the expression level of Hyal1 is positively correlated with the occurrence and development of CRC. Bouga et al. found that Hyal1, Hyal2, Hyal3, and PH20 were obviously overexpressed in CRC and normal tissue extracts, with the highest expression in the late stage [10]. From the clinical data, it can be seen that Hyal1 promotes CRC occurrence and development. However, there is no other related research that can further confirm the influencing mechanism of Hyal1 on CRC. Therefore, we initially analyze the role of Hyal1 in CRC in the face of the increasing incidence of CRC by detecting Hyal1 in colon carcinoma (CC) cell lines with different metastatic potential.

2. Data and Methods

2.1. Cell Data. SW480, SW620, and HCT116, which were human CRC cell strains, were supplied by the Cell Bank of Chinese Academy of Sciences Shanghai Branch. The above cells were then cultured. The medium was RPM1640 plus fetal bovine serum diluted at 10% as well as penicillin-streptomycin at the concentration of 100 U/ml, and the conditions were 37°C and 5% CO_2 in air.

2.2. Detection of Hyal1 Levels in Cells. ELISA and western blot detected supernate Hyal1 expression. ELISA kits were provided by Wuhan Fine Biotech, and the operation process was carried out in strict accordance with the manufacturer's recommendations. In addition, RIPA lysate was used to lysate the cells and extract the total protein. After the purity was verified, the proteins were transferred to PVDF membranes via SDS-PAGE electrophoresis, and the primary antibodies Hyal1 (1 : 500) and β-actin (1 : 1,000) were added and blocked overnight at 4°C. After the primary antibody incubation overnight, the membrane was washed with TBST five times for a total of 35 min. The second antibody (1 : 1,000) was added for 1 hour incubation. Then, the secondary antibody is also washed with TBST five times and the gray value of proteins was analyzed by ImageJ software.

2.3. Cell Multiplication Testing. Cells (5×10^3/well) were inoculated in the wells of a 96-well plate for 6 days of cultivation, and the solution was changed every 2 days. Ten microliters of CCK-8 reagent were added to each well at an interval of 24 h and incubated for 2 h at 37°. The absorbance$_{450nm}$ value was read with the use of a microplate reader, and the growth curve was plotted.

2.4. Cell Migration Testing. After the cells were digested and plated, 5×10^5 cells were added to each well. When the cells covered the bottom of the plate, the 20 μL pipette tip was used to draw lines vertically. After the old medium was aspirated, PBS was applied twice to remove the cells scratched by the pipette tip. Then, a culture medium comprising 1% FBS was added to each well, and the cell migration distance was observed and the mobility was calculated after 24 hours of continuous culture.

2.5. Cell Invasiveness Testing. The logarithmic growth cells were digested, resuspended, and inoculated into the upper chamber of the transwell chamber at 2.5×10^5/ml. A complete culture medium (500 μL) was added to the lower chamber for 48 h. The chamber was removed, Matrigel was wiped with *Q*-tips, and the transmembrane cells were stained with 95% ethanol and 1% crystal violet after washing with PBS, for microscopical counting.

2.6. Statistical Processing. Data was processed by SPSS22.0. Quantitative data were recorded by ($\chi \pm s$), and the differences were determined via independent sample *t*-test. The comparison of three and more groups used one-way ANOVA. $P < 0.05$ was the threshold of significance.

3. Results

3.1. Hyal1 Expression in CRC Cells. ELISA showed no distinct difference in supernatant Hyal1 expression in HCT116 and SW620 cells at 48 h ($P > 0.05$), higher than SW480 ($P < 0.05$). At 72 h, supernatant Hyal1 level was the lowest in SW480, highest in HCT116, with the level in SW620 in between ($P < 0.05$). No evident difference was identified by western blot in Hyal1 protein expression among the three cells ($P > 0.05$) (Figure 1).

3.2. Impacts of Hyal1 on CRC Cell Proliferation. As indicated by CCK-8 experimental results, the three cells had similar proliferation ability ($P > 0.05$) (Figure 2).

3.3. Impacts of Hyal1 on CRC Cell Migration. In the scratch assay, highest cell migration was observed in HCT116 and lowest in SW480, with that of SW620 in between ($P < 0.05$) (Figure 3).

3.4. Impacts of Hyal1 on CRC Cell Invasion. Similarly, the Transwell test showed highest invasiveness in HCT116, followed by SW620, with that of SW480 being the lowest ($P < 0.05$) (Figure 4).

4. Discussion

As one of the most frequently occurring tumors in clinical practice, the potential threat of CRC to patients deserves clinical attention [11, 12]. At present, the research on small molecule RNAs in neoplastic diseases is the focus of clinical research. As an important substance participating in

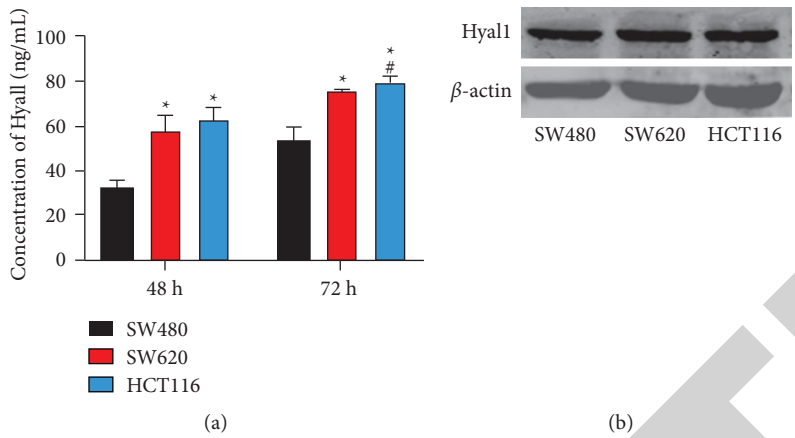

Figure 1: Hyal1 expression in CRC cells. (a) The expression of Hyal1 was detected by ELISA. (b) The expression of Hyal1 was detected by western blot. Compared with SW480, $^{*}P < 0.05$. Compared with SW620, $^{\#}P < 0.05$.

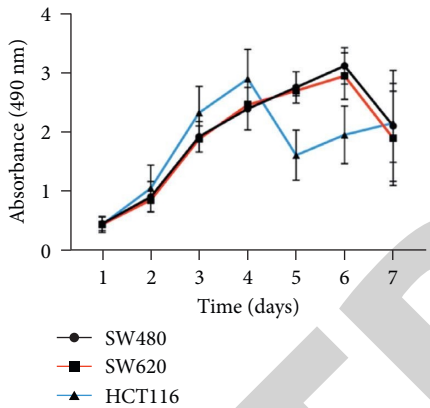

Figure 2: Impacts of Hyal1 on CRC cell proliferation.

multiple life cycles of human organs, tissues and cells, the significance of small molecule RNA research lies in the following aspects: (1) they are expected to become new clinical markers that can assist in assessing the occurrence and development of tumour diseases; (2) as molecular therapeutic targets for neoplastic diseases, they can be used to optimize the killing effect of current radiotherapy and chemotherapy on tumor cells [13, 14]. For Hyal1, it has been confirmed to present abnormal expression in bladder carcinoma, pancreatic carcinoma and other diseases [15–17], but there is still a lack of relevant studies to confirm its exact role in occurrence and development of CRC. Therefore, this study, by exploring the connection between Hyal1 and CRC, has great reference significance for clinical practice, which can also lay a foundation for follow-up research.

In this experiment, we found that Hyal1 expression had a synergistic effect with the invasiveness and migration of CRC cells, and the cells with higher Hyal1 expression had significantly stronger activity, which shows that highly expressed Hyal1 plays the role of oncogene in CRC. However, Hyal1 was found to be in a low expression state in the studies of Puissant et al. [18, 19], contrary to our findings. Based on previous studies, we believe that whether Hyal1 promotes or inhibits tumor formation depends on two factors, one is the tumor type, and the other is the concentration of Hyal1. Lokeshwar et al. showed that Hyal1 inhibited or promoted the formation of prostate carcinoma (PC) depending on the level of Hyal1 in PC tissues and cells. At the background level, Hyal1 promotes the growth, invasiveness, and vascular formation of PC, but when Hyal1 is overexpressed by gene transfection (Hyal1 > 100 milliunits/10^6 cells), it inhibits PC formation and growth via inducing apoptosis [20]. When Jacobson tested Hyal1 expression in a Hyal1-overexpressed model of rabbit CC cells, it was found that Hyal1 reached 220–360 milliunits/10^6 cells, far exceeding the background level of 20 milliunits/10^6 cells of CC cells [21]. Therefore, in this study, the high level of Hyal1 is consistent with the high invasiveness and metastasis capacities of CC, which preliminarily indicates that upregulated Hyal1 promotes the occurrence and development of CRC.

Inhibition of Hyal1 has been shown to inhibit tumor formation of PC and bladder carcinoma, where Hyal1 overexpression is most typical [22]. Sulfated hyaluronan (sHA), as an inhibitor of Hyal1, can inhibit PC cell growth, migration, and infiltration, downregulate Bcl-2 and p-Bad to induce apoptosis, and downregulate androgen receptor activation, NFkb activation, and VEGF expression via inhibiting the PI3K-AKT axis, which has been verified in animal models [23]. In bladder carcinoma, sHA also inhibits tumor formation by suppressing PI3K-AKT axis [24]. Therefore, the inhibition of Hyal1 is a novel approach for the treatment of Hyal1-overexpressed tumors, and inhibiting Hyal1 provides a new idea and method to treat CRC. However, at present, sHA is the only one known to inhibit cell function among Hyal1 inhibitors [25]. In the future, we plan to apply the Hyal1 inhibitor sHA to CC cells and detect its inhibition on CRC cell function. Besides, we need more experiments to verify Hyal1 expression in CRC, and further confirm its impacts on CRC *in vivo* through tumorigenesis experiments in nude mice.

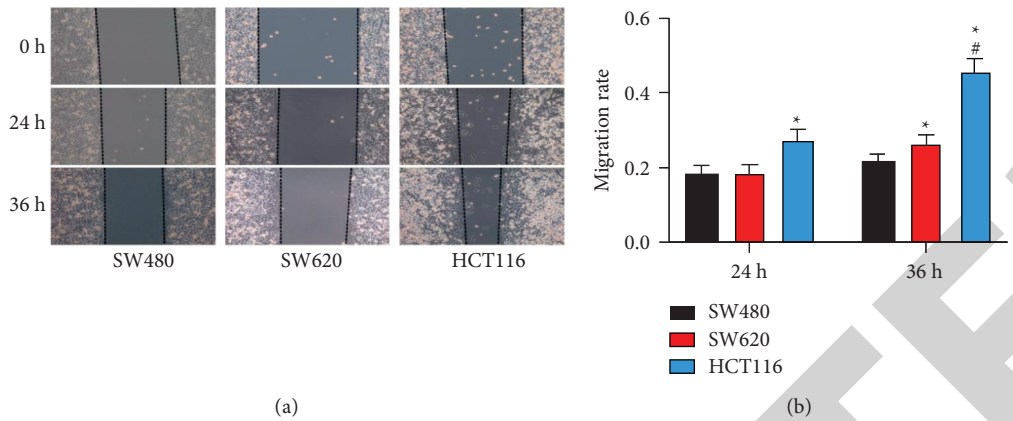

Figure 3: Impacts of Hyal1 on CRC cell migration. (a) Cell scratch assay. (b) Cell migration rate. Compared with SW480, $^{*}P < 0.05$. Compared with SW620, $^{\#}P < 0.05$.

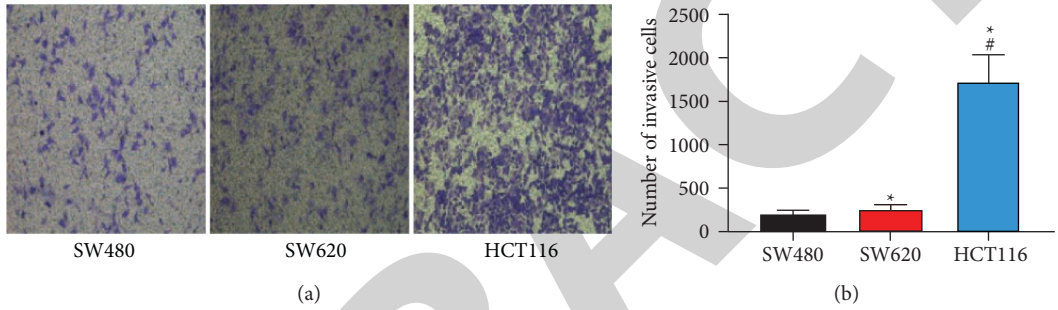

Figure 4: Impacts of Hyal1 on CRC cell invasion. (a) Invasive cell staining. (b) Number of cells invaded. Compared with SW480, $^{*}P < 0.05$. Compared with SW620, $^{\#}P < 0.05$.

5. Conclusion

This study finds that Hyal1 expression remains at a high level in CRC, which is consistent with the capacities of CRC cells to invade and metastasize. Also, it was initially shown that upregulated Hyal1 promoted the occurrence and development of CRC. Inhibition of Hyal1 inhibits tumor formation of CRC. It is hoped that this research can provide reference for future prevention and treatment of CRC.

Data Availability

The data can be obtained from the author upon reasonable request.

Conflicts of Interest

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Retraction

Retracted: The Effectiveness Comparison of Different Acupuncture-Related Therapies on Knee Osteoarthritis: A Meta-Analysis

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

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[1] C. Ye, J. Zhou, M. Wang, S. Xiao, A. Lv, and D. Wang, "The Effectiveness Comparison of Different Acupuncture-Related Therapies on Knee Osteoarthritis: A Meta-Analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2831332, 6 pages, 2022.

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Research Article

The Effectiveness Comparison of Different Acupuncture-Related Therapies on Knee Osteoarthritis: A Meta-Analysis

Chun Ye,[1] Jianlong Zhou,[2] Miaofen Wang,[3] Shasha Xiao,[4] Aihua Lv,[1] and Dejin Wang[4]

[1]*Department of Emergency, Ningbo Traditional Chinese Medicine Hospital, Ningbo, Zhejiang Province 315010, China*
[2]*Hand and Foot Trauma Surgery, Ningbo Ninth Hospital, Ningbo, Zhejiang Province 315032, China*
[3]*Department of Traditional Chinese Medicine, Community Health Service Center, Baihe Street, Yinzhou District, Ningbo City, Zhejiang Province 315153, China*
[4]*Department of Acupuncture and Moxibustion, Ningbo Medical Centre Lihuili Hospital, Ningbo University, Ningbo, Zhejiang 315040, China*

Correspondence should be addressed to Dejin Wang; wdj_911@sina.com

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Objective. This meta-analysis aims to assess the efficacy of acupuncture-related therapy on knee osteoarthritis (KOA) patients. *Method*. We searched PubMed, Embase, and CNKI databases to screen eligible trials between 2017 and 2022. All trials that used acupuncture/moxibustion of KOA patients were included. Study selection and data extraction were performed by 2 researchers independently. The statistics was performed by using R 4.1.1. *Results*. A total of 17 trials were included in our meta-analysis. Meta-analysis results showed the evidence of the relation of several common acupunture/moxibustion treatments by network meta-analysis. In the fixed effect model, acupuncture/moxibustion has superior therapy efficacy than sham treatment (mean difference = −0.34, 95% confidence interval = (−0.52,−0.16), $P = 0.95$). In fixed effect model, specific acupuncture/moxibustion has superior therapy efficacy than usual acupuncture/moxibustion (mean difference = –0.45, 95% confidence interval = (−0.62, −0.29), $P < 0.01$). *Conclusion*. Acupuncture/moxibustion has superior therapy efficacy than sham treatment. Specific acupuncture/moxibustion has superior therapy efficacy than usual acupuncture/moxibustion.

1. Introduction

Osteoarthritis (OA) is the most frequent reason for activity limitation in adults and is the most common type of arthritis [1, 2]. OA affects more than 240 million people in the world [1]. Patients with OA have more comorbidities than those without OA. Common management exercises, weight loss, education, and oral nonsteroidal anti-inflammatory drugs for patients without contraindications is given [3, 4]. Knee osteoarthritis (KOA) is the most common type of OA clinically [4–6]. Acupuncture and moxibustion are frequent traditional treatments for Chinese KOA patients.

Acupuncture and moxibustion are two traditional medical treatments in Chinese for thousands of years [7, 8]. Clinically, acupuncture and moxibustion are frequently used to apply to KOA [9, 10]. However, the effectiveness of acupuncture on KOA is still controversial. Acupuncture is considered to have little or no effect in reducing pain compared with sham treatment [4]. The evidence of the effectiveness of acupuncture on OA is limited and conflicting. We conduct this meta-analysis to investigate the therapeutic efficacy of acupuncture/moxibustion of KOA.

2. Method

2.1. Literature Search. We searched PubMed, Embase, and CNKI to identify trials published from 2017 to 2022.

We searched PubMed with worlds "*osteoarthritis Acupuncture*" in all fields and limit to "*Clinical trial*" and "*Randomized Controlled Trial*" from 2017 to 2022.

We searched Embase PICO with the following strategy that "osteoarthritis"/exp AND "acupuncture"/exp AND "clinical trial"/exp AND [2017–2022]/py.

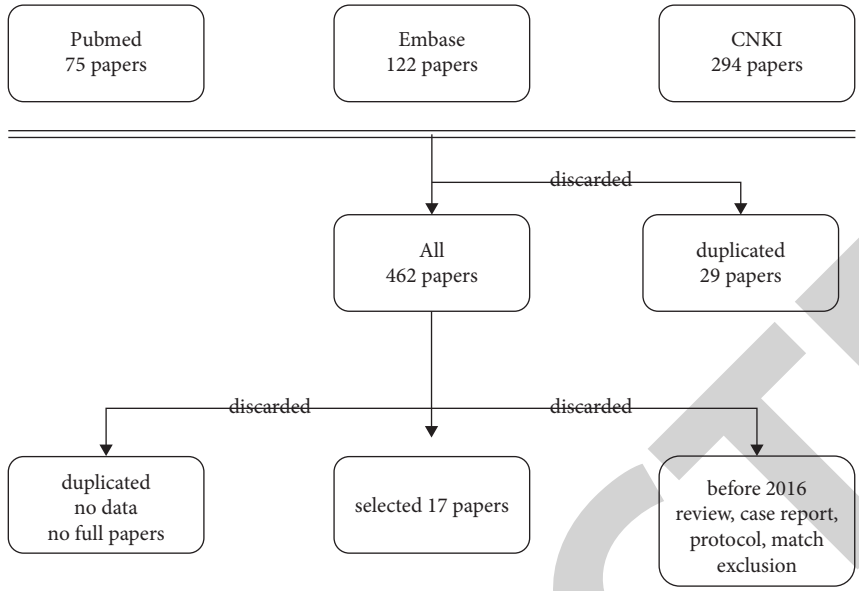


Figure 1: Flowchart of study screening.

We searched CNKI with the following strategy in Chinese that *osteoarthritis Acupuncture* in *theme*. (Subject: Knee Arthritis (Precise)) AND (Subject: Acupuncture or Moxibustion (Precise)).

2.2. Inclusion Criteria. We included patients with KOA. Studies conducted interventions that moxibustion and acupuncture were included in our study. Acupuncture that electroacupuncture, manual acupuncture, and some other specific acupunctures were included. The intervention duration was usually 4 weeks or 8 weeks.

2.3. Exclusion Criteria. The intervention of literature that included pharma, rehabilitation, or excise was excluded from our study. Literature review, case report, or protocols were excluded.

2.4. Outcomes and Data Extraction. The primary outcome was the response rate after interventions. The secondary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function scale. The two outcomes were extracted from the original literature. Two researchers conducted literature selection individually.

2.5. Statistical Analysis. We performed network meta-analyses to compare data from individual trials. Fixed effects meta-analyses were used to incorporate data from individual trials separately. Effects on continuous outcomes were measured by mean differences (MDs). Sensitivity analyses were performed to test the robustness of the estimates so that the exclusion of studies was with a high overall risk of bias. The *gemtc*, *rjags*, and *meta* package in R version 4.1.1 were used for the statistic and plotting.

3. Results

3.1. Study Screening. We found 462 papers in PubMed, Embase, and CNKI. After literature selection, we finally selected 17 papers for our study (Figure 1). All of the 17 studies reported the primary outcome and 10 of them report the WOMAC function score. The control arm was sham acupuncture or sham moxibustion in 5 of the 17 studies. The control arm was acupuncture in 6 of the 17 studies (Table 1).

3.2. Network of the Response Rate. In all selected 17 literature, the relationship between acupuncture and electroacupuncture and the relationship between acupuncture and moxibustion show stronger evidence than other acupuncture-related treatments (Figure 2).

3.3. Comparison between Acupuncture/Moxibustion and Sham Treatment. 5 studies reported WOMAC functional scores. When a paper published by Zhao 2021 [20] is included, $I^2 = 95\%$ (Figure 3(a)). We next did sensitivity analysis of these 5 literature. Also, the paper by Zhao et al. [20] showed a high overall risk of bias (Figure 3(b)). So, we excluded the paper by Zhao et al. [20] and analyzed it again (Figure 3(c)). As shown in Figure 3(c), in the fixed effect model, acupuncture/moxibustion had a superior therapy effect than sham treatment.

3.4. Comparison between Specific Acupuncture and Usual Acupuncture. We compared specific acupuncture/moxibustion vs. usual acupuncture in the fixed effect model. As shown in Figure 4(a), specific acupuncture/moxibustion had a superior therapy effect than usual acupuncture. Also, the sensitivity analysis of the 6 papers was not shown a risk of bias (Figure 4(b)).

Table 1: Patients' characteristic of the included studies.

Author	year	Experiment	Fluquency	Duration time	e.N	e.WOMAC function score	Control	con.N	con.WOMAC function score
Ton et al. [11]	2021	Acupuncture	—	—	120	—	No acupuncture	179	—
Wang et al. [12]	2020	Electroacupuncture	—	8w	15	—	Sham electroacupuncture	15	—
Chen et al. [13]	2020	Electroacupuncture	—	—	28	—	Acupuncture	28	—
Liang et al. [14]	2019	Soft-tissue relaxing needing	1 time/2 d	4times	20	—	Electroacupuncture	20	—
Chen et al. [15]	2018	Acupuncture	—	—	30	—	-	—	—
Chen et al. [15]	2018	Aconite cake-separated moxibustion	—	—	30	—	Moxibustion	30	—
Deng et al. [16]	2020	Stuck-needle technique	—	—	33	—	Regular acupuncture	32	—
Wang et al. [17]	2017	Warm needling moxibustion	—	—	25	11.0 ± 8.99	Sham	21	15.86 ± 11.30
Wang et al. [18]	2020	Electroacupuncture	—	8 W	43	11.39 ± 7.34	Acupuncture	30	14.86 ± 8.06
Shi et al. [19]	2020	Electroacupuncture	—	8 w	28	11.39 ± 7.34	Manual acupuncture	30	14.86 ± 8.06
Zhao et al. [20]	2021	Laser moxibustion	—	4 w	193	11.69 ± 14.19	Sham laser control group	177	1.38 ± 6.35
Lin et al. [21]	2020	Intensive acupuncture	3 sessions/w vs.1 session/w	8 w	30	14.5 ± 8.3	Acupuncture	30	17.5 ± 6.9
Chen et al. [22]	2020	Moxibustion	—	4 w	28	14.86 ± 4.03	Acupuncture	28	23.75 ± 6.88
Yu W	2021	Acupuncture	—	—	61	27.89 ± 16.85	Sham acupuncture	31	32.58 ± 18.58
Fu et al. [23]	2021	Fire needling	—	2 w	26	7.92 ± 3.89	Regular acupuncture	26	11.58 ± 7.60
Tu et al. [24]	2021	Electro-acupuncture	3 times/w normal, 3 times/w, 20 w	8 w	151	9.26 ± 7.03	Sham acupuncture	146	11.78 ± 8.17
Fu et al. [25]	2020	Miao crossbow needle		46 d	149	9.35 ± 6.73	Acupuncture	152	11.41 ± 7.49

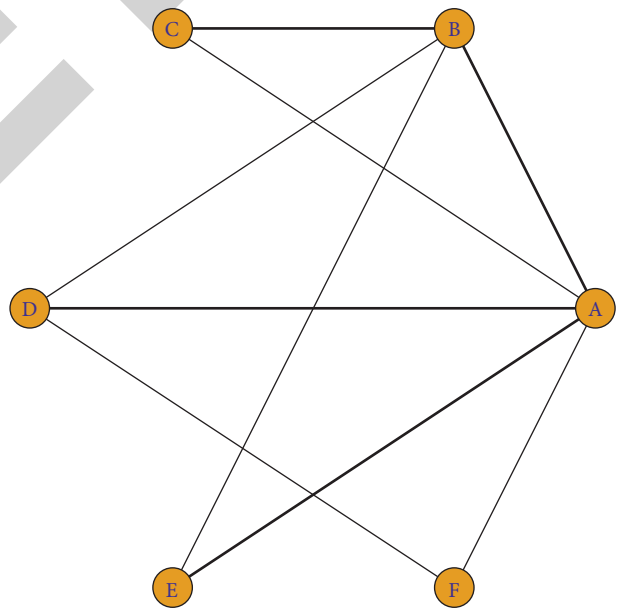
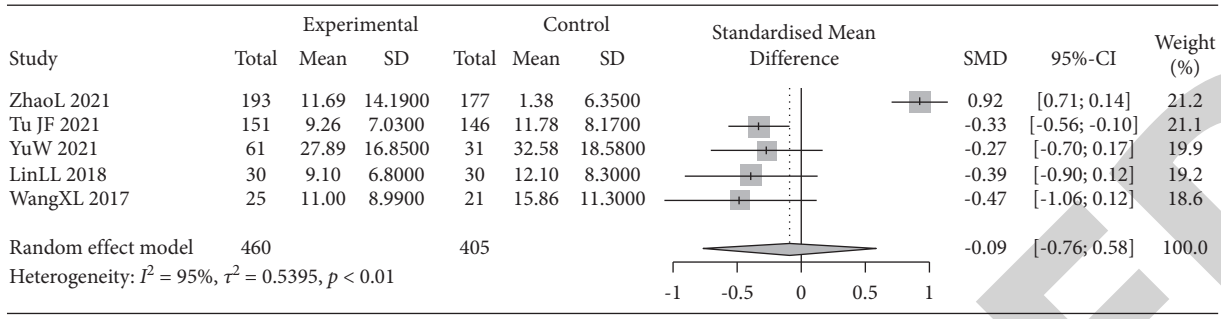
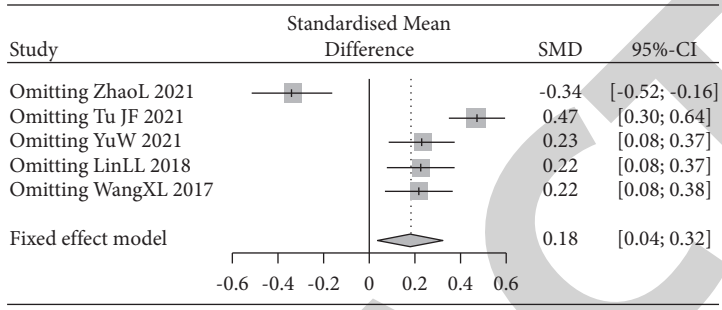


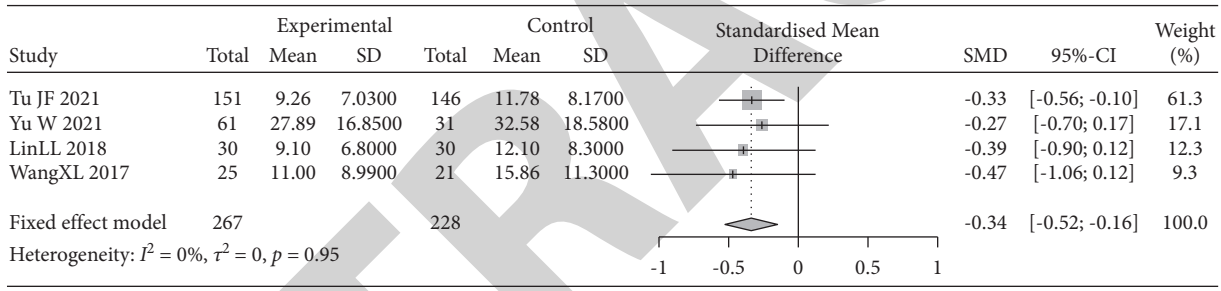
Figure 2: Network of the response rate of the selected papers. A: acupuncture; B: electroacupuncture; C: sham; D: moxibustion; E: special acupuncture; F: special moxibustion.



(a)

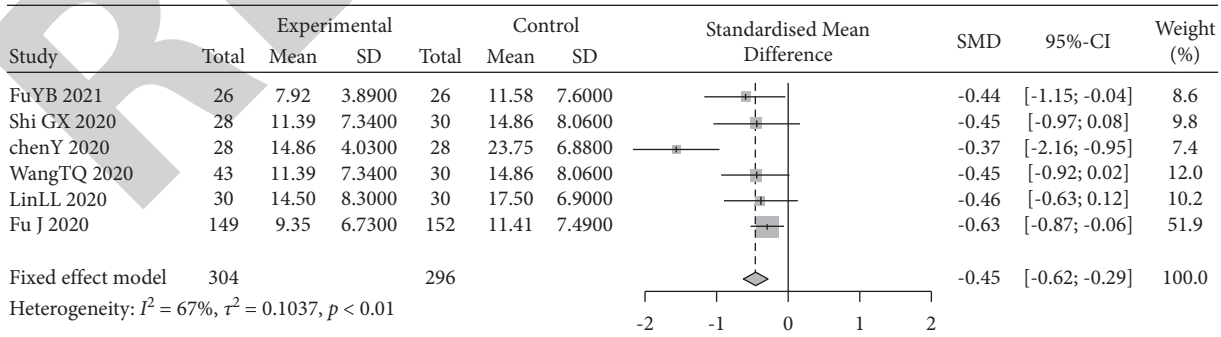


(b)



(c)

Figure 3: Analysis of comparison between acupuncture/moxibustion vs. sham treatment. (a) Forest plot of data included in the study by Zhao et al. [20]. (b). Sensitivity analysis of data included in the study by Zhao et al. [20]. (c). Forest plot of data without the study by Zhao et al. [20].



(a)

Figure 4: Continued.

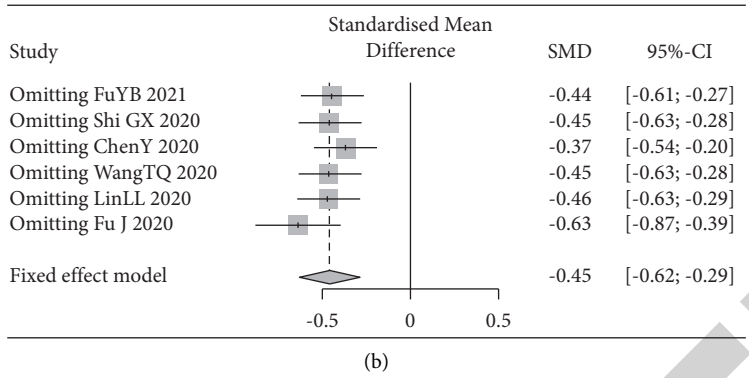


Figure 4: Analysis of comparison between specific acupuncture/moxibustion vs. usual acupuncture. (a) Forest plot of specific acupuncture/moxibustion vs. usual acupuncture. (b) Sensitivity analysis of the 6 literature.

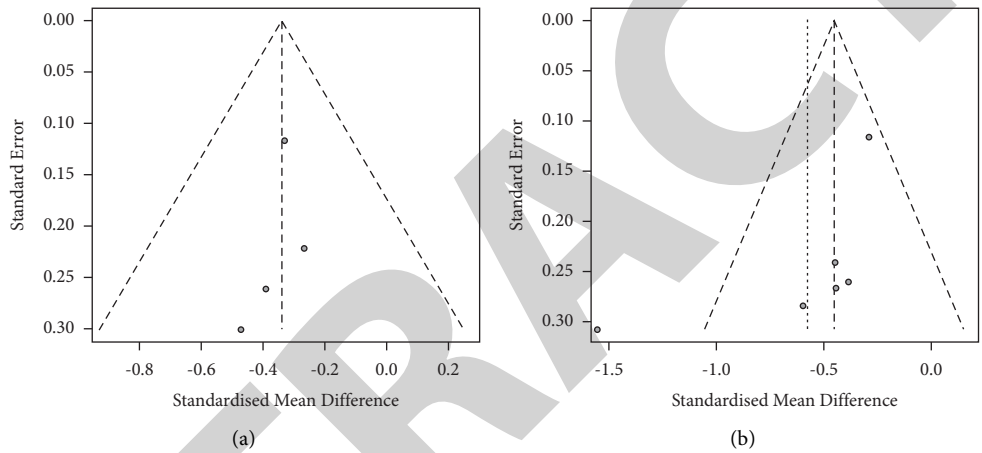


Figure 5: Funnel plot of the papers reported WOMAC. (a) Funnel plot of comparison of acupuncture/moxibustion and sham treatment. (b) Funnel plot of comparison of specific acupuncture/moxibustion and usual acupuncture.

3.5. Publish Bias. A significant publication bias was found for both the comparison of acupuncture/moxibustion vs. sham treatment and the comparison of specific acupuncture/moxibustion vs. usual acupuncture (Figures 5(a) and 5(b)).

4. Discussion

The meta-analysis included 17 trials to assess the efficacy of acupuncture/moxibustion in treating KOA. Network analysis of the comparison between acupuncture/moxibustion, sham treatment, or specific acupuncture/moxibustion shows that evidence mainly among the relation between acupuncture, electroacupuncture, and moxibustion in KOA patients (Figure 2). Meta-analysis of comparison between acupuncture/moxibustion vs. sham treatment shows that acupuncture/moxibustion has superior therapy efficacy to sham treatment in KOA patients on WOMAC function (Figure 3). Meta-analysis of comparison between specific acupuncture/moxibustion has superior therapy efficacy than usual acupuncture in KOA patients on WOMAC function (Figure 4). Herein, the effects of acupuncture and moxibustion therapy on the WOMAC function scale were investigated. We compare the WOMAC function score for most studies that have reported it. Moreover, electroacupuncture was superior to sham treatment.

In Liu et al.'s study, the result of a network meta-analysis was to draw a familiar conclusion to our analysis [26]. Similar to our result, moxibustion is effective and the level of evidence is moderate in Choi et al.'s paper [27]. A meta-analysis of previous online studies on the subject found that warm needle and electroacupuncture were probably the best acupuncture modalities for treating KOA [28]. Lots of papers report the efficacy of acupuncture [26, 28, 29]. However, few of them have firm foundation data. That is why the efficacy of acupuncture and moxibustion is contradictory in the world.

Because acupuncture and moxibustion are traditional therapy in China and most of the literature has come from China, there is an unavoidable publish bias that existed. The low quality of the selected literature may lead to adventurous conclusions, which should be carefully analyzed.

In conclusion, our meta-analysis indicated that acupuncture/moxibustion has superior therapeutic efficacy than sham treatment. Also, specific acupuncture/moxibustion has superior therapy efficacy than usual acupuncture/moxibustion.

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Retraction

Retracted: Serum Cystatin C Level Monitoring for Intervention Opportunity of CBP in Children with Severe Sepsis

Evidence-Based Complementary and Alternative Medicine

Received 18 July 2023; Accepted 18 July 2023; Published 19 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] W. Wang, Y. Qiang, Z. Tao et al., "Serum Cystatin C Level Monitoring for Intervention Opportunity of CBP in Children with Severe Sepsis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 8571203, 6 pages, 2022.

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Research Article

Serum Cystatin C Level Monitoring for Intervention Opportunity of CBP in Children with Severe Sepsis

Weikai Wang,[1] Yi Qiang,[2] Zhongbin Tao,[3] Baowang Yang,[4] Bin Yan,[5] Xilong Chen,[5] and Ruifeng Xu[5]

[1]*Department of PICU, Gansu Provincial Maternity and Child-Care Hospital, The First Clinical Medical College of Gansu University of Chinese Medicine, Lanzhou 730050, Gansu, China*
[2]*Cardiovascular Diseases Center, Gansu Provincial Maternity and Child-Care Hospital, Lanzhou 730050, Gansu, China*
[3]*Department of PICU, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu, China*
[4]*Department of PICU, The Second Hospital of Lanzhou University, Lanzhou 730030, Gansu, China*
[5]*Department of PICU, Gansu Provincial Maternity and Child-Care Hospital, Lanzhou 730050, Gansu, China*

Correspondence should be addressed to Ruifeng Xu; xuruifeng0413@163.com

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Objective. The aim of this study is to investigate the instruction value of the serum cystatin C (Cys C) level monitoring for intervention opportunity of continuous blood purification technology (CBP) in children with severe sepsis. *Methods.* 67 children with severe sepsis in the pediatric intensive care unit (PICU) with CBP treatment were retrospectively selected from May 2016 to April 2020. According to the time intervals between the time point of serum Cys C level began to increase (>15 mg/L) and the time point of CBP began, all children were divided into group A (<24 h, 29 cases), group B (24–48 h, 22 cases), and group C (>48 h, 16 cases). The children's general characteristics, vital signs, biochemical parameters, acute physiology and chronic health evaluation (APACHE II), and sequential organ failure assessment (SOFA) scores were evaluated. The influence factors of prognosis of children with severe sepsis were analyzed by multivariate regression analysis. *Results.* The intervals between the time point of PICU hospitalization and the time point of CBP began and the times of CBP in group A were significantly more than those in group B and C ($P < 0.05$). There was no statistically significant duration of CBP among three groups ($P > 0.05$). After follow-up of 28 d, there was no significant difference on the occurrence of coagulation disorders and hypovolemic shock induced by CBP among three groups ($P > 0.05$). However, the mortality of children in group A was lower than that in group C ($P < 0.05$). Children in group A had lower APACHE II scores, SOFA scores, serum K+, blood urea nitrogen (BUN), serum creatine (SCr), partial pressure of carbon dioxide (PCO_2), and higher partial pressure of oxygen (PO_2) than those of children in group C after CBP. ($P < 0.05$). SOFA scores ≥5 after CBP treatment and the time intervals between the time point of serum Cys C level began to increase (>15 mg/L) and the time point of CBP began ≥24 h were the independent influence factors on the prognosis by multivariate regression analysis. *Conclusion.* There are significant evidences that continuous blood purification technology within 24 h of serum Cys C level may better control the condition of children with severe sepsis.

1. Introduction

Sepsis is one of the main critical illnesses in the pediatric intensive care unit (PICU), with a high in-hospital mortality rate, and more than 40% of children with sepsis will be accompanied by an acute kidney injury (AKI) [1]. Continuous blood purification (CBP) is a widely used technique for the extracorporeal circulation support therapy in PICU [2]. In 2012, the "Expert Consensus on Continuous Blood Purification for the Treatment of Severe Sepsis in Children" drafted by 18 Chinese experts proposed that CBP should be used for the treatment of severe sepsis in children. However, the timing of CBP intervention in children with severe sepsis has been controversial. Most scholars believe that early intervention of CBP can reduce the mortality of children with a septic acute kidney injury [3]. However, there is no

consensus on the definition of "early". Finding sensitive indicators to start CBP has always been a difficult problem for PICU doctors to solve. In adult patients with sepsis, serum creatinine (SCr) and 24-hour urine output are often used as indicators of CBP initiation [4]. However, the creatinine value of children varies at different ages and is susceptible to the interference of tubular secretion and other nonrenal factors [5]. As the urination of infants is often involuntary, the collection of urine from infant patients is difficult. Therefore, It is not accurate to use serum creatinine and 24h urine volume as indicators of CBP intervention, which may easily lead to missed diagnosis or delayed treatment. Serum cystatin C (Cys C) is a kind of endogenous small molecule protein, which is continuously expressed at a constant rate in various nucleated cells and excreted by the kidneys. It is considered to be a sensitive indicator of early renal injury [6]. Here, we studied the renal replacement therapy for children with severe sepsis under the guidance of serum Cys C levels and compared the efficacy of starting CBP at different times.

2. Materials and Methods

2.1. Clinical Data. The clinical data of 67 children with sepsis who received CBP treatment in the PICU of our hospital from May 2016 to April 2020 were retrospectively analyzed. Among them, 40 were male and 27 were female. The age ranged from 28 days to 12 years old, the average age was (5.27 ± 3.32) years old; blood/deep sputum specimens/pleural effusion were cultured in all the children, among which 41 cases were positive (12 cases of *Pseudomonas aeruginosa*, 7 cases of methicillin-resistant coagulase-negative staphylococci, 5 cases of methicillin-resistant *Staphylococcus aureus*, 5 cases of *Streptococcus pneumoniae*, 4 cases of *Klebsiella pneumoniae* subsp. ppneumonia, 3 cases of hemolytic streptococcus, 2 cases of *Escherichia coli*, 1 case of *Pseudomonas aeruginosa*, 1 case of *Enterococcus faecalis*, methicillin-resistant hemolytic grape 1 case of cocci), and the other 2 cases were positive for EB virus DNA.

2.1.1. Diagnostic Criteria for Severe Sepsis. The diagnostic criteria were as follows: ①All children meet the diagnostic criteria for sepsis in the "China Guidelines for Diagnosis and Treatment of Severe Sepsis/Septic Shock (2014 Edition)" issued by the Chinese Society of Critical Care Medicine: the presence of definite or suspected systemic inflammatory response syndrome systemic inflammatory response syndrome (SIRS) and typical symptoms of infection: body temperature >38°C or <36°C, tachycardia, dyspnea, lethargy, edema, hyperglycemia (without history of diabetes), abnormal blood routine index, hypotension, organ dysfunction, hyperlactatemia, etc. In addition, combined with cerebral edema, liver failure, acute respiratory distress syndrome (ARDS), severe acid-base imbalance and electrolyte imbalance, conventional therapy is difficult to correct. ②with persistent involvement of more than one organ failure for more than 48 hours or local complications; and ③sequential organ failure assessment (SOFA) ≥3 points; acute physiology and chronic health evaluation II (APACHE II) score ≥8 points; modified CT severity index score ≥4 point. All patients sign an informed consent form.

2.1.2. Inclusion Criteria. The inclusion criteria were as follows: ①Children who meet the diagnostic criteria for severe sepsis in "China Guidelines for Diagnosis and Treatment of Severe Sepsis/Septic Shock (2014 Edition)". ②Age ≤18 years old. ③Admission to hospital within 48 hours after onset. ④Patients who continue to receive CBP treatment for more than 24 hours.

2.1.3. Exclusion Criteria. The exclusion criteria were as follows: ①Children who do not meet the above inclusion criteria. ②Children with a history of renal transplantation or renal replacement therapy. ③Persons with glomerulonephritis, interstitial nephritis, renal vasculitis, and end-stage renal disease. ④Combined kidney tumors, immune system, blood system diseases, and severe bleeding tendency.

2.2. Treatment

2.2.1. Conventional Treatment. All children were treated in accordance with the "Chinese Guidelines for Diagnosis and Treatment of Severe Sepsis/Septic Shock (2014 Edition)", including antibiotics within 1 hour of diagnosis, completion of fluid resuscitation within 6 hours, maintenance of acid-base balance and electrolyte balance, early body fluid resuscitation, strengthen parenteral nutrition, etc.

2.2.2. CBP Treatment. If the child's condition is relieved after conventional treatment or the following indications occur, CBP treatment should be given immediately: ① Severe hyperkalemia: serum potassium >6.5 mmol/L. ② Water intoxication: Heart failure, severe hyperkalemia caused by excessive volume overload hypertension or pulmonary edema. ③ Severe metabolic acidosis: blood pH < 7.20, blood HCO_3- <12 mmol/L. ④ Serum urea nitrogen (BUN) >28.7 mmol/L (80 mg/dl) or SCr >442 μmol/L (6 mg/dl). ⑤ Decreased urine output: anuria for 2 days or oliguria for more than 4 days. Femoral vein or internal jugular vein catheterization was performed using the Seldinger technique, vascular access was established, and the Prismaflex (Gambro, Sweden) or BM25 (Baxter, USA) continuous blood purification system was used, 16–18 *G* single lumen (≤1 year old), 6.5–11.5 *F* single-needle double-lumen tube (>1 year old), and child-type tube. Children with a body weight <20 kg should choose 0.2–0.4 m^2 polysulfone membrane, those weighing 20–30 kg should choose 0.4–0.8 m^2 polysulfone membrane, and those above 30 kg should choose 0.8–1.0 m^2 polysulfone membrane. The hemofiltration machine produces the replacement fluid online. The blood flow rate is 3–5 ml/(kg h), the dialysate is 30–50 ml/(kg h), the pre-replacement: the post-replacement ≈1 : 2, and the dehydration amount is 0–2 ml/(kg h); the amount of ultrafiltration is adjusted according to the condition and clinical needs of the child. Each child is treated 1-

2 times according to the condition. In addition, low-molecular-weight heparin anticoagulation or low-molecular-weight heparin anticoagulation can be selected according to the condition of the child, and no heparin treatment can be used when there is a tendency to bleeding.

2.3. Monitoring and Grouping of the Serum Cys C Level. Daily blood samples were collected from children, and serum Cys C levels were remeasured by particle-enhanced transmission immunoturbidimetry. The time interval between the start of serum Cys C level and the initiation of CBP was recorded, and 67 patients were divided into group A (<24 h, 29 cases), group B (24–48 h, 22 cases), and group C (>48 h, 16 cases).

2.4. Indicator Observation

2.4.1. General Clinical Data. The gender and age of the children were included, and the duration of CBP (d) and the 28-day mortality were recorded.

2.4.2. Vital Signs. The body temperature, heart rate, respiratory rate, and urine output of the children before and 48 hours after CBP treatment were recorded.

2.4.3. Biochemical Parameters. Blood routine, liver function electrolytes, arterial blood gas analysis, and other indicators were included.

2.4.4. Disease Severity Score. The APACHE II score and SOFA score of the children were evaluated depending on the daily condition of the children.

2.5. Statistical Processing. Input the data into SPSS17.0 statistical software for processing and analysis, the measurement data conforming to the normal distribution are expressed as $(\chi \pm s)$, the data between the two groups are compared by an independent sample t-test, and the same group at different time points. The variables were compared using paired samples t-test; data comparison between multiple groups was performed using one-way ANOVA analysis. The enumeration data were expressed as (%), and the χ^2 test was used, and $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Comparison of Baseline Data of the Three Groups of Children. The basic information, vital signs, and main biochemical parameters of the children in group A, group B, and group C at admission were compared. The age, gender composition, heart rate, APACHE II score, SOFA score, basal body temperature, urine volume, alanine transaminase (ALT), aspartate aminotransferase (AST), serum HCO_{3-}, serum potassium level, BUN, SCr, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (partial pressure) of carbon dioxide (PCO_2), oxygenation index (PO_2/FiO_2), and etiological test results were basically the same, with no statistical difference ($P > 0.05$), which was comparable as shown in Table 1.

3.2. CBP Treatment of Children in the Three Groups. The time interval of CBP intervention in the three groups was 2 h–96 h after admission, and the total treatment time was 10 h–76 h. The time from admission to CBP intervention, the number of interventions, and the treatment time were compared among the three groups. As for the time of CBP intervention and the number of interventions, it was found that the children in groups B and C were significantly more than those in group A, and the difference was statistically significant ($P < 0.05$) as shown in Table 2.

3.3. Comparison of Clinical Outcomes of the Three Groups of Children. During the 28-day follow-up, there was no significant difference in the incidence of complications such as coagulation dysfunction and hypovolemic shock among the three groups ($P > 0.05$). The mortality rate of children in group C and group B was slightly higher than that of children in group A and there was a statistical difference $P < 0.05$. For children with coagulation dysfunction, plasma, platelets, and protamine were transfused according to the situation, and the coagulation function gradually returned to normal. For 1 child with embolism, thrombolysis with urokinase was administered in time, and heparin sodium and dextran were used for anticoagulation without serious consequences. For the 3 children with hypovolemic shock, normal saline volume expansion was given first, which was quickly corrected and then continued CBP therapy as shown in Table 3.

3.4. Changes of Vital Signs and Biochemical Indexes in the Three Groups of Children after Treatment. After CBP intervention, compared the vital signs and main biochemical parameters of the children in groups A, B, and C at admission, the heart rate, basal body temperature, serum HCO_{3-}, ALT, AST, and PO_2/FiO_2 of the three groups were basically the same, there was no statistical difference ($P > 0.05$); but after CBP intervention, the APACHE II score, SOFA score, serum potassium level, BUN level, SCr level, and PCO_2 value of the children in group A were significantly lower than those in the children in group C, and the difference was statistically significant ($P > 0.05$). Meanwhile, after CBP intervention, the APACHE II score, SOFA score, serum potassium level, BUN level, SCr level, and PCO_2 value of the children in group A were also significantly lower than those in the children in group B. However, the PO_2 value was higher than that of the children in group C, indicating the recovery rate of renal function in children with sepsis, and the difference was statistically significant ($P < 0.05$) as shown in Table 4.

3.5. Analysis of Factors Affecting the Prognosis of Children. Taking the treatment outcome of the children as the dependent variable (death was assigned a value of 1 and

Table 1: Comparison of basic clinical data, vital signs, and main biochemical parameters of the three groups of children on admission.

Index	Group A ($n = 29$)	Group B ($n = 22$)	Group C ($n = 16$)	F/χ^2	P value
Old (year)	5.12 ± 3.14	5.31 ± 2.72	5.23 ± 3.59	0.024	0.977
Male/female	17/12	14/8	9/7	0.235	0.889
Heart rate (bpm)	107.41 ± 14.29	112.65 ± 17.20	104.72 ± 16.31	1.290	0.282
APACHE II score	25.93 ± 5.54	23.86 ± 5.75	23.90 ± 6.23	1.039	0.360
SOFA score	9.24 ± 2.37	9.08 ± 2.45	8.81 ± 2.92	0.148	0.862
Basal body temperature (°C)	37.91 ± 0.80	37.82 ± 0.81	37.89 ± 0.76	0.084	0.920
24 h urine output (mL)	1357 ± 1026	1185 ± 835	1039 ± 968	0.602	0.551
HCO_3^- (mmol/L)	16.38 ± 4.85	16.11 ± 4.34	15.49 ± 5.26	0.179	0.837
ALT (U/L)	559.28 ± 411.46	517.97 ± 390.16	530.82 ± 375.23	0.074	0.929
AST (U/L)	662.21 ± 617.48	656.15 ± 633.80	629.24 ± 598.37	0.020	0.980
BUN (mmol/L)	20.91 ± 9.10	16.65 ± 9.48	17.82 ± 10.70	1.330	0.272
SCr (μmol/L)	282.73 ± 79.42	245.23 ± 99.47	240.79 ± 113.42	1.437	0.245
Serum potassium (mmol/L)	4.78 ± 0.97	4.11 ± 0.85	4.42 ± 1.05	3.129	0.051
PO_2 (mmHg)	87.45 ± 37.84	95.86 ± 35.89	107.95 ± 39.49	1.539	0.222
PCO_2 (mmHg)	36.72 ± 13.29	32.57 ± 9.87	35.11 ± 11.23	0.778	0.464
PO_2/FiO_2 (mmHg)	205.78 ± 121.96	217.86 ± 98.59	244.53 ± 118.40	0.598	0.553

APACHE II: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; SCr: serum creatinine; PO_2: partial pressure of blood oxygen; PCO_2: partial pressure of carbon dioxide; PO_2/FiO_2: oxygenation index.

Table 2: Treatment of CBP in the three groups of children.

Group	Intervention time of CBP ($\bar{\chi} \pm s$, h)	2 CBP interventions (cases, %)	Length of CBP treatment ($\bar{\chi} \pm s$, h)
Group A ($n = 29$)	11.30 ± 5.81	0	45.10 ± 19.83
Group B ($n = 22$)	32.77 ± 6.57[a]	5 (22.73)[a]	47.24 ± 23.25
Group C ($n = 16$)	52.46 ± 5.34[ab]	5 (31.25)[a]	44.64 ± 23.87
F	254.931	9.500	0.083
P value	0.000	0.009	0.920

Compared with group A, [a]$P < 0.05$; compared with group B, [b]$P < 0.05$.

Table 3: Comparison of clinical outcomes and complications among the three groups of children (cases, %).

Group	Death	Coagulation disorders	Embolism	Hypovolemic shock
Group A ($n = 29$)	6 (20.69)	3 (10.34)	0	0
Group B ($n = 22$)	10 (45.45)	5 (22.73)	0	1 (4.55)
Group C ($n = 16$)	9 (56.25) a	5 (31.25)	0	1 (6.25)
F	7.887	3.113	—	1.666
P value	0.019	0.211	—	0.435

Compared with group A, [a]$P < 0.05$.

Table 4: Comparison of vital signs and main biochemical parameters of the three groups of children after treatment.

Index	Group A ($n = 29$)	Group B ($n = 22$)	Group C ($n = 16$)	F	P value
Heart rate (bpm)	82.81 ± 11.79	87.37 ± 14.98[a]	98.39 ± 14.72[ab]	6.794	0.002
Apache II score	9.86 ± 4.10	13.32 ± 4.53[a]	14.75 ± 4.45[a]	7.751	0.001
SOFAscore	4.39 ± 1.94	5.73 ± 2.10[a]	6.52 ± 2.29[a]	5.991	0.004
Basal body temperature (°C)	37.31 ± 0.56	37.39 ± 0.61	37.40 ± 0.65	0.164	0.849
HCO_3- (mmol/L)	24.22 ± 5.95	24.07 ± 6.86	22.49 ± 7.10	0.398	0.673
ALT (U/L)	177.38 ± 179.84	186.24 ± 157.58	210.43 ± 148.06	0.208	0.813
AST (U/L)	295.86 ± 211.50	324.19 ± 185.47	330.79 ± 195.25	0.205	0.815
BUN (mmol/L)	10.18 ± 4.17	12.63 ± 5.06	14.81 ± 4.73[a]	5.425	0.007
SCr (μmol/L)	86.89 ± 50.33	125.61 ± 43.78[a]	162.78 ± 61.25[ab]	11.739	0.000
Serum potassium (mmol/L)	1.27 ± 0.76	1.65 ± 0.72*	1.99 ± 0.90[a]	4.548	0.014
PO_2 (mmHg)	214.32 ± 38.59	200.57 ± 32.47	179.34 ± 51.30[a]	3.916	0.025
PCO_2 (mmHg)	10.45 ± 7.58	15.28 ± 9.02[a]	20.76 ± 8.17[a]	8.270	0.001
PO_2/FiO_2 (mmHg)	347.15 ± 138.49	310.54 ± 107.92	256.57 ± 140.34	2.522	0.088

APACHE II: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; SCr: serum creatinine; PO_2: partial pressure of blood oxygen; PCO_2: partial pressure of carbon dioxide; PO_2/FiO_2: oxygenation index; compared with group A, [a]$P < 0.05$; compared with group B, [b]$P < 0.05$.

survival was assigned a value of 0), and the above variables with statistical differences after CBP intervention were used as independent variables; the forward stepwise (conditional) regression model was used for multivariate analysis. The results showed that the SOFA score ≥5 points after CBP intervention and the time from serum Cys C elevation to CBP intervention ≥24 hours were independent risk factors affecting the prognosis of children ($P < 0.05$). The prediction accuracy of the regression equation was 72.35%. Hosmer and Lemeshow Test was used to test the fit of the equation. There was no deviation between the fitted equation and the real equation ($P = 0.764$). As shown in Table 5.

4. Discussion

Sepsis is one of the common critical illnesses in PICU with a complex etiology and rapid disease progression. In-hospital mortality is particularly high in children with severe sepsis. In recent years, with the maturation and standardization of CBP treatment technology, its application has become more and more extensive. It has not only been limited to the treatment of children with acute kidney injury but has gradually expanded to the application of various critical cases in the PICU, including the treatment of patients with severe sepsis. Increasing attention has been paid to the treatment of children [7]. In the past, most scholars believed that the initial indication of CBP treatment was acute kidney damage, such as serum potassium concentration higher than 6.5 mmol/L, pulmonary edema, heart failure, and sudden increase in blood pressure, or only when symptoms of uremia appeared. CBP [8]. However, because many clinical indicators in children vary with age and weight, there is some uncertainty. Especially in infants, vital signs and blood biochemical indicators vary greatly from those of adults, and it is difficult to collect urine, making the timing of initiation of CBP still highly controversial. l.

Serum Cys C belongs to a class of small molecule endogenous cystinase inhibitors. Unlike SCr, Cys C is almost exclusively secreted constantly by nucleated cells and excreted by the kidneys, with stable expression in peripheral blood and less interference from nonrenal factors [9]. Blood samples are easy to obtain, and the detection operation is simple and fast, and it is currently widely used in clinical practice. However, most studies focused on the changes of serum Cys C levels before and after CBP treatment, and few studies have evaluated the value of serum Cys C as the basis for CBP initiation in children with sepsis. Scholars such as Al-Beladi [10] have found through experiments that serum Cys C can diagnose acute renal injury 1.5 d–2 d earlier than SCr. Moradkhani et al. [11] also confirmed that Cys C can be used as an early diagnostic indicator of acute kidney injury associated with sepsis in children. In this study, we divided 67 children with severe sepsis into three groups according to the time interval from the time point of serum Cys C >15 mg/L to the time point of CBP initiation. The data, vital signs, main biochemical indicators (including SCr, BUN), and etiological test results were basically consistent and comparable. All the children received CBP intervention, the earliest was 2 hours after admission and the latest was 96 hours after admission. The total treatment time was 10 hours and 76 hours. The frequency was significantly more than that of group A children. In addition, after CBP intervention, the APACHE II score, SOFA score, serum potassium level, BUN level, SCr level, and PCO_2 value in group A were significantly lower than those in group C, while the PO_2 value was higher than that in group C. This indicated that when the serum creatinine, blood urea nitrogen, and other indicators were at the same level in the three groups, the shorter the time interval between the time point of serum Cys C elevation and the initiation of CBP, the higher the recovery rate of renal function in children with sepsis. This is basically consistent with the research conclusions of Hou et al. [12] Hou indicates that monitoring serum Cys C levels has an important guiding value for the clinical treatment of patients with sepsis complicated with multiple organ dysfunction and suggest that patients with elevated serum Cys C levels have an important guiding value suggesting that a good prognosis can be obtained with continuous renal replacement therapy within 48 hours.

In order to remove inflammatory mediators, cytokines, or endotoxins as soon as possible and prevent further deterioration of organ function, many foreign scholars recommend starting CBP therapy within 24 hours after admission to the ICU [13]. However, some multicenter clinical studies have confirmed that early continuous blood purification cannot significantly improve blood inflammatory indicators and prognosis in children with severe sepsis, but it has certain effects on improving oxygenation and tissue metabolism, and shortening the length of stay in PICU. Influence [14]. Therefore, the so-called early concept cannot simply be defined as the time interval between admission to the PICU and initiation of CBP. In this study, we took the time interval from the time point of serum Cys C level>15 mg/L to the time point of CBP initiation <24 h as the early treatment group (i.e., group A) and found that the mortality rate of children in group A was significantly lower at 28 days in group C, and the difference was statistically significant. It is suggested that taking the time of serum Cys C elevation as a reference index for starting CBP therapy has a high clinical outcome value. Subsequently, we further analyzed the multivariate logistic regression and found that the time interval between the time point of CBP intervention and the time point of SOFA score ≥5 and serum Cys C level >15 mg/L to the time point of CBP initiation was ≥24 hours was an independent risk factor affecting the prognosis of children. The APACHE II scoring system and the SOFA scoring system are the most commonly used quantitative assessment tools for nonspecific disease severity in clinical practice and are recognized and confirmed by most critical care medicine experts at home and abroad. However, the APACHE II scoring system is complex, and the assessment content includes the disease at the time of onset and the previous health status, and the clinical operability is poor, especially for critically ill children, it cannot make rapid, timely, and accurate judgments. In comparison, the SOFA scoring system is simple to operate, easy to collect data, and can quickly and effectively evaluate the renal function of children. Therefore, we suggest that the SOFA score and the

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Retraction

Retracted: Correlation and Prognostic Action of SAA, Hcy, and BNP Levels with the Condition of Patients with Spontaneous Intracerebral Hemorrhage

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] W. Xu, J. Wang, and H. Yang, "Correlation and Prognostic Action of SAA, Hcy, and BNP Levels with the Condition of Patients with Spontaneous Intracerebral Hemorrhage," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 1126611, 5 pages, 2022.

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Research Article

Correlation and Prognostic Action of SAA, Hcy, and BNP Levels with the Condition of Patients with Spontaneous Intracerebral Hemorrhage

Weiwei Xu,[1] Jing Wang,[2] and Hong Yang[3]

[1]*The Nanhua Affiliated Hospital, Department of Neurosurgery, Hengyang Medical School, Universitity of South China, Hengyang, Hunan 421001, China*
[2]*The Nanhua Affiliated Hospital, Department of Spinal Surgery, Hengyang Medical School, Universitity of South China, Hengyang, Hunan 421001, China*
[3]*The Affiliated Nanhua Hospital, Office of Educational Administration, Health School of Neuclear Industry, Hengyang, Hunan 421001, China*

Correspondence should be addressed to Hong Yang; yanghong1001@yeah.net

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Objective. To explore the correlation of serum amyloid A (SAA), homocysteine (Hcy), and plasma B-type brain natriuretic peptide (BNP) levels in patients with spontaneous intracerebral hemorrhage (SICH) and their predictive value for the status and prognosis of SICH patients. *Methods*. 82 SICH patients admitted to our hospital from March 2017 to March 2020 were selected. According to the Glasgow coma scale (GCS) score, the patients were divided into GCS > 8 group ($n = 44$) and the GCS ≤ 8 group ($n = 38$). Based on the bleeding volume, the patients were divided into the massive bleeding group (>30 ml) ($n = 21$), the moderate bleeding group (10~30 ml) ($n = 28$), and the small bleeding group (<10 ml) ($n = 33$). Based on the prognostic status of patients after 28 days of admission, they were divided into the survival group ($n = 64$) and the death group ($n = 18$). Serum SAA, Hcy, and plasma BNP levels of patients in different groups were compared, and the correlation between serum SAA, Hcy and plasma BNP levels with GCS score, cerebral hemorrhage, and the prognostic value of patients was analyzed. *Results*. Serum SAA, Hcy, and plasma BNP levels in patients with GCS ≤ 8 groups were higher than those in GCS > 8 groups ($P < 0.05$). Serum SAA, Hcy, and plasma BNP levels of patients in the massive bleeding group were higher than those in the moderate and small bleeding groups. Besides, the level of serum SAA, Hcy, and plasma BNP in the moderate bleeding group was higher than that in the small bleeding group ($P < 0.05$). Serum SAA, Hcy and plasma BNP levels of patients were negatively correlated with GCS scores but positively correlated with bleeding volume ($P < 0.05$). The levels of serum SAA, Hcy and plasma BNP in dead patients were higher than those in the survival patients ($P < 0.05$). The combined prediction of serum SAA, Hcy, and plasma BNP for the prognosis of SICH patients was 0.910 (95% CI: 0.984~0.837), which was higher than the serum SAA, Hcy, and plasma BNP alone predicted AUC 0.679 (95% CI: 0.564~0.795), 0.720 (95% CI: 0.603~0.836), and 0.726 (95% CI: 0.616~0.849). *Conclusion*. The levels of serum SAA, Hcy, and plasma BNP have a correlation with the severity and prognosis of patients with SICH, which is a feasible index for judging the prognosis of SICH. The levels of serum SAA, Hcy, and plasma BNP are conducive to timely judgment of the progression and prognosis of SICH patients.

1. Introduction

Spontaneous intracerebral hemorrhage (SICH) is a non-traumatic cerebral parenchymal hemorrhage with complex pathogenesis and severe progression. SICH is characterized by high morbidity, mortality, and disability rates, which affect the quality of life of patients and brings a heavy burden to their families and society [1]. Amyloid A (SAA) is a highly sensitive protein produced by macrophages and fibroblasts activated in the liver in the acute phase of the disease [2]. Studies have shown that SAA rises sharply in the early phase of inflammatory response, which is considered to be

involved in the process of arteriosclerosis in cerebrovascular diseases and is critical for the prognosis of cerebral infarction and other diseases [3]. Homocysteine (Hcy), a sulfur-containing amino acid mainly produced by red blood cells, is involved in the secondary damage of acute cerebral hemorrhage and is a key independent risk factor for cardiovascular and cerebrovascular diseases [4]. B-type brain natriuretic peptide (BNP) belongs to the neurohormones and is widely present in cardiomyocytes and brain tissue. The concentration of BNP fluctuates significantly in subarachnoid hemorrhage and acute traumatic brain injury, which is closely related to disease progression [5]. In this study, by measuring the levels of serum SAA, Hcy, and plasma BNP in patients with SICH, we explored the correlation relationship between SAA, Hcy, and BNP with the condition of SICH patients and their predictive effect on the prognosis of patients with SICH.

2. Materials and Methods

2.1. General Information. A total of 82 SICH patients admitted to our hospital from March 2017 to March 2020 were selected, including 52 males and 30 females, with an average age of 63.28 ± 8.16 years. Head CT examination showed the location of hematoma in patients: 23 cases were located in the left basal ganglia, 39 cases were located in the right basal ganglia, and 20 cases were located in the lobe of the brain. The average blood loss was 19.52 ± 10.21 ml. Inclusion criteria: in line with the "Guidelines for Diagnosis and Treatment of Cerebral Hemorrhage in China (2014)" [6]; The patient was admitted to the hospital within 12 hours of onset, and was confirmed to be SICH by immediate head CT examination; only medical treatment was performed; clinical data and follow-up data were complete. Exclusion criteria: bleeding into the ventricle; history of previous stroke or traumatic brain injury; complicated with dysfunction of vital organs such as the heart, lung, liver, and kidney; died within 24 hours of admission or received surgical treatment due to the changes in condition during the observation period. The severity of the patient's condition was evaluated according to the Glasgow coma scale (GCS) score and the amount of bleeding. According to the GCS score, 44 cases were grouped with a GCS >8 and 38 cases were grouped with a GCS ≤8. According to the amount of bleeding, they were divided into massive bleeding group (>30 ml), 21 cases; moderate bleeding group (10–30 ml), 28 cases; and small bleeding group (<10 ml), 33 cases. This study was approved by the hospital ethics committee, and all patients and their families voluntarily signed informed consent. Also, the clinical baseline data of 82 patients was statistically insignificant.

2.2. Research Methods. General information such as gender, age, underlying disease, and past history was recorded for all patients upon admission. Immediately after admission, venous blood is drawn from the patient for a routine biochemical examination and GCS scoring. The amount of cerebral hemorrhage is estimated according to the Tada formula for the CT membrane of the patient's head at the time of admission; that is, the amount of bleeding (ml) = the length (cm) of the $\pi \times$ the width (cm) $\times$ the width (cm) $\times$ height (cm)/6. All patients underwent routine medical diagnosis and treatment and were given dehydration to reduce intracranial pressure, control blood pressure, regulate blood sugar, and prevent complications. After 28 days of admission, patients were divided into survival group and death group according to the prognosis of patients.

2.3. Observation Indicators. Then, 5 ml of venous blood was drawn from all patients immediately after admission, and serum SAA and Hcy levels were detected by immunoturbidimetry and enzyme-linked immunosorbent assay (ELISA), respectively. Plasma BNP levels were detected by ELISA. All reagents were purchased from Shanghai Yinggong Biotechnology Co., Ltd., and the operations were carried out in strict accordance with the kit instructions. The serum SAA, Hcy, and plasma BNP levels of patients in different groups were compared. The correlations of serum SAA, Hcy, and plasma BNP levels with GCS score and intracerebral hemorrhage and their predictive effects on the prognosis of spontaneous intracerebral hemorrhage were analyzed.

2.4. Statistical Methods. The SPSS 22.0 software was used to process experimental data. Measurement data are expressed as mean ± standard deviation ($\overline{X} \pm S$). Enumeration data are expressed as (%). Pairwise comparisons of measurement data between groups were analyzed by the t-test. The multigroup comparison of intergroup metrological data is a one-way ANOVA. Enumeration data were analyzed by the χ^2 test. The test level was $\alpha = 0.05$, and $P < 0.05$ or $P < 0.01$ was considered statistically significant.

3. Results

3.1. Comparison of Serum SAA, Hcy, and Plasma BNP Levels in Patients with Different GCS Scores. The levels of serum SAA, Hcy, and plasma BNP in the GCS ≤8 group were higher than those in the GCS >8 group, and the differences were statistically significant ($P < 0.05$), as shown in Table 1.

3.2. Comparison of Serum SAA, Hcy, and Plasma BNP Levels in Patients with Different Bleeding Volumes. The levels of serum SAA, Hcy, and plasma BNP in the massive hemorrhage group were higher than those in the moderate hemorrhage group and the minor hemorrhage group, and the moderate hemorrhage group was higher than the minor hemorrhage group, and the differences were statistically significant ($P < 0.05$), as shown in Table 2.

3.3. Correlation of Serum SAA, Hcy, and Plasma BNP Levels with GCS Score and Bleeding Volume. Serum SAA, Hcy, and plasma BNP levels were negatively correlated with the GCS score ($P < 0.05$) and positively correlated with the bleeding volume ($P < 0.05$), as shown in Table 3.

Table 1: Comparison of serum SAA, Hcy, and plasma BNP levels in patients with different GCS scores (n, $\overline{X} \pm S$).

Group	Number of cases	SAA (mg/L)	Hcy (μmol/L)	BNP (pg/ml)
GCS > 8 group	44	23.46 ± 5.72	16.41 ± 3.84	86.92 ± 27.61
GCS ≤ 8 group	38	37.84 ± 7.65	26.95 ± 4.92	117.29 ± 31.05
t value		9.717	10.884	4.688
P value		0.000	0.000	0.000

Table 2: Comparison of serum SAA, Hcy, and plasma BNP levels in patients with different bleeding volumes (n, $\overline{X} \pm S$).

Group	Number of cases	SAA (mg/L)	Hcy (μmol/L)	BNP (pg/ml)
Minor hemorrhage group	33	22.43 ± 5.07	15.92 ± 4.52	68.37 ± 20.46
Moderate hemorrhage group	28	31.37 ± 6.49[a]	20.64 ± 5.81[a]	92.83 ± 25.17[a]
Massive hemorrhage group	21	40.55 ± 9.13[ab]	27.95 ± 6.37[ab]	163.15 ± 31.54[ab]
F value		6.159	5.169	3.428
P value		0.000	0.000	0.004

Note: compared with the minor bleeding group, [a]$P < 0.05$; compared with the moderate bleeding group, [b]$P < 0.05$.

Table 3: Correlation of serum SAA, Hcy, and plasma BNP levels with GCS score and bleeding volume.

Indicator	GCS score		Bleeding volume	
	r value	P value	r value	P value
SAA	−0.518	0.018	0.541	0.016
Hcy	−0.553	0.014	0.605	0.011
BNP	−0.665	0.007	0.731	0.003

3.4. Comparison of Serum SAA, Hcy, and Plasma BNP Levels between Survival Group and Death Group. After 28 days of admission, 64 patients survived and 18 died. The levels of serum SAA, Hcy, and plasma BNP in the death group were higher than those in the survival group, and the differences were statistically significant ($P < 0.001$), as shown in Table 4.

3.5. The Predictive Effect of Serum SAA, Hcy, and Plasma BNP Levels on the Prognosis of Patients with SICH. The combined AUC of serum SAA, Hcy, and plasma BNP in predicting the prognosis of patients with SICH was 0.910 (95% CI: 0.984–0.837), which was higher than the AUC of 0.679 (95% CI: 0.564–0.795) predicted by serum SAA, Hcy, and plasma BNP alone, 0.720 (95% CI: 0.603~0.836), and 0.726 (95% CI: 0.616~0.849). The combined sensitivity of serum SAA, Hcy, and plasma BNP in predicting the prognosis of patients with SICH was 92.7%, which was higher than the sensitivities of serum SAA, Hcy, and plasma BNP alone, 81.4%, 86.2%, and 87.9%. The specificity of serum SAA, Hcy, and plasma BNP combined to predict the prognosis of patients with SICH was 87.8%, which was higher than the serum SAA, Hcy, and plasma BNP alone (52.7%, 52.9%, and 65.7%), as shown in Table 5 and Figure 1.

4. Discussion

SICH is a nontraumatic sudden intraparenchymal hemorrhage caused by single or multiple factors, accounting for 10% to 15% of strokes, which is a common acute cerebrovascular disease [7]. The pathological injuries and physiological processes stimulated by the pathogenesis of SICH are complex and changeable, closely related to the response of inflammatory mediators and vasoactive substances [8]. Due to the special location of the disease in patients with SICH, the disease is dangerous, changes rapidly, and the prognosis is poor. Early and timely judgment of the progress of the patients is critical for the treatment [9].

SAA is an acute response protein. The level of SAA changes rapidly in the process of the inflammatory response, which is closely related to the secondary injury of brain tissue after cerebral hemorrhage [10]. Hcy is a vital risk factor for the onset of cardiovascular and cerebrovascular diseases. High Hcy affects the body's coagulation system, disrupts its balance, and further aggravates the symptoms of cerebral hemorrhage [11]. BNP is a cardiac hormone synthesized primarily by cardiomyocytes. Under normal physiological conditions, bnp synthesis and secretion are low, which is an important indicator for the detection of heart failure and coronary artery lesions. The synthesis and secretion of BNP are low under normal physiological conditions. BNP has an effect on diuretic, sodium excretion, vasodilation, and antagonistic renin-angiotensin-aldosterone (RAS) system in the neuroendocrine changes of heart failure [12]. Recent studies have shown that the expression of plasma BNP in patients with traumatic brain injury, etc. is significantly higher than that in healthy people, and the concentration of BNP is positively correlated with the amount of cerebral hemorrhage and the degree of cerebral edema, and also has a correlation with the degree of neurological deficit, suggesting that BNP is useful for the diagnosis and treatment of cerebrovascular diseases [13, 14]. The results of this study showed that levels of serum SAA, Hcy and plasma BNP in the GCS ≤8 groups were higher than those in the GCS >8 groups, and the serum SAA, Hcy, and

Table 4: Comparison of serum SAA, Hcy, and plasma BNP levels between the survival group and the death group (n, $\overline{X} \pm S$).

Group	Number of cases	SAA (mg/L)	Hcy (μmol/L)	BNP (pg/ml)
Survival group	64	26.74 ± 5.18	19.26 ± 4.82	80.35 ± 23.59
Death group	18	42.16 ± 7.32	28.53 ± 6.07	174.39 ± 32.76
t value		10.136	6.798	13.655
P value		0.000	0.000	0.000

Table 5: Predictive effects of serum SAA, Hcy, and plasma BNP levels on the prognosis of patients with SICH (n, %).

Indicator	AUC	Asymptotic 95% confidence interval		Best cutoff	Sensitivity (%)	Specificity (%)
		Upper limits	Lower limits			
SAA	0.679	0.564	0.795	0.341	81.4	52.7
Hcy	0.720	0.603	0.836	0.391	86.2	52.9
BNP	0.726	0.616	0.849	0.536	87.9	65.7
Joint forecast	0.910	0.837	0.984	0.805	92.7	87.8

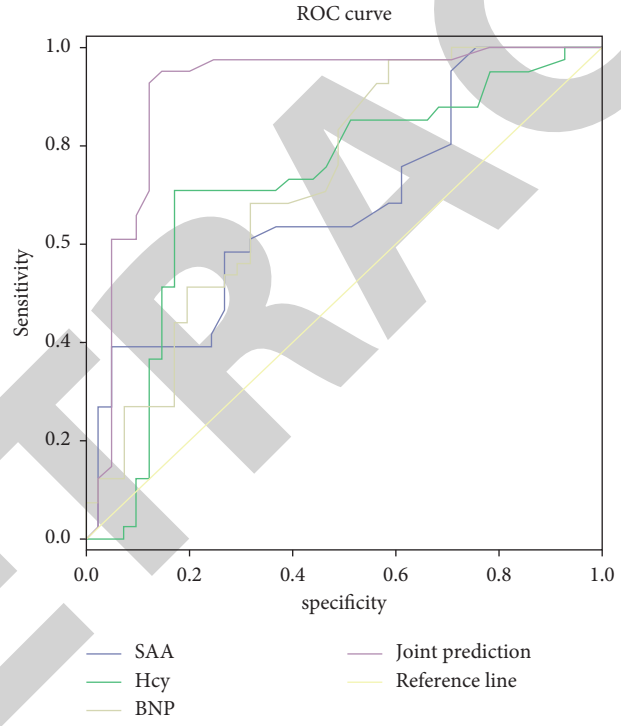

Figure 1: ROC curve of serum SAA, Hcy, and plasma BNP levels predicting the prognosis of patients with SICH.

plasma BNP levels in the massive bleeding group were higher than those in the moderate bleeding group and the minor bleeding group, and the moderate bleeding group was higher than the small bleeding group. It is suggested that the lower GCS score and greater bleeding volume in SICH patients indicate higher serum SAA, Hcy, and plasma BNP levels. Therefore, SAA, Hcy, and BNP are all involved in the pathogenesis of SICH patients, which have possible evaluating capacities for the severity of SICH patients [15].

Some studies have shown that SAA is involved in the whole process of arteriosclerosis and is closely related to the prognosis and classification of cerebrovascular diseases such as cerebral infarction [16]. Elevated HCY levels in patients with SICH promote oxidative stress in vivo, irritate the vascular wall, which in turn damages the vascular endothelium and accelerates the formation of plaque on the vascular wall and secondary injury in patients with cerebral hemorrhage [17]. During the stressful process of SICH patients, ischemia and hypoxia, hematoma compression, etc. can lead to an increase in BNP secretion [18]. The results of this study showed that serum SAA, Hcy, and plasma BNP levels were negatively correlated with GCS score and positively correlated with bleeding volume, which suggests that serum SAA, Hcy, and plasma BNP levels are significantly correlated with the severity of the patients.

In this study, 82 patients were admitted to the hospital. Twenty-eight days later, 64 patients survived and 18 died. The levels of serum SAA, Hcy, and plasma BNP in the death

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Research Article

Improvement of Biosynthetic Ansamitocin P-3 Production Based on Oxygen-Vector Screening and Metabonomics Analysis

Xiaolin Zhu,[1] Kaiyao Hou,[2] Peiyang Zheng,[1] Wenya Zhong,[1] Jing Guo,[1] Xiyue Zhao,[1] Tingting Hong,[1] and Zhiqiang Cai[1]

[1]*Laboratory of Applied Microbiology and Enzyme Engineering, School of Pharmacy, Changzhou University, Changzhou 213164, Jiangsu, China*
[2]*Wuxi Big Bridge Academy, Wuxi 214115, Jiangsu, China*

Correspondence should be addressed to Zhiqiang Cai; zhqcai@cczu.edu.cn

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A novel approach involving exogenous oxygen vectors was developed for improving the production of biosynthetic Ansamitocin P-3 (AP-3). Four types of oxygen vectors including soybean oil, n-dodecane, n-hexadecane, and Tween-80 were applied to explore the effect of exogenous oxygen vectors on AP-3 yield. It was observed that soybean oil exhibited a better ability for promoting AP-3 generation than the other three oxygen vectors. Based on the results of the single-factor experiment, response surface methodology was employed to obtain the optimal soybean oil addition method. The optimum soybean oil concentration was 0.52%, and the addition time was 50 h. Under this condition, the yield of AP-3 reached 106.04 mg/L, which was 49.48% higher than that of the control group without adding oxygen vectors. To further investigate the influence of dissolved oxygen on precious orange tufts actinomycetes variety *A. pretiosum* strain metabolism and AP-3 yield, metabolomics analysis was carried out by detecting strain intermediate metabolites at various stages under different dissolved oxygen levels. Moreover, differential metabolite screening and metabolic pathway enrichment analysis were combined to exploit the effect mechanism of soybean oil on AP-3 production. Results suggested that primary metabolic levels of the TCA cycle and amino acid metabolism increased with the increase in dissolved oxygen level, which was beneficial to the life activities of bacteria and the synthesis of secondary metabolic precursors, thus increasing the production of AP-3.

1. Introduction

Maytansine has attracted tremendous attention due to its significant antitumor effect [1, 2]. Nevertheless, it is difficult to synthesize maytansine due to its complex chemical structure, and the chemical synthesis method is limited to laboratory research. Moreover, the plants containing lignin alkaloids exist in tropical regions, and the maytansine content in plants is low. Therefore, it is necessary to look for compounds with similar biological activity to maytansine. Biogenic ansamitocin is considered a suitable alternative since it possesses similar antitumor properties as maytansine. Higashide et al. first isolated ansamitocin from *Nocardia sp*., and this group of new components presented strong antitumor characteristics [3]. Different types of side chains can be modified to the Ansamitocin C-3 hydroxyl group to obtain amitocin homologues, including Ansamitocin P-0, Ansamitocin P-1, Ansamitocin P-2, Ansamitocin P-3, Ansamitocin P-3′, and Ansamitocin P-4. Among these homologues, Ansamitocin P-3 (AP-3) containing isobutyryl side chain shows prominent antitumor activity and has attracted increasing attention in secondary metabolite research [4–8]. The antibody-drug coupling (ADC) agent T-DM1 has achieved desirable results in the treatment of breast cancer [9–13]. In 2019, trastuzumab emtansine, the first ADC drug for early breast cancer treatment in China, was approved in the United States at an expensive price of about ¥ 20,000. High production cost of AP-3 due to low production efficiency is one of the main problems restricting its wide application in the pharmaceutical field.

The commonly used strains for biosynthesizing AP-3 include the precious orange tufts actinomycetes variety *A. pretiosum* and the miracle fasciculus actinomycetes *A. mirum*. Nowadays, increasing the yield of AP-3 is still a hot research area because of the low production of AP-3 fermentation. To promote the biosynthesis of AP-3, researchers have adopted various strategies including mutant screening, medium optimization, and genetic modification [14–18]. It is of great significance to the industrial application of AP-3. Desirable strains are the basis of fermentation, and the mutagenesis breeding method is usually adopted to obtain the mutant strains with a high secondary metabolite yield. In addition, the optimal medium has an important effect on increasing AP-3 production. As the basic elements for promoting strain growth and proliferation, the medium components can provide energy for strain metabolism and regulate the primary and secondary metabolism of strains. For instance, glycerol and glucose synergistically promoted the production of AP-3. As a delayed carbon source, glycerol could provide nutrients for strain growth in the late fermentation period [19]. Since fructose offered precursors for AP-3 biosynthesis, the yield of AP-3 reached 144 mg/L in the optimized medium with fructose as the main carbon source [20].

In the process of industrial fermentation of aerobic microorganisms, the level of dissolved oxygen in the fermentation broth is one of the key factors affecting the product yield. The formation of mycelium is able to increase the fermentation broth viscosity, resulting in a rapid decrease in the dissolved oxygen level. Increasing the rotational speed and utilizing pure oxygen can solve the problem of oxygen transfer restriction. Nevertheless, the shear force caused by high stirring and ventilation has adverse effects on mycelium morphology and product yield. In addition, increased ventilation can lead to higher energy consumption. It is necessary to develop an effective way to improve the oxygen transfer rate during aerobic microbial fermentation. The oxygen transfer rate from the gas phase to microbial cells can be improved by adding certain organic liquids to the fermentation broth. These liquids are commonly referred to as oxygen vectors and include n-alkanes, n-fluorocarbons, esters, fatty alcohols, and oils [21–26]. Since the solubility of oxygen in these organic liquids is several times or dozens of times higher than that in the medium, these oxygen vectors are widely used in the field of biochemical engineering [26]. Compared with traditional fermentation systems, oxygen vectors can enhance the oxygen transfer rate without additional energy supply. Moreover, low-dose oxygen vectors have nontoxic effects on microorganisms and may become additional substrates. Therefore, oxygen-vector-based fermentation systems have attracted extensive attention. For instance, Meyer et al. adopted bioinert perfluorocarbons to improve oxygen transfer in 96-well plates [27]. It was found that PFCs were able to influence the solubility and transport of oxygen without interfering with the medium composition. As a common oxygen vector, n-alkanes play an important role in the fermentation process of polysaccharides and antibiotics. This type of oxygen vector can quickly transfer oxygen to the fermentation liquid and improve the oxygen uptake rate of bacteria. An additional 4% n-hexadecane was added to the culture medium of *S. cerevisiae* [28]. The results indicated that n-hexadecane could increase glucose consumption and reduce ethanol accumulation, facilitating *S. cerevisiae* growth and adenosine-methionine synthesis. To increase the available dissolved oxygen, Ciobanu et al. utilized 2% n-dodecane as the oxygen vector [29]. The production of β-galactosidase could be enhanced. To the best of our knowledge, few studies have specifically focused on investigating the effect of oxygen vectors on the production of biosynthetic AP-3.

Metabolomics is an emerging field of systems biology that aims to comprehensively analyze metabolites of cells at certain times and under certain environmental conditions [30]. It has also become a popular tool in biotechnology nowadays. Metabolomics is the systematic study of all metabolites and their concentrations that are affected by pathological and physiological changes. Metabolic changes present the complicated interaction between gene expression, enzyme activity, and metabolic reactions. Metabolomics is mainly applied for studying structurally different and physicochemically different molecules, including lipids, sugars, ions, metabolic intermediates, and biochemical reaction products, as well as the building blocks of proteins, nucleic acids, and cell membranes. This results in the technical barriers in terms of dynamic range and comparability. Technological developments, along with new data analysis methods, have played a key role in the field of metabolomics. Metabolomics has been applied to various aspects of microbiology, such as phenotypic classification, fermentation processes, and metabolic pathways [31–34]. Metabolite mapping facilitates the discovery of biological and chemical diversity from analytical data, further promoting the understanding of species, phenotypes, and functional genomics. Therefore, metabolomics is considered an important topic in microbial taxonomy and physiological research. Smedsgaard et al. used metabolite profiles to analyze the information related to *Penicillium* species. Phenotypes were effectively identified and classified by integrating efficient analytical methods, data processing techniques, and intelligent screening [35]. Dalluge et al. utilized liquid chromatography-electrospray tandem mass spectrometry (MS) to rapidly quantify underived amino acids. The metabolism of 20 amino acids was able to be monitored during microbial fermentation [36]. Although detailed metabolic networks have been established for some model strains, information about the relationships between primary and secondary metabolites and the transition patterns of entire microorganism metabolites is unclear. It is necessary to develop a more comprehensive method based on metabolomics for analyzing these secondary metabolite production pathways. Untargeted metabolomics was used to analyze the secondary Streptococcus A3(2) cultured in two different media, and the production of specific secondary metabolites was analyzed by the metabolic pathway, which could be applied to further optimize the production of schizopeptide [37].

To take advantages of both oxygen vectors and metabolomics, herein, the oxygen utilization efficiency of AP-3

production strains was improved by utilizing an oxygen vector and the effect mechanism of dissolved oxygen on AP-3 biosynthesis was investigated via metabonomics analysis (Figure 1). The influence of different types of oxygen vectors on AP-3 yield was explored by using the single-factor experiment. To further improve AP-3 production and offer a reference for other antibiotic fermentation methods with high production, response surface methodology (RSM) was applied for choosing the optimal oxygen-vector addition method. The effect of dissolved oxygen on cell metabolism in the biosynthesis of AP-3 was analyzed by untargeted metabonomics. The comparative analysis of the relationship between oxygen vectors and cells facilitated the investigation of the AP-3 yield enhancement mechanism of the oxygen vector during the fermentation process, providing a metabolic regulation approach to improve AP-3 yield. This work opens the way to applying oxygen vectors in the industrial production of AP-3.

2. Materials and Methods

2.1. Strain and Medium. The precious orange tufts actinomycetes variety *A. pretiosum* strain B24-13 was obtained by UV-induced mutation. Before the fermentation process, the basal medium was prepared. The basal medium composition was as follows: saccharose 2.5 g/L, glycerin 1.5 g/L, corn plasm 2.5 g/L, isobutanol 0.2 g/L, calcium carbonate 0.7 g/L, magnesium sulfate heptahydrate 0.05 g/L, L-valine 0.05 g/L, and iron sulfate heptahydrate 0.001 g/L. The spores were germinated, and the cells were grown at 28°C in an incubator shaker, at 220 rpm, for 7 days.

2.2. Screening Optimal Oxygen Vectors. Four types of oxygen vectors including soybean oil, n-hexadecane, n-dodecane, and Tween-80 were investigated in this experiment. Soybean oil and Tween-80 were directly sterilized, and n-hexadecane and n-dodecane were filtered for sterilization. A shaker fermentation medium without oxygen vectors was used as the control. The initial addition concentration was 1% (v/v), and each group performed 3 parallel experiments. After fermentation, the optimal oxygen vector promoting AP-3 biosynthesis was selected by detecting the dry weight of bacteria and AP-3 production in each shaker. After screening the optimal oxygen vector, oxygen-vector concentrations of 0%, 0.5%, 1.0%, 2.0%, and 4.0% (v/v) were examined and 3 parallel experiments were set up in each group. Furthermore, the oxygen vector with the optimal concentration was designed to be added at 0 h, 24 h, 48 h, 72 h, 96 h, and 120 h after inoculation and culture. After fermentation, the optimized addition time of the oxygen vector was explored via the detection of dry weight and AP-3 yield of bacteria. Based on the results of the single-factor optimization experiment, RSM was applied to optimize the addition process of the oxygen vector by choosing AP-3 production as the testing parameter. Design-Expert software was utilized to carry out experimental design and data analysis of the optimal oxygen-vector addition program. The response surface model was further verified by investigating the reliability and accuracy of the optimal oxygen-vector additive process optimized by the model.

2.3. Measurement and Analysis Methods. The AP-3 amount accumulated during fermentation was analyzed by the HPLC approach (Agilent 1260 system utilizing a Shim-pack GIST C_{18} column 250×4.5 mm, 5 μm) with 70% methanol as the mobile phase. The mobile phase flow rate was 0.8 mL/min, and the analysis temperature was 25°C. The HPLC system was equipped with a PDA detector. AP-3 was detected at 254 nm. Moreover, metabolite analysis was performed by using HPLC-MS (ACQUITY UPLC HSS T3 column 100×2.1 mm, 1.8 μm, mobile phase: (A) 0.1% formic acid solution and (B) 0.1% formic acid-acetonitrile solution, at a flow rate of 0.35 mL/min). For sample pretreatment, about 1 mL of the culture was pumped into precooled methanol-water solution (V : V = 4 : 1) with a rapid sampler within 0.2 s, and then, 200 μL of precooled chloroform was added. The mixture was crushed by ultrasonic method in an ice bath and transferred to the EP tube. Subsequently, 20 μL of internal standard (L-2-chlorophenylalanine) was added, and the sample was put into vials and dried. After being dissolved in 200 μL methanol-water solution, the sample was stored at −20°C for 2 h and then centrifuged. The supernatant of 150 μL was filtered through an organic filter and transferred to a sample vial, and metabolites were detected by LC-MS. For MS assay, an electrospray ion source was chosen and MS was performed in the positive or negative ionization mode. The experiments were repeated three times, and the average value of measured parameters was utilized in calculations. For dry cell weight detection, the centrifugated bacteria were washed twice with distilled water and then dried in an oven at 60°C and the mass gain was measured.

3. Results and Discussion

3.1. Effect of Oxygen Vector on AP-3 Production. Four types of oxygen vectors including soybean oil, n-dodecane, n-hexadecane, and Tween-80 were investigated to improve AP-3 production. As shown in Figure 2, oxygen vectors except n-dodecane can promote strain growth. AP-3 production decreased in the order of soybean oil > n-hexadecane > Tween-80. The most efficient fermentation for AP-3 production (101.66 mg/L) was that by choosing soybean oil as the oxygen vector. In addition, soybean oil could be used as a carbon source in the fermentation medium, facilitating strain B24-13 differentiation, sporulation, and secretion of secondary metabolites. Nevertheless, AP-3 yield of the Tween-80 group reduced when compared to that of the control group. It might be attributed to the fact that Tween-80 could be applied as a nutritional resource for microbial growth. Since the biosynthesis of AP-3 was influenced by various factors, Tween-80 was not suitable for promoting AP-3 generation. Therefore, soybean oil was selected as the optimum oxygen vector for in-depth research.

The impact of different concentrations of soybean oil on AP-3 production was investigated in this research. It was

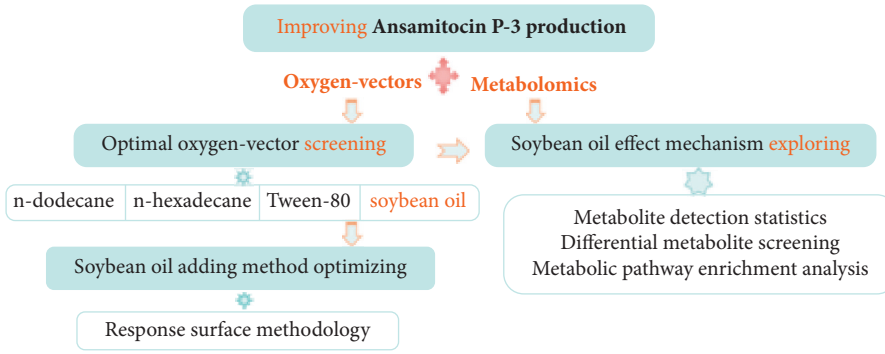


Figure 1: Schematic drawing of improving AP-3 production based on oxygen-vector screening and metabonomics analysis.

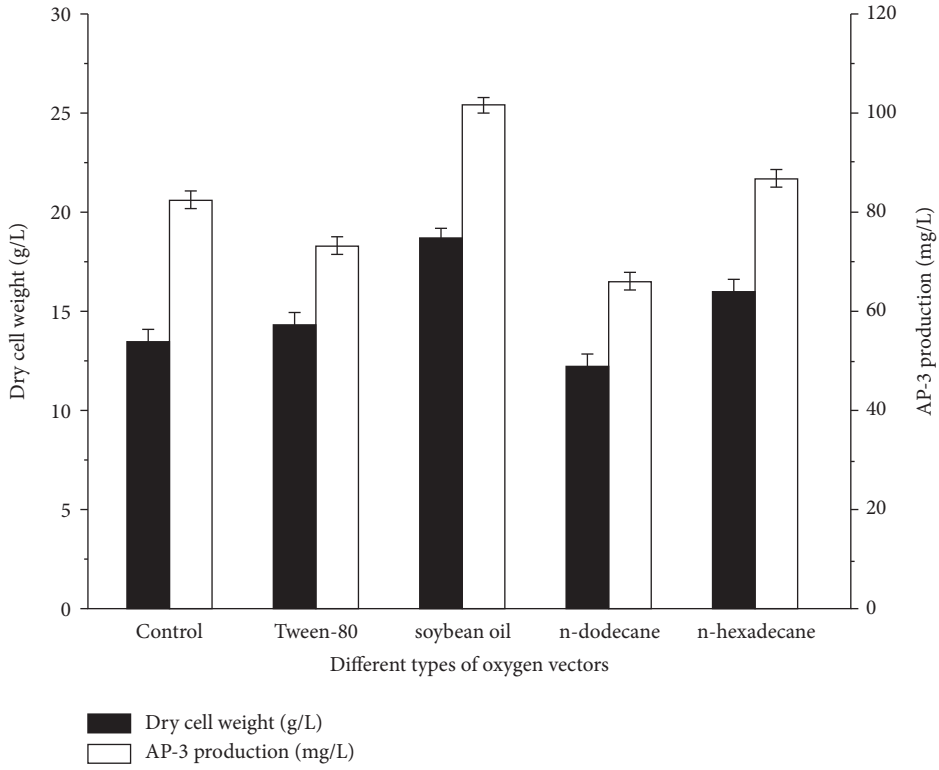


Figure 2: Effect of oxygen-vector types on AP-3 biosynthesis.

observed that AP-3 production could reach 100.33 mg/L when adding only 0.5% soybean oil. However, AP-3 production decreased slightly with soybean oil concentration increasing from 0.5% to 4%. It was found that 4% soybean oil was unfavorable for producing AP-3 and could inhibit cell growth. This phenomenon might be attributed to the fact that more water loss occurred in the fermentation medium under the condition of less liquid content and higher dissolved oxygen. Therefore, 0.5% was chosen as the optimum soybean oil concentration. Furthermore, the effect of the soybean oil addition time on AP-3 biosynthesis was explored. The microbial growth speed and AP-3 production were enhanced obviously when soybean oil was added after 48 h inoculation. Since large amounts of lactic acid and ethanol existed in the fermentation medium, the strain was in a state of oxygen starvation. The addition of soybean oil could effectively solve the dissolved oxygen limitation that occurred in the fermentation system of strain B24-13.

3.2. Response Surface Methodology. Based on single-factor tests, the RSM was used to optimize the addition strategy of soybean oil. As presented in Table 1, the factor levels were coded as −1 and +1 and central points were coded as zero values. Two axial points on the axis of each design variable at a distance of $\pm\alpha$ from the design centre were chosen as $\pm\alpha$. A total of 13 experiments were conducted (Table 2). The fitting equation of AP-3 production and the test variables (A: soybean oil concentration and B: soybean oil addition time) was $Y = -384.549 + 98.065A + 18.387B + 3.25\text{AB}-$

Table 1: Test factors and levels.

Level	Factors	
	A: soybean oil concentration (%)	B: soybean oil addition time (h)
$-\alpha$	0.22	39.51
−1	0.3	42
0	0.5	48
1	0.7	54
α	0.78	56.49

Table 2: Response surface experiment approach and results.

No.	Factor 1 A: soybean oil concentration (%)	Factor 2 A: soybean oil addition time (h)	Response AP-3 production (mg/L)
1	0.7	54	98.3
2	0.5	48	109.4
3	0.78	48	87.3
4	0.3	54	90.5
5	0.5	39.51	79.2
6	0.3	42	91.3
7	0.5	48	107.1
8	0.22	48	85.6
9	0.5	56.49	105.7
10	0.5	48	104.5
11	0.5	48	108.6
12	0.7	42	83.5
13	0.5	48	107.3

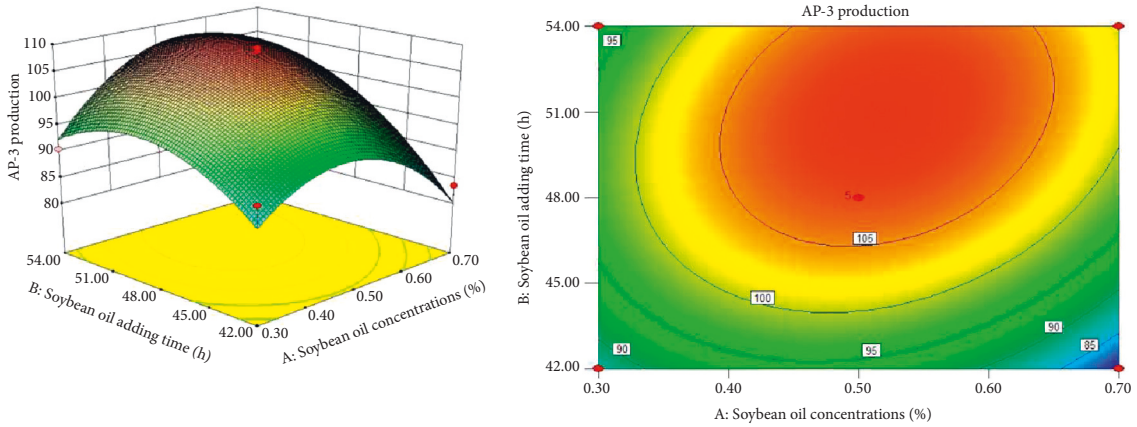
Table 3: Variance analysis of regression model.

Variation source	Quadratic sum	Degree of freedom	Mean square	F-value	P value (prob > F)
Model	1339.6	5	267.92	21.37	0.0004*
A: soybean oil concentrations (%)	0.72	1	0.72	0.058	0.8172
A: soybean oil addition time (h)	331.23	1	331.23	26.42	0.0013*
AB	60.84	1	60.84	4.85	0.0635
A^2	709.99	1	709.99	56.62	0.0001*
B^2	350.93	1	350.93	27.99	0.0011*
Residual error	87.77	7	12.54		
Lack of fit	73.82	3	24.61	7.06	0.0448*
Pure error	13.95	4	3.49		
Total error	1427.37	12			

*Significance.

$252.563A^2$–$0.197B^2$. Variance analysis and significance test were applied for exploring regression effects. The analysis of variance is given in Table 3. The model F-value of 21.37 indicated that the model was significant. As we know, the smaller the magnitude of the P value, the more significant is the corresponding coefficient. And, a P value less than 0.05 demonstrates that the model terms are significant. Therefore, the Fisher F-test with a low probability value (model P value (Prob > F) = 0.0004) also suggested a high significance for the regression model and verified the adequacy of the quadratic model. The regression coefficient of this fitting result was 0.94 (R^2), indicating that the fitting data were in good correlation with the monitoring data. As seen in Figure 3, the optimum soybean oil concentration was 0.52% and the addition time was 50 h. The theoretical maximum yield of AP-3 (108.95 mg/L) could be calculated by substituting levels of the factors into the regression equation. Moreover, the maximum AP-3 production obtained experimentally under the optimized condition was 106.04 mg/L, an improvement of 49.48% compared with that of the control group without adding oxygen vectors.

3.3. Fermentation Curve. After 48 h from the start of fermentation, AP-3 production increased obviously and the dry cell weight increased rapidly because of the addition of soybean oil (Figures 4(a) and 4(b)). The results indicated that the level of dissolved oxygen directly influenced the growth state of strain B24-13, further affecting the synthesis efficiency of metabolites. During the fermentation process of



(a) (b)

Figure 3: (a) Response surface and (b) contour map of the effect of soybean oil concentration and addition time on AP-3 production.

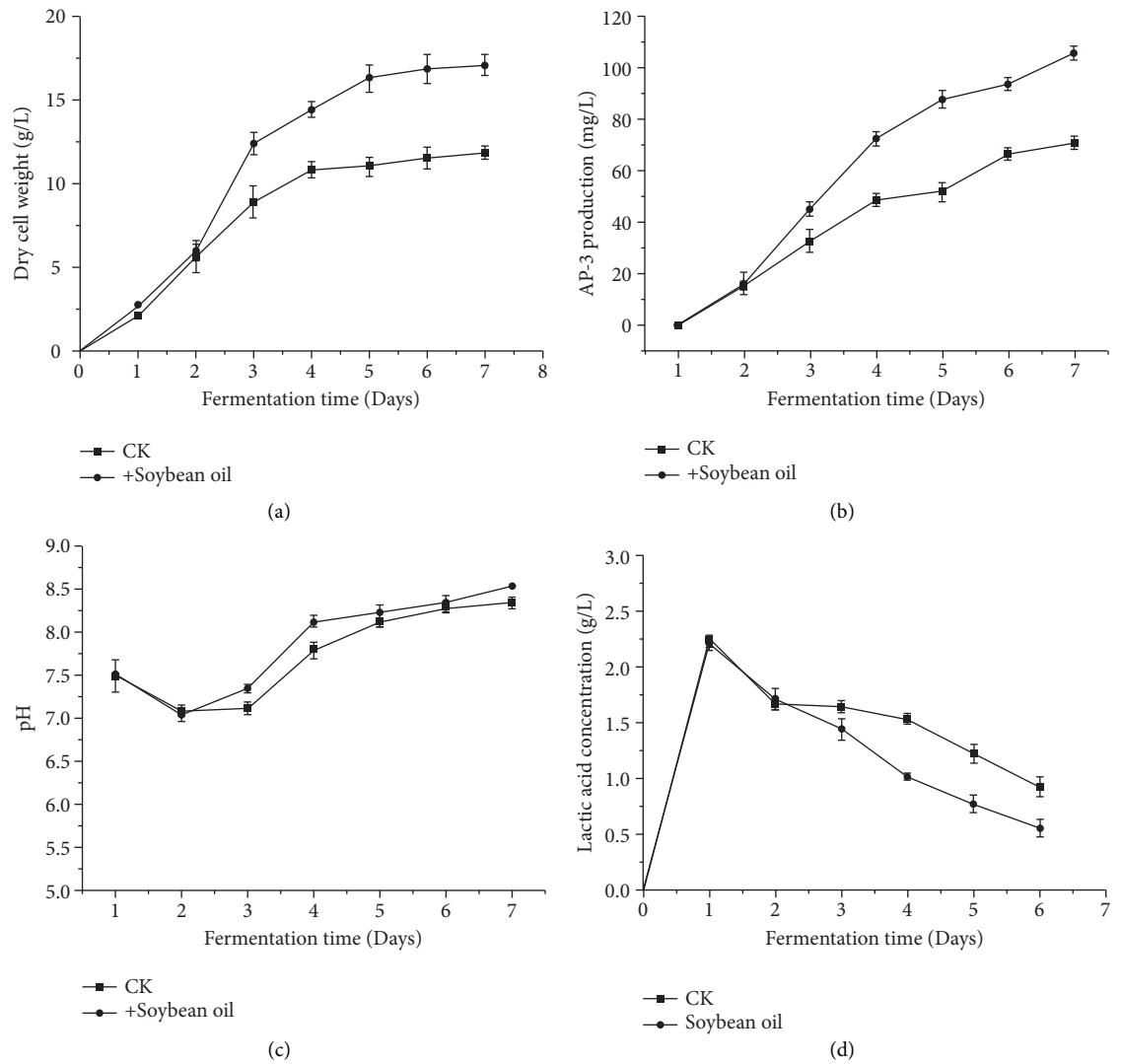


Figure 4: (a) DCW, (b) AP-3 production, (c) pH, and (d) lactic acid content before and after adding soybean oil.

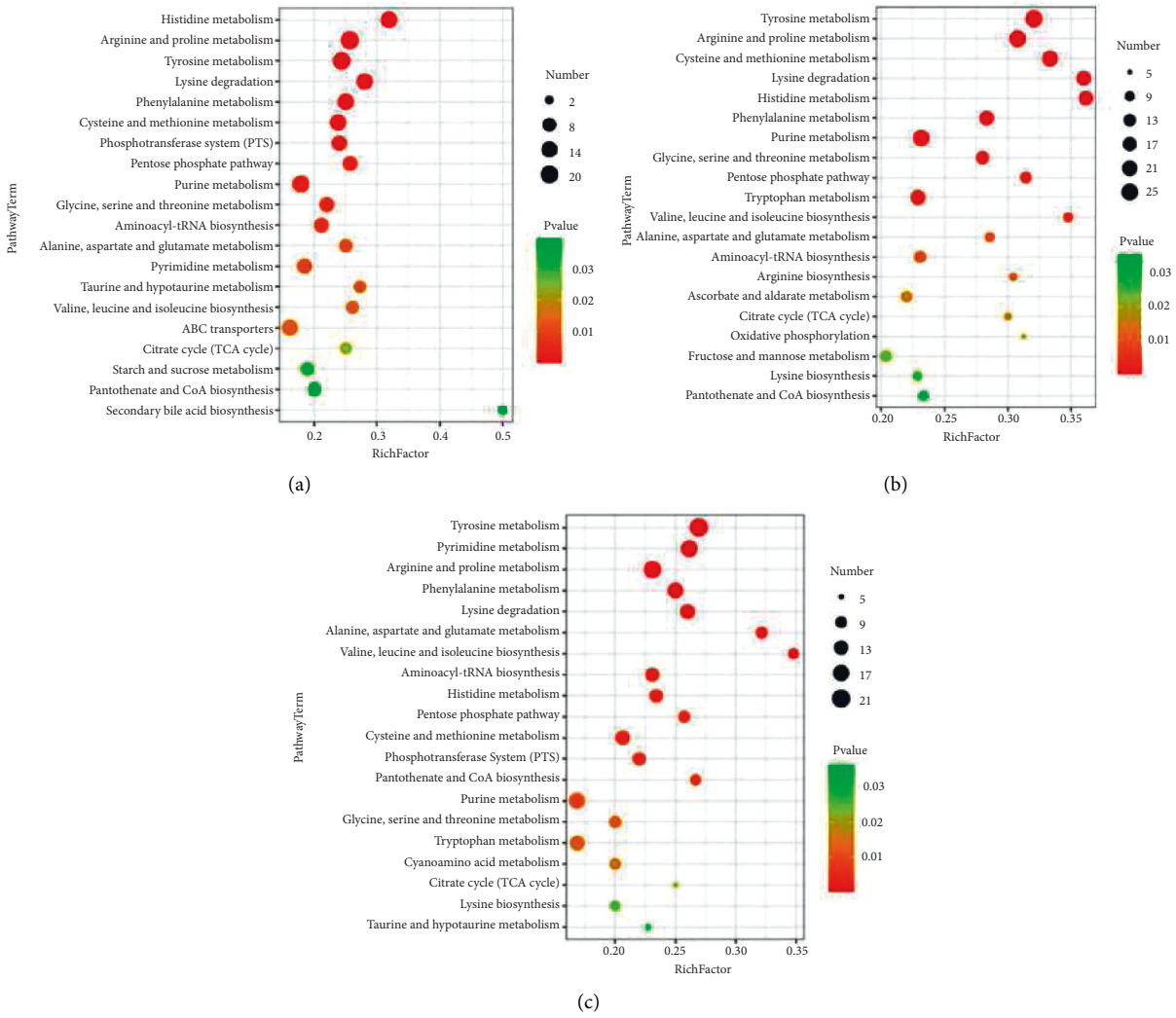


Figure 5: KEGG pathway enrichment analysis of differential metabolites on (a) day 3, (b) day 5, (c) and day 7.

microorganisms, higher oxygen supply promoted the aerobic metabolism of strain B24-13, facilitating AP-3 biosynthesis and strain growth. When strain B24-13 was in the stable phase, the secondary metabolism took place. And, AP-3 production of the experimental group was 106.04 mg/L, 49.48% higher than that of the control group (Figure 4(a)). Under the condition of insufficient dissolved oxygen, pyruvate anaerobic respiration could produce lactic acid. It was observed that the pH value of the control group was lower than that of the experimental group after 48 h of fermentation, suggesting that the utilization of soybean oil was able to enhance the oxygen uptake ability of the strains (Figure 4(c)). To further explore the underlying causes of improving AP-3 production via soybean oil, the metabolites from fermentation were used for metabonomics studies.

3.4. Metabolite Detection Statistics and Differential Metabolite Screening. All metabolites obtained were analyzed qualitatively and quantitatively. Positive and negative models were developed for screening 3765 and 1709 metabolites, respectively. To obtain the pathway information with high genetic similarity with strain B24-13, the identified metabolites were matched with the KEGG database. The related metabolites were screened, including (1) amino acids such as tyrosine (Tyr), proline (Pro), and arginine (Arg); (2) intermediate metabolites in the glycolysis pathway such as glucose-6-phosphate (G6P), 3-phosphoglyceride (3PGA), and pyruvic acid (Pyr); (3) organic acid in the tricarboxylic acid (TCA) cycle such as citric acid, ketoglutaric acid (Akg), and oxaloacetic acid (Oaa); and (4) precursor substances in the Ap-3 biosynthesis process such as UDP-glucose (UDPG) and methoxymalonyl-ACP. These differential metabolites almost cover the AP-3 biosynthesis pathway, facilitating the investigation of intracellular states of strain B24-13 at different dissolved oxygen levels for producing AP-3. To further explore the differences between metabolites, more work still needs to be focused on analyzing the enrichment pathway of differential metabolites.

3.5. Enrichment Analysis of Metabolic Pathways. KEGG pathway enrichment analysis (P value ≤ 0.05) of strain B24-13 differential metabolites in different fermentation stages was carried out (Figure 5). The results indicated that the addition of soybean oil could obviously affect the amino

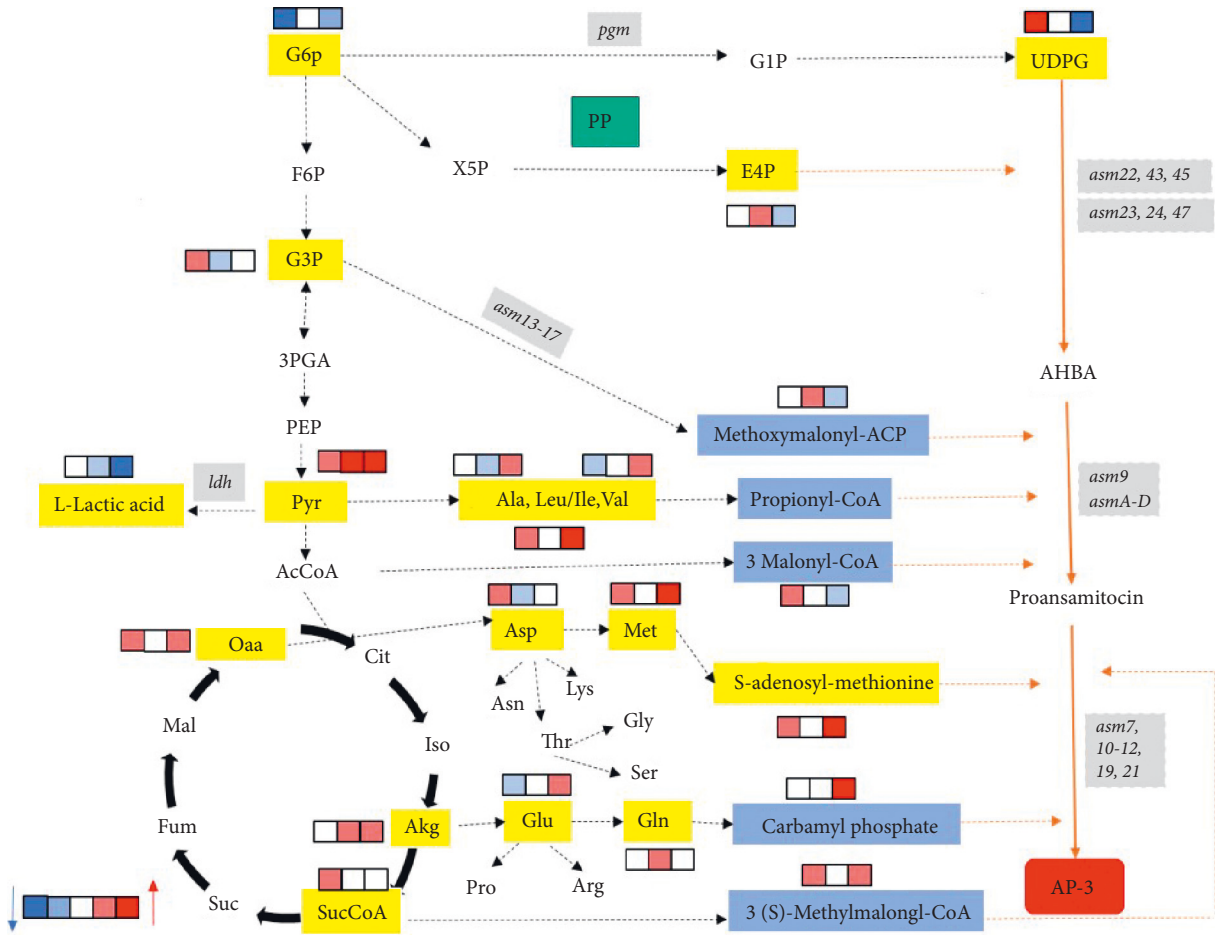


Figure 6: Changes in the AP-3 biosynthetic pathway affected by soybean oil.

acid-related metabolic pathways. And, metabolite enrichment of tyrosine metabolism, lysine degradation, and arginine and proline metabolism was the most significant. The pentose phosphate pathway (PPP) and the tricarboxylic acid cycle (TCA) ran through the entire fermentation stage of strain B24-13. When the strain entered the stable phase from the logarithmic phase, we found that the time of producing enzymes coincided with the time when a series of amino acid metabolic pathways were significantly enriched. This suggested that the metabolism of amino acids into tissue proteins and their metabolites could promote AP-3 biosynthesis. The metabolic enrichment changes of alanine, aspartic acid, and glutamic acid metabolism and valine, leucine, and isoleucine biosynthesis were significant. Therefore, the application of the soybean oil oxygen vector facilitated various amino acid metabolisms, further motivating AP-3 production.

3.6. Analysis of Significant Metabolic Pathways of Differential Metabolites. To further explore the effect of dissolved oxygen on the metabolism of strains and the improvement of AP-3 production, changes in the intracellular metabolite content in the presence of oxygen vector were explored by analyzing central carbon metabolism, amino acid metabolism, and AP-3 synthesis pathway. As seen in Figure 6, the pentose phosphate pathway (PP) and glycolysis pathway (EMP) were downregulated, indicating that the added soybean oil could increase the oxygen uptake rate of strain B24-13 and consume primary metabolic intermediates for aerobic metabolism. Nevertheless, the intermediate metabolites of the tricarboxylic acid (TCA) cycle were upregulated, suggesting that soybean oil was able to enhance the TCA cycle metabolism, further providing precursors for biosynthesizing AP-3. This result coincided with the utilization of oxygen vectors for improving *Streptomyces albus* PD-1 metabolism to synthesize β-phospholipase [38]. The intermediate metabolites produced by central carbon metabolism including erythritol-4-phosphate (E4P), phosphoenolpyruvic acid, propionyl-CoA, methylmalonyl-ACP, and methylmalonyl-CoA were precursors of AP-3 biosynthesis.

The relative content of pyruvate (Pyr) in the EMP pathway was significantly upregulated. On the one hand, Pyr came into contact with amino acid metabolic pathways or lactic acid. On the other hand, Pyr went into TCA cycle metabolism through acetyl-CoA. Therefore, changes in pyruvate concentration might reveal changes in dissolved oxygen levels in the fermentation environment, which played an important role in metabolic regulation. Moreover,

the intermediate products of the TCA cycle including α-ketoglutarate (Akg), succinic acid-CoA, and oxaloacetic acid (Oaa) were significantly upregulated during the stationary phase of fermentation. These metabolites could be converted to precursors for AP-3 biosynthesis. These results highlighted the critical influence of oxygen vectors on the efficiency of biological processes and the metabolic behavior of host cells, which directly affected the production of metabolites.

As shown in Figure 6, the relative contents of amino acids were significantly upregulated in the presence of soybean oil, indicating that the addition of soybean oil increased the dissolved oxygen level of fermentation, further promoted the bacteria, and synthesized a large number of amino acids for AP-3 biosynthesis. The aspartic acid (Asp) and the glutamate (Glu) were used as ammonia donors for, respectively, biosynthesizing methionine (Met) and glutamine (Gln), further providing compounds for producing carbamoyl phosphate, S-adenosine-methionine, and other AP-3 precursors. Pyruvate-derived alanine (Ala), valerian (Val), leucine (Leu), and isoleucine (Ile) were the precursors of methylmalonyl-CoA biosynthesis. The relative contents of these amino acids were significantly upregulated, which was beneficial to AP-3 production.

UDP-glucose (UDPD) was the important precursor of AP-3 biosynthesis, and it could be converted to glucose 1-phosphate (G1P) by using glucose 6-phosphate mutase (PGM). Subsequently, G1P was converted to UDPD and produced 3-amino-5-hydroxyl-benzoic acid (AHBA) precursor through the amino-shikimate route. It was observed that the phosphorylation level was significantly increased and the relative content of UDPD was significantly upregulated when the dissolved oxygen level was high. During the AP-3 rapid synthesis period, the UDPD concentration decreased rapidly because of synthesizing AP-3. This was similar to the effect of adding oxygen vectors on metabolic flux distribution in *Bacillus subtilis* NX-2 fermentation process [39]. As a precursor of AP-3 biosynthesis, S-adenosyl-methionine could participate in the extension and modification process of the polyketone carbon chain. When the dissolved oxygen level was high, S-adenosyl-methionine concentration upregulated during the stationary phase, facilitating the increase in AP-3 yield. In conclusion, the addition of soybean oil increased the dissolved oxygen level in the fermentation process, which was beneficial to the energy metabolism of strains, further improving AP-3 production.

3.7. VGB Gene Expression in the A. pretiosum Strain B24-13. To further improve the yield of AP-3, the genetic performance of strain B24-13 was improved via genome shuffling technology. In this work, three strategies including PEG-mediated protoplast transformation, electrotransformation, and conjugation transformation were applied to introduce the exogenous VGB gene into the A. *pretiosum* strain B24-13. By promoting oxygen delivery, oxygen utilization, cell growth, respiration, metabolism, and AP-3 biosynthesis yield might be improved. The recombinant plasmid pET28a-VGB was transformed into *E. coli* BL 21, and the expression level of VHb protein was analyzed by using SDS-PAGE. Unfortunately, no transformant was obtained when recombinant plasmid pIJ86-VGB was constructed for protoplast transformation and electrotransformation. The conditions of the transformant need to be further explored. In addition, the recombinant plasmid PIB139-VGB was constructed and the conjugation transformation condition was investigated. The optimal medium was determined to be the MS medium. The concentration ratio of the donor and recipient was 1 : 1, and the best coverage period of the antibiotic solution was 18 h. More effort needs to be put into screening positive zygotes.

4. Conclusion

Four types of oxygen vectors including soybean oil, Tween-80, n-dodecane, and n-hexadecane were utilized to improve AP-3 yield. Results suggested that soybean oil was the optimum oxygen vector. As the concentration of the oxygen vector was an important factor in the AP-3 biosynthesis process, the impact of different concentrations of soybean oil on AP-3 production was investigated in this research. The optimized addition concentration of soybean oil was 0.5%, and the addition time was 48 h. Furthermore, the optimal addition strategy of soybean oil was explored by using RSM based on the single-factor optimization experiment. We found that the optimum addition amount of soybean oil was 0.52% and the addition time was 50 h. Under this condition, the maximum AP-3 production was 106.04 mg/L. In comparison with the control group without adding soybean oil, an improvement of 49.48% was observed. Metabonomics analysis based on LC-MS was carried out to investigate the intermediate metabolites of the strain at various stages at different dissolved oxygen levels. Positive and negative models were developed for quantitatively screening 3765 and 1709 metabolites, respectively. The metabolites associated with precious orange tufts actinomycetes include amino acids, EMP intermediate metabolites, organic acids in the TCA cycle, and precursors of the AP-3 biosynthesis pathway. The enrichment results of metabolic pathways and the fermentation metabolism curve showed that the TCA cycle and amino acid metabolism increased with the increase in fermentation dissolved oxygen level, which promoted the life activities of bacteria and improved metabolic flux of secondary metabolism. In addition, genetic engineering was investigated to obtain oxygen-carrying genes to improve the oxygen utilization rate of strains. Further work needs to be focused on screening desirable zygotes.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Exploration on the Improvement of Cognitive Function and Inflammatory Response in Perimenopausal Patients with Mild Cognitive Impairment by Self-Prepared Ningshen Prescription

Wei Yang, Yumei Ye, Yan Cai, Guiyan Wang, Menghao Wang, and Xiaodan Zhang

Department of TCM, Seventh People's of Shanghai University of TCM, Shanghai 200137, China

Correspondence should be addressed to Xiaodan Zhang; daidai811126@sina.com

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Objective. To investigate the improvement of cognitive function and inflammatory response in perimenopausal patients with MCI by kidney-tonifying, blood-activating, and mind-nourishing. *Methods*. 80 perimenopausal patients with MCI who met the diagnostic criteria were divided into a therapy group ($n = 40$) and a control group ($n = 40$) according to the treatment method. The control group was given nimodipine (Bayer Pharmaceuticals) 30 mg, 3 times/day orally, while the therapy group was given a decoction of self-prepared Ningshen prescription on the top of the control group (glossy privet fruit, mulberry, aizoon stonecrop, dan-shen root, tuber fleeceflower stem, cyperus rotundus, citron). Patients in the 2 groups were assessed on the MocA scale, ADL scale, and TCM symptom score before and after 2 months of treatment, respectively, to observe whether there was any change in the scale scores and in the levels of inflammatory factors (hs-CRP, Hcy, and IL-1β) Pre- and posttherapy in the 2 groups. Observe the improvement of clinical symptoms and their safety in both groups (liver and kidney function indicators such as ALT, AST and Cr, dizziness, headache, decrease in blood pressure, flushing, and gastrointestinal reactions). *Results*. The efficacy of the therapy group was better than that of the control group; the MocA scale and ADL scale scores improved and the TCM symptom score decreased in both groups posttherapy, with the MocA scale and ADL scale scores improving more and the TCM symptom score decreasing more in the therapy group compared with the control group during the same period ($p < 0.05$). The serum levels of hs-CRP, Hcy, and IL-1β decreased in both groups posttherapy, with the serum levels of hs-CRP, Hcy, and IL-1β decreasing more in the therapy group compared to the control group during the same period ($p < 0.05$). The difference in adverse events between the two groups was not statistically significant when compared by a chi-square test ($p > 0.05$). The differences in ALT, AST, and Cr levels between the control group and the treatment group before and after treatment were not significant ($p > 0.05$). *Conclusion*. Ning Shen prescription can effectively prevent the continued development of cognitive dysfunction in perimenopausal patients with MCI, delay its natural course, and can improve the patients' ability to perform daily activities and improve their TCM symptoms.

1. Foreword

Perimenopause is a period of physiological changes that every woman goes through around the time of menopause. During this period, some women experience menstrual disorders, sweating, irritability, and mild cognitive impairment such as difficulty concentrating and reduced learning and memory skills due to changes in ovarian function and reduced production of sex hormones [1, 2]. Patients with mild cognitive impairment (MCI) do not meet the diagnostic criteria for dementia in terms of severity of cognitive function but fall between normal aging of memory and dementia, which may eventually progress to Alzheimer's disease or other types of dementia, and are generally prevented and treated by medical researchers as a predementia stage [3]. In recent years, the incidence of various geriatric diseases, such as dementia, has been increasing due to the ageing of the population. Dementia and MCI, which are

characterised by impairment of intelligence, pose a number of medical and social problems, particularly for family members, which are particularly acute in modern, fast-paced society [4, 5].

There is still a lack of authoritative statements on the pathogenesis of MCI, and the drugs that are more widely used clinically for treatment are those that mainly improve symptoms, such as cholinesterase inhibitor (acetylcholinesterase inhibitor, AchEI) and ionotropic glutamate receptor antagonist (N-methyl-D-aspartate receptor), but according to the available findings [6, 7], there is still no significant evidence on the efficacy of these drugs in intervening the conversion rate of MCI to dementia, and further studies are needed to confirm this. In recent years, with in-depth research on MCI, Chinese medicine has achieved good results in improving symptoms, delaying the disease, and improving patients' quality of life, and the investigation of its intrinsic mechanism has received a lot of attention from clinical workers [8, 9]. Cognitive disorder is the name of a modern medical disease, but Chinese medicine does not have an exact name for it, rather it is classified as a disease related to "dementia," "forgetful" and other mental illnesses based on its clinical manifestations in memory, thinking and language [10]. Chinese medicine believes that the disease of good forgetfulness is located in the brain and its pathological changes are closely related to the heart, spleen, and kidney. In recent years, several studies [11, 12] have classified statistics on the TCM typology of MCI, and the typology of MCI is based on the common features of MCI such as kidney deficiency, liver depression, and phlegm and blood stasis, which brings new ideas to the treatment of MCI.

In this study, after collecting clinical data and collating the literature, we selected MCI patients with kidney deficiency and blood stasis as the study subjects to observe the clinical effectiveness and drug safety of treatment with Ning Shen prescription in MCI patients with kidney deficiency and blood stasis.

2. Information

2.1. General Data. 80 cases of perimenopausal female MCI patients in our hospital from October 2020 to October 2021 were selected and divided into 40 cases each in the therapy group (Ning Shen prescription) and the control group (nimodipine treatment), and the general information of the 2 groups is compared in Table 1.

2.2. Diagnostic and Identification Criteria

2.2.1. Western Medical Diagnosis. Diagnostic criteria for MCI in perimenopause were developed based on previously published literature related to diagnostic criteria for MCI [13], and perimenopausal characteristics [14]. (i) Women aged 40–60 years; (ii) self-reported memory loss or informed reports of memory loss; (iii) MOCA scale score <26, plus 1 point if the patient has less than or equal to 12 years of education; General Decline Scale (GDS) = 2-3 or Clinical Dementia Rating Scale (CDR) = 0.5; (iv) Normal daily living: score of <26 on the Ability to Perform Daily Living Scale (ADL); (v) whose cognitive decline has not yet met the diagnostic criteria for dementia.

2.2.2. Diagnosis in Chinese Medicine. By reviewing the literature [15, 16], the diagnostic criteria for perimenopausal MCI of the kidney deficiency and blood stasis type were developed: (i) women aged 40–60 years; (ii) main symptoms: forgetfulness and memory loss; (iii) secondary symptoms: soreness and weakness of the waist and knees, tiredness and sleepiness, dizziness and tinnitus, heavy limbs, headache like a thorn or a pain that does not move, dark purple in the mouth and claws, and dry skin; and (iv) tongue and pulse: purple tongue or petechiae, dark veins under the tongue, fat tongue, greasy coating; sluggish or sunken pulse. The diagnosis can be made by having one of the main symptoms plus two of the secondary symptoms combined with the tongue and pulse.

2.3. Inclusion Criteria. Incluion criteria were as follows:

(i) Those who met the above diagnostic and identification criteria in Western medicine and Chinese medicine

(ii) Those who were perimenopausal women aged 40~60 years old and had no reproductive plans

(iii) Those who met the Kupperman Index (KI) score ≥15 on the Modified KI Scale

(iv) Those who did not receive other drugs or methods of treatment for cognitive impairment 4 weeks prior to this treatment

2.4. Exclusion Criteria. Exclusion criteria were as follows:

(i) Cognitive dysfunction caused by other diseases

(ii) Those who were using drugs prohibited by the study and cannot stop

(iii) Combination of serious primary diseases such as severe cardiovascular, hepatic, renal and hematopoietic system, psychiatric patients, or systemic diseases such as pain, fever, cough, surgery.

(iv) Those with severe neurological deficits who could not cooperate with the physician to complete the relevant tests

(v) Alcohol and drug abusers; patients who had undergone surgery or medical conditions that affect pharmacokinetics such as gastrointestinal surgery or disease

2.5. Treatment. Those who met the inclusion criteria were randomly divided into the therapy group and the control group. Both groups were given conventional medication for the underlying disease, such as hypertension and diabetes mellitus patients with antihypertensive drugs and hypoglycemic drugs, respectively, and those without

Table 1: Comparison of general data between the two groups.

Data		Control group ($n = 40$)	Therapy group ($n = 40$)	t or χ^2 value	p value
Age distribution (n, %)	40~45 years	9 (22.50)	7 (17.50)	0.825	0.843
	46~50 years	14 (35.00)	12 (30.00)		
	51~55 years	13 (32.50)	16 (40.00)		
	56~60 years	4 (10.00)	5 (12.50)		
Age at menarche (years, $\overline{x} \pm s$)		15.12 ± 1.37	14.89 ± 1.43	0.735	0.465
Duration of disease (months, $\overline{x} \pm s$)		4.03 ± 0.91	4.06 ± 0.93	0.146	0.884
Menopause (n, %)		9 (22.50)	7 (17.50)	0.313	0.576
Level of education (n, %)	Illiterate	4 (10.00)	6 (15.00)	1.376	0.711
	Primary school	13 (32.50)	12 (30.00)		
	Lower secondary	16 (40.00)	18 (45.00)		
	High school and above	7 (17.50)	4 (10.00)		
Personal history (n, %)	Smoking	9 (22.50)	11 (27.50)	0.267	0.606
	Alcohol consumption	7 (17.50)	10 (25.00)	0.672	0.412
MocA (points, $\overline{x} \pm s$)		21.32 ± 1.34	21.51 ± 1.43	0.613	0.542
ADL (points, $\overline{x} \pm s$)		45.51 ± 8.27	46.27 ± 7.87	0.421	0.675
TCM symptom score (points, $\overline{x} \pm s$)		16.23 ± 4.10	16.57 ± 4.23	0.365	0.716
hs-CRP (μmol/L, $\overline{x} \pm s$)		15.87 ± 2.63	15.42 ± 2.66	0.761	0.449
Hcy (μmol/L, $\overline{x} \pm s$)		14.21 ± 4.69	14.87 ± 4.76	0.625	0.534
IL-1β (ng/L, $\overline{x} \pm s$)		50.22 ± 13.18	50.46 ± 12.69	0.083	0.934
ALT (U/L, $\overline{x} \pm s$)		24.23 ± 4.07	23.95 ± 3.89	0.315	0.754
AST (U/L, $\overline{x} \pm s$)		19.08 ± 3.72	19.14 ± 4.03	0.069	0.945
Cr (μmol/L, $\overline{x} \pm s$)		80.24 ± 13.15	81.07 ± 13.99	0.273	0.785

contraindications to aspirin were treated with aspirin 0.1 g, 1 time/day.

In the control group, nimodipine (Bayer Pharmaceuticals) 30 mg was given orally 3 times/day. In the therapy group, Ning Shen prescription was added to the control group with water decoction; 150 ml/time, 2 times/day, for 2 months. Ning Shen prescription consists of glossy privet fruit, mulberry, aizoon stonecrop, dan-shen root, tuber fleeceflower stem, cyperus rotundus, and citron.

2.6. Observation Indicators

(i) Patients were assessed on the Montreal Cognitive Assessment Scale (MoCA), ADL scale, and TCM symptom score pre- and posttherapy, respectively. The MocA scale was used to assess the cognitive function of patients pretherapy and after 12 weeks of therapy. The scale consists of 11 entries in 8 cognitive domains, specifically concentration, memory, language, computation and orientation, executive function, visual structure skills, and abstract thinking, with a total score of 30, and a score of 26 and above was considered normal. Patients' self-care ability was assessed by using the ADL scale, with a total score of 100, less than or equal to 19 being completely unable to take care of themselves, 20–39 being in need of greater assistance, 40–59 being partially in need of assistance, and 60 being basically able to take care of themselves. The higher the score, the better the patient's ability to take care of himself/herself.

(ii) To observe whether there was any change in the scale scores pre- and posttherapy and whether there was any change in the levels of inflammatory factors (hs-CRP, IL-1β, and TNF-α) pre- and posttherapy in the 2 groups. Before and after therapy, 2 ml of elbow vein blood was drawn in the morning on an empty stomach, and the serum was centrifuged at 3000 r/min for 10 minutes to obtain the serum, which was labeled and stored at −80°C in the refrigerator for batch determination. The TNF-6 and IL-6 levels were measured by radioimmunoassay, and the kits were obtained from the Northern Immunological Reagent Institute of China Isotope Company. The level of hs-CRP in serum was measured by the immunoturbidimetric method by the professional laboratory staff of the Department of Laboratory Medicine of the hospital, using a Hitachi 7180 fully automatic biochemical analyzer and reagents from Shenzhen Jingmei Biotechnology Co.

(iii) To observe the improvement of clinical symptoms and their safety in both groups (liver and kidney function indicators such as ALT, AST and Cr, dizziness, headache, decrease in blood pressure, flushing, and gastrointestinal reactions).

(iv) Efficacy assessment criteria [17] were divided into effective, efficient, and ineffective; the MocA score was used as the main reference index and combined with the improvement of clinical symptoms to make a comprehensive evaluation, MOCA score = [(posttherapy score − pretherapy score)/pretherapy score] × 100%. ① Significant effect: MOCA score ≥40%, clinical symptoms and signs improved significantly. ② Effective: 20% ≤ MOCA < 40%, clinical symptoms and signs have improved. ③ Invalid: MOCA score <20%, or even decreased, clinical symptoms and signs did not improve significantly, or even worsened.

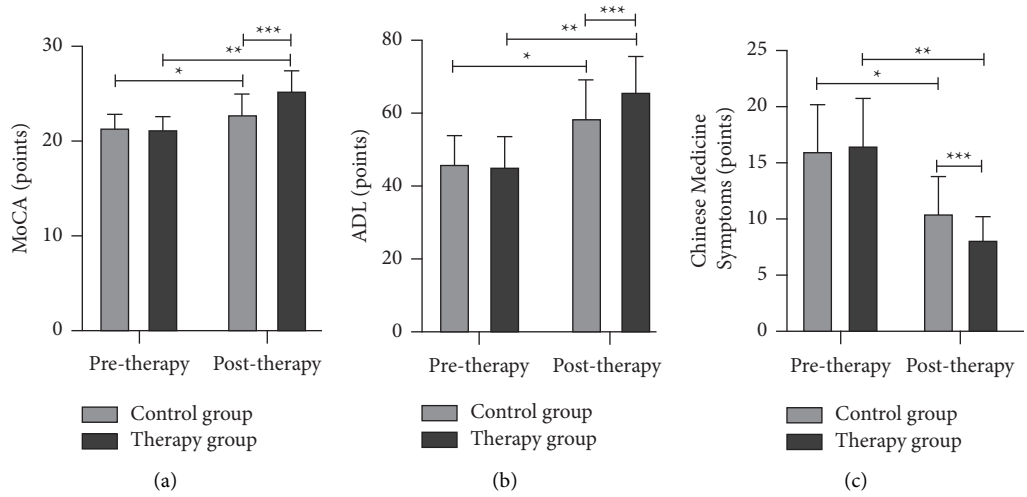

Figure 1: Comparison of MocA scale, ADL scale scores, and TCM symptom scores between the 2 groups ($\overline{x} \pm s$). (a) The MocA scale score, (b) the ADL scale score, and (c) the TCM symptom score. The special symbol * is the difference between the control group pre- and posttherapy $p < 0.05$, ** is the difference between the therapy group pre- and posttherapy $p < 0.05$, and *** is the difference between the control group and the therapy group during the same period $p < 0.05$.

2.7. Statistical Method. The data of this study were statistically analyzed using SPSS22.0 software. Count data were expressed as n (%) with χ^2 test; measurement data were described as the mean ± standard deviation ($\overline{x} \pm s$) with t-test; differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Comparison of General Information of the Two Groups. According to Table 1, there were no significant differences in age distribution, age at menarche, proportion of menopause, education level, personal history, initial MocA, ADL, TCM symptom score and initial hs-CRP, Hcy and IL-1β levels in the 2 groups of MCI patients ($p > 0.05$).

3.2. Comparison of MocA Scale, ADL Scale Scores, and TCM Symptom Scores Pre- and Posttherapy between the Two Groups. According to Figure 1, the differences in MocA scale, ADL scale scores, and TCM symptom scores between the 2 groups of MCI patients pretherapy were not significant ($p > 0.05$). Posttherapy, the MocA scale and ADL scale scores of the two groups improved, and the TCM syndrome points decreased ($p < 0.05$). Among them, the MocA scale and ADL scale scores improved more and the TCM syndrome points decreased more in the therapy group compared with the control group ($p < 0.05$).

3.3. Comparison of Inflammatory Factor Levels Pre- and Posttherapy between the Two Groups. According to Figure 2, the differences in the serum levels of hs-CRP, Hcy, and IL-1β between the 2 groups of MCI patients pretherapy were not significant ($p > 0.05$). Posttherapy, the serum levels of hs-CRP, Hcy and IL-1β decreased in both groups ($p < 0.05$); the serum levels of hs-CRP, Hcy and IL-1β decreased more in the therapy group compared with the control group ($p < 0.05$).

3.4. Comparison of the Clinical Efficacy of the Two Groups. According to Figure 3, the apparent, effective, and null rates of MCI patients in the control group were 20.00%, 60.00%, and 20.00%, respectively, while the apparent, effective, and null rates of MCI patients in the therapy group were 40.00%, 55.00%, and 5.00%, respectively. The overall effective rate of treatment was found to be better than that of the control group ($p < 0.05$).

3.5. Comparison of Adverse Events between the Two Groups. The incidence of adverse events such as dizziness, headache, decreased blood pressure, flushed face, and gastrointestinal reactions during treatment in the control group of MCI patients was 5.00%, 2.50%, 2.50%, 2.50%, 2.50%, and 7.50%, respectively. The incidence of adverse events such as dizziness, headache, decreased blood pressure, flushed face, and gastrointestinal reactions during treatment in the MCI patients in the therapy group was 2.50%, 2.50%, 2.50%, 5.00%, and 5.00%, respectively. According to Figure 4, the overall incidence of adverse events such as dizziness, headache, decreased blood pressure, flushed face, and gastrointestinal reactions during treatment was not significantly different between the two groups of MCI patients ($p > 0.05$).

3.6. Comparison of Treatment Safety between the Two Groups. According to Figure 5, the differences in ALT, AST, and Cr levels between the 2 groups of MCI patients before and after treatment were not significant ($p > 0.05$). The differences in ALT, AST, and Cr levels between the control group and the treatment group before and after treatment were not significant ($p > 0.05$).

4. Discussion

With the improvement of modern quality of life and medical care and the increasing ageing of society, the number of

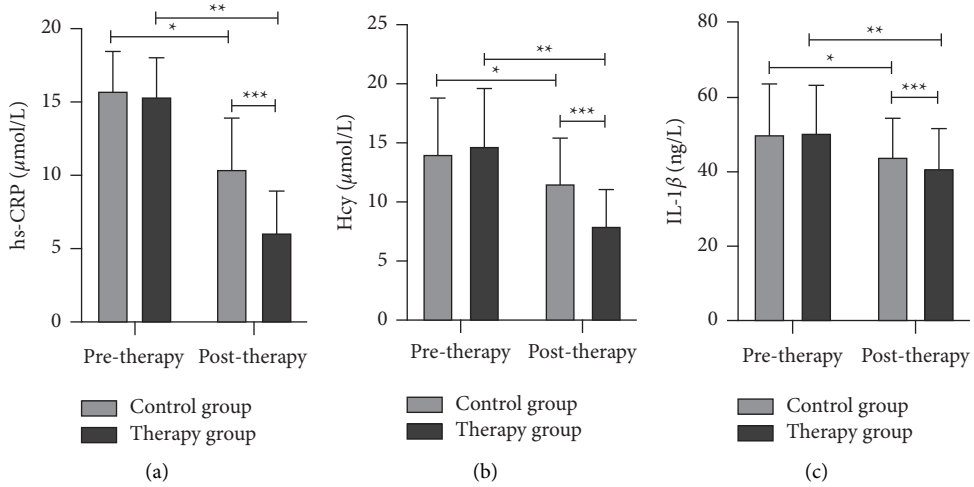

Figure 2: Comparison of serum hs-CRP, Hcy, and IL-1β levels in the 2 groups ($\overline{x} \pm s$). (a) The hs-CRP level, (b) the Hcy level, and (c) the IL-1β level. The special symbol * is the difference between the control group pre- and posttherapy $p < 0.05$, ** is the difference between the therapy group pre- and posttherapy $p < 0.05$, and *** is the difference between the control group and the therapy group during the same period $p < 0.05$.

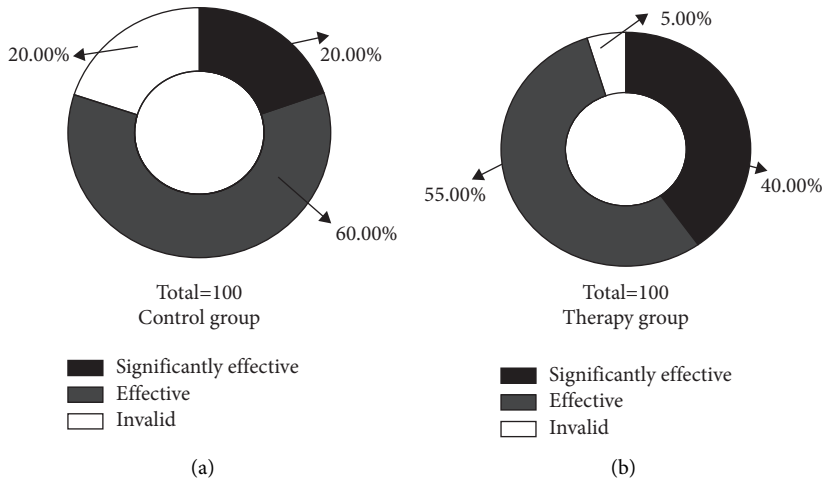

Figure 3: Comparison of clinical outcomes between the 2 groups (n, %). (a) The distribution of efficacy in the control group and (b) the distribution of efficacy in the therapy group.

patients with Alzheimer's disease (AD) is increasing every year. AD is the most common cause of death in the elderly after tumors, cardiovascular diseases, stroke, and other diseases, which brings great burden and challenges to countless patients, families, and society [18]. Among the factors associated with the onset of AD, age, genetics, gender, and endocrine metabolism are the most predominant; the incidence of DA increases with age, and the clinical presentation differs between men and women, with a preference for women [19]. In addition, some studies [20, 21] have found that cognitive function is much more impaired in women than in men at the same stage of AD, which may be related to abnormal estrogen levels in peri- or postmenopausal women. MCI is often seen as a pre-AD state and a high risk factor for developing AD. Therefore, effective interventions for perimenopausal patients in the pre-AD

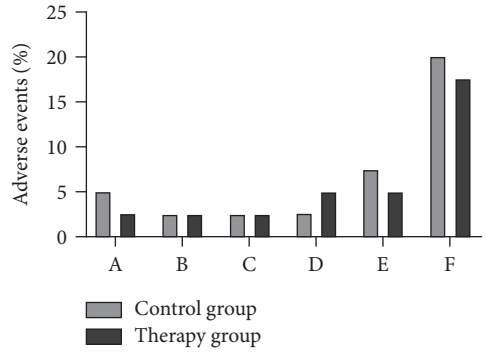

Figure 4: Comparison of adverse events in 2 groups (n, %). *Note.* In the graph, A indicates dizziness, B indicates headache, C indicates decreased blood pressure, D indicates flushed face, E indicates gastrointestinal reactions, and F indicates total incidence of adverse events.

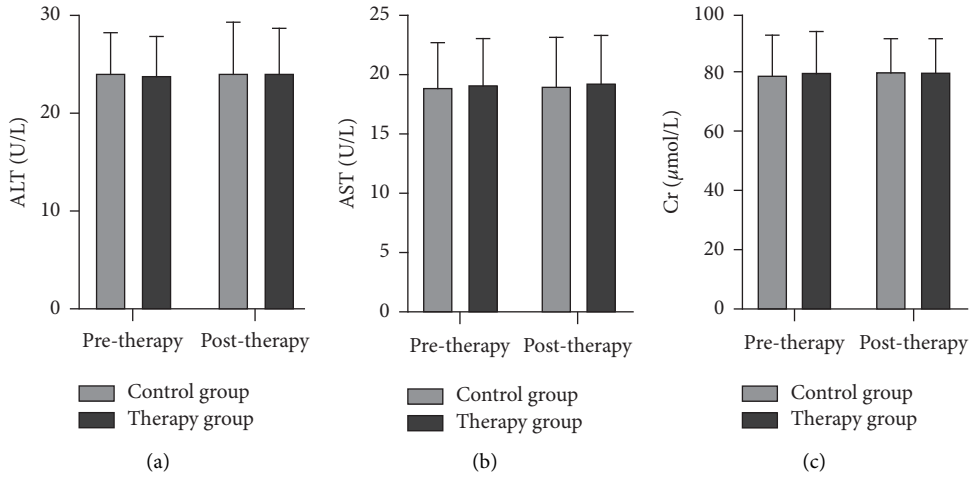

Figure 5: Comparison of treatment safety between the 2 groups ($\overline{x} \pm s$). (a) The serum ALT level, (b) the serum AST level, and (c) the serum Cr level.

state to improve symptoms and prevent or delay the onset of AD as much as possible is one of the current hot topics of research.

Western drugs such as brain cell activators and cerebral vasodilators are currently used in clinical work for the treatment of MCI, with average overall effects. In recent years, with the continuous development of Chinese medicine in China, herbal treatment has gained great achievements in many fields and has certain advantages in the clinical treatment of MCI [22]. According to the Chinese medical knowledge of the pathogenesis of MCI, the disease is located in the brain and is closely related to the kidney. The loss of kidney qi, insufficient qi and blood, and internal stagnation of stagnant blood cause the brain marrow and head orifices to lose moistening, and gradually the marrow sea is not filled, resulting in the loss of the use of the mental organ and causing the disease [23, 24]. In this study, treatment with the self-prepared Ning Shen prescription showed that the treatment group showed significantly higher improvements in cognitive ability, activities of daily living, inflammatory factor levels, and TCM symptom scores than the control group after treatment. The whole formula works together to nourish the liver and kidney, and to calm the mind. It also enriches the marrow to enable the brain to control the mental thinking and visceral functions of the body, which in turn helps to improve the symptoms of MCI. In addition, when the essence in the kidney is full, the marrow sea is nourished and the marrow is full, the brain spirit can effectively control the movement of the limbs, which helps to improve many symptoms of MCI. Modern pharmacological studies have confirmed that the liver and kidney tonics such as glossy privet fruit [25] and mulberry [26] can promote Bcl-2 gene expression in the body, reduce neuronal apoptosis, and improve blood viscosity and microcirculation to enhance blood flow to brain tissue and improve central nervous system function. Modern pharmacological research [27] found that Danshen contains tanshinone I and cryptotanshinone and other quinones, which can dilate coronary arteries and peripheral blood vessels and increase coronary blood flow, and its combined use with Panax ginseng has the functions of delaying brain aging and protecting nerve cells. In this study group, we combined Western medicine treatment with Chinese medicine diagnosis theory to treat perimenopausal women with MCI by Ning Shen prescription. The combination of Chinese and Western medicine worked in synergy, resulting in more significant improvements in cognitive function, quality of life, symptomatology, and inflammatory response in the therapy group. In addition, there were no patients with serious significant adverse reactions in either group throughout the clinical observation trial. The values of ALT, AST, and Cr in the therapy and control groups before and after the whole trial were not significantly different ($p > 0.05$). The statistical results basically indicated that the treatment and control groups had no serious effects on the liver and kidney functions of the patients in the short term and had a certain degree of safety.

In conclusion, the combination of Ning Shen prescription with western medicine can significantly improve the cognitive function, quality of life, and symptoms of perimenopausal female MCI patients, and the efficacy of Chinese medicine symptoms can be improved. There were no uncomfortable symptoms related to Chinese medicine during the study, no serious adverse events, and no significant effects on the liver and kidney functions of the patients in the short term, so the safety profiles were all excellent.

Data Availability

Data are available from the corresponding author on reasonable request.

Ethical Approval

This study has been approved by the ethics committee (2019004E).

Conflicts of Interest

The authors declare that there are no conflicts of interest in any respect.

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