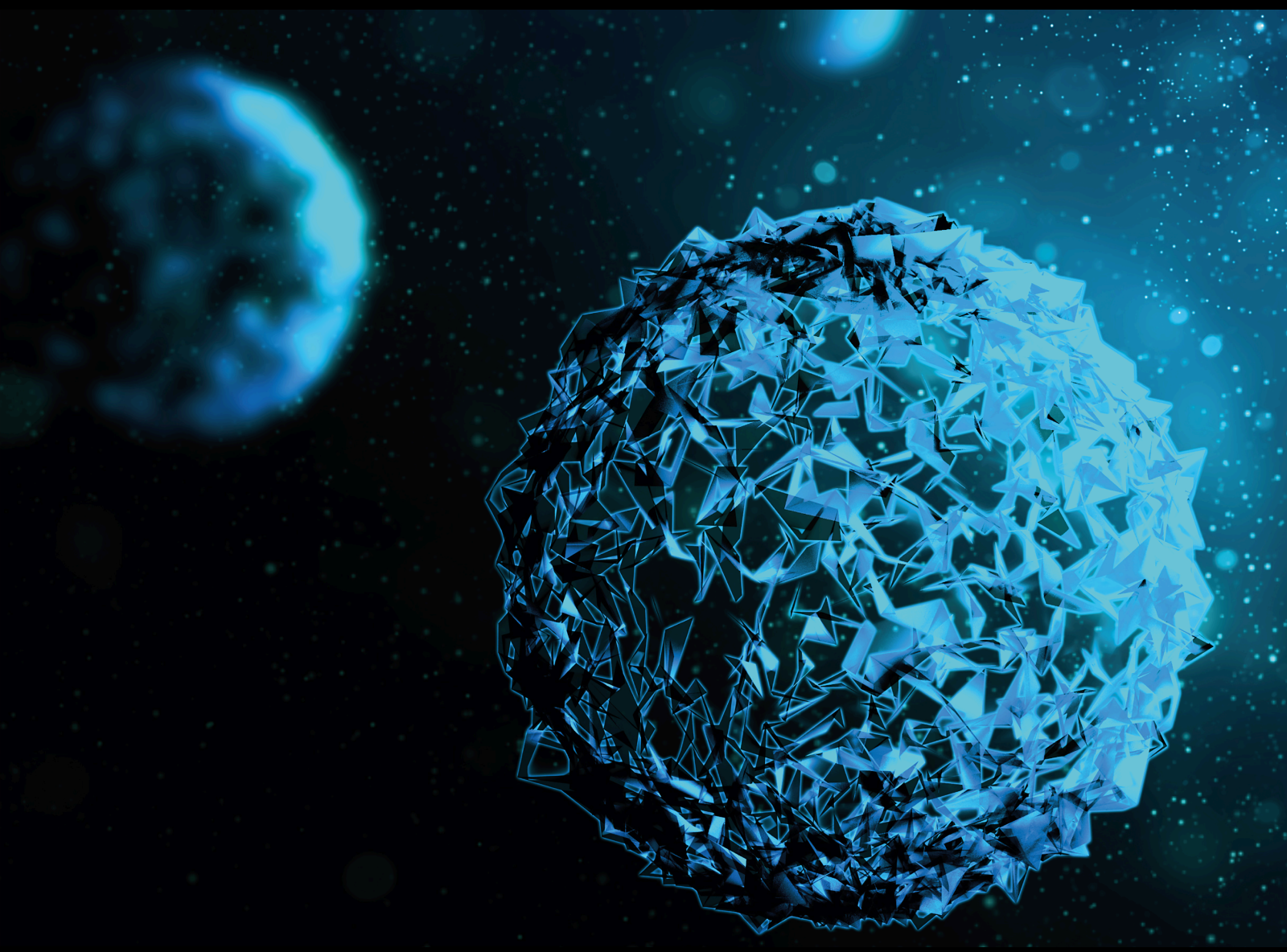
BioMed Research International

Molecular Biomarkers in the Prediction, Diagnosis, and Prognosis of Neurodegenerative Diseases

Lead Guest Editor: Yuzhen Xu
Guest Editors: John H. Zhang, Jun Xu, Xuejun Chai, and Zhenpeng Song



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Retraction

Retracted: Zonisamide's Efficacy and Safety on Parkinson's Disease and Dementia with Lewy Bodies: A Meta-Analysis and Systematic Review

BioMed Research International

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1].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) Manipulated or compromised peer review

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] L. Kong, J. Xi, Z. Jiang, X. Yu, H. Liu, and Z. Wang, "Zonisamide's Efficacy and Safety on Parkinson's Disease and Dementia with Lewy Bodies: A Meta-Analysis and Systematic Review," *BioMed Research International*, vol. 2022, Article ID 4817488, 17 pages, 2022.

Hindawi
BioMed Research International
Volume 2023, Article ID 9895340, 1 page
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Retraction

Retracted: Effect of Cold Fluid Compensatory Swallowing Combined with Balloon Dilation on the Treatment of Poststroke Cricopharyngeal Achalasia: A Pilot Randomized Controlled Trial

BioMed Research International

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Hindawi
BioMed Research International
Volume 2023, Article ID 9856426, 1 page
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Retraction

Retracted: The Function of Retinal Thickness and Microvascular Alterations in the Diagnosis of Systemic Sclerosis

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[1] X. Fang, S. Yu, Y. Peng et al., "The Function of Retinal Thickness and Microvascular Alterations in the Diagnosis of Systemic Sclerosis," *BioMed Research International*, vol. 2023, Article ID 1805938, 10 pages, 2023.

Hindawi
BioMed Research International
Volume 2023, Article ID 9873070, 1 page
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Retraction

Retracted: The Understanding of Vital Pulp Therapy in Permanent Teeth: A New Perspective

BioMed Research International

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[1] W. Shang, Z. Zhang, X. Zhao, Q. Dong, G. Schmalz, and S. Hu, "The Understanding of Vital Pulp Therapy in Permanent Teeth: A New Perspective," *BioMed Research International*, vol. 2022, Article ID 8788358, 11 pages, 2022.

Hindawi
BioMed Research International
Volume 2023, Article ID 9841310, 1 page
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Retraction

Retracted: Effect of Core Stability Training on Correction and Surface Electronic Signals of Paravertebral in Adolescent Idiopathic Scoliosis

BioMed Research International

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[1] H. Weng and Q. Li, "Effect of Core Stability Training on Correction and Surface Electronic Signals of Paravertebral in Adolescent Idiopathic Scoliosis," *BioMed Research International*, vol. 2022, Article ID 1819606, 6 pages, 2022.

Hindawi
BioMed Research International
Volume 2023, Article ID 9794063, 1 page
https://doi.org/10.1155/2023/9794063

Retraction

Retracted: N-myc Downstream-Regulated Gene 1 (NDRG1) Regulates Vascular Endothelial Growth Factor A (VEGFA) and Malignancies in Glioblastoma Multiforme (GBM)

BioMed Research International

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Hindawi
BioMed Research International
Volume 2023, Article ID 9862183, 1 page
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Retraction

Retracted: PRISM: A Novel Visual Instrument to Facilitate Self-Reflection and Learning Progress in Undergraduate Dental Education

BioMed Research International

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[1] G. Schmalz, T. Sensky, H. Kullmann, S. Büchi, and D. Ziebolz, "PRISM: A Novel Visual Instrument to Facilitate Self-Reflection and Learning Progress in Undergraduate Dental Education," *BioMed Research International*, vol. 2022, Article ID 2009894, 12 pages, 2022.

Hindawi
BioMed Research International
Volume 2023, Article ID 9827617, 1 page
https://doi.org/10.1155/2023/9827617

Retraction

Retracted: Effect of Exercise Intervention on Internet Addiction and Autonomic Nervous Function in College Students

BioMed Research International

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[1] W. Zhang and R. Xu, "Effect of Exercise Intervention on Internet Addiction and Autonomic Nervous Function in College Students," *BioMed Research International*, vol. 2022, Article ID 5935353, 7 pages, 2022.

Hindawi
BioMed Research International
Volume 2023, Article ID 9830254, 1 page
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Retraction

Retracted: Review on the Effect of Exercise Training on Immune Function

BioMed Research International

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[1] F. Du and C. Wu, "Review on the Effect of Exercise Training on Immune Function," *BioMed Research International*, vol. 2022, Article ID 9933387, 6 pages, 2022.

Hindawi
BioMed Research International
Volume 2023, Article ID 9820954, 1 page
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Retraction

Retracted: Analysis of Effect of Six Sigma Method Combined with CI Strategy on Improving of Nursing Quality in Outpatient Infusion Rooms

BioMed Research International

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Hindawi
BioMed Research International
Volume 2023, Article ID 9803031, 1 page
https://doi.org/10.1155/2023/9803031

Retraction

Retracted: Solitaire™ Stent Thrombectomy System in the Treatment of Acute Lower-Limb Ischemia: Comparisons in Safety and Effectiveness with Conventional Catheter-Directed Thrombolysis Therapy

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Hindawi
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Volume 2023, Article ID 9801654, 1 page
https://doi.org/10.1155/2023/9801654

Retraction

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BioMed Research International
Volume 2023, Article ID 9789807, 1 page
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Retraction

Retracted: Clinical Analysis of 85 Cases of External Auditory Canal Cholesteatoma Surgery under Specialized Endoscopy

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Hindawi
BioMed Research International
Volume 2023, Article ID 9785616, 1 page
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Retraction

Retracted: Vacuum Sealing Drainage for Primary Thoracolumbar Spondylodiscitis: A Technical Note

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Hindawi
BioMed Research International
Volume 2023, Article ID 9782565, 1 page
https://doi.org/10.1155/2023/9782565

Retraction

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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] Y. Xu, M. Cheng, P. Zhu, S. Yang, C. Lai, and S. Xu, "Influence of P(VDF-TrFE) Membranes with Different Surface Potentials on the Activity and Angiogenic Function of Human Umbilical Vein Endothelial Cells," *BioMed Research International*, vol. 2022, Article ID 5693994, 12 pages, 2022.

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BioMed Research International
Volume 2023, Article ID 9765130, 1 page
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Retraction

Retracted: Efficacy of Balloon Guide Catheter-Assisted Thrombus Repair in Stroke Treatment: A Retrospective Survey in China

BioMed Research International

Received 20 June 2023; Accepted 20 June 2023; Published 21 June 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.

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[1] Q. Li, T. Zhou, Y. He et al., "Efficacy of Balloon Guide Catheter-Assisted Thrombus Repair in Stroke Treatment: A Retrospective Survey in China," *BioMed Research International*, vol. 2022, Article ID 4278048, 7 pages, 2022.

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Retraction

Retracted: Clinical Indications for Extubation in Coma Patients with Severe Neurological Craniocerebral Injury with Meta-Analysis

BioMed Research International

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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.

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[1] H. Ma, Z. Han, W. He, and G. Liu, "Clinical Indications for Extubation in Coma Patients with Severe Neurological Craniocerebral Injury with Meta-Analysis," *BioMed Research International*, vol. 2022, Article ID 8012018, 9 pages, 2022.

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Retraction

Retracted: *Astragalus membranaceus* and *Salvia miltiorrhiza* Ameliorate Hypertensive Renal Damage through lncRNA-mRNA Coexpression Network

BioMed Research International

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[1] L. Zhou, C. Han, Y. Liu et al., "*Astragalus membranaceus* and *Salvia miltiorrhiza* Ameliorate Hypertensive Renal Damage through lncRNA-mRNA Coexpression Network," *BioMed Research International*, vol. 2022, Article ID 3002353, 14 pages, 2022.

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Retraction

Retracted: A Rehabilitation Model Conducive to Postoperative Recovery of Endometrial Cancer Patients after Laparoscopy

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[1] L. Yang and F. Han, "A Rehabilitation Model Conducive to Postoperative Recovery of Endometrial Cancer Patients after Laparoscopy," *BioMed Research International*, vol. 2022, Article ID 9910841, 7 pages, 2022.

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Retraction

Retracted: Cell Division Cycle-Associated Protein 3 (CDCA3) Is a Potential Biomarker for Clinical Prognosis and Immunotherapy in Pan-Cancer

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[1] Y. Xu, M. Shen, Y. Peng et al., "Cell Division Cycle-Associated Protein 3 (CDCA3) Is a Potential Biomarker for Clinical Prognosis and Immunotherapy in Pan-Cancer," *BioMed Research International*, vol. 2022, Article ID 4632453, 28 pages, 2022.

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Retraction

Retracted: The Function of Retinal Thickness and Microvascular Alterations in the Diagnosis of Systemic Sclerosis

BioMed Research International

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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.

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[1] X. Fang, S. Yu, Y. Peng et al., "The Function of Retinal Thickness and Microvascular Alterations in the Diagnosis of Systemic Sclerosis," *BioMed Research International*, vol. 2023, Article ID 1805938, 10 pages, 2023.

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Research Article

The Function of Retinal Thickness and Microvascular Alterations in the Diagnosis of Systemic Sclerosis

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In this study, we aim to investigate retinal thickness (RT) and superficial vascular density (SVD) differences between patients with systemic sclerosis (SSc) and healthy controls (HCs) by optical coherence tomography angiography (OCTA). Sixteen patients with a definitive SSc diagnosis without clinical signs of retinopathy and 16 normal control subjects were recruited. All individuals underwent OCTA scanning to assess macular RT and SVD. We divided each image into nine subregions as the early treatment diabetic retinopathy study (ETDRS). Visual acuity (VA) was considerably different between patients with SSc (32 eyes) and control subjects (32 eyes) ($p < 0.001$). Compared to the control group, individuals with SSc had decreased inner RT in inner superior, outer superior, outer temporal, inner temporal, center, and inner nasal regions ($p < 0.05$). Outer RT was decreased in the outer and inner temporal regions, and full RT was decreased in the regions of outer superior, inner superior, inner temporal, and outer temporal, in comparison to the control group ($p < 0.05$). Patients with SSc had significant reduction of SVD in the inner and outer of both superior and temporal, besides outer nasal regions than controls. ($p < 0.05$). Moreover, SVD was significantly associated with the outer temporal region of patients suffering from SSc ($p < 0.05$). Diagnostic Sensitivity of RT and SVD of Inner Superior Regions in SSc, as indicated by areas under curves of the Receiver Operating Characteristic (ROC), were 0.874 (95% CI: 0.786–0.962) and 0.827 (95% CI: 0.704–0.950), respectively. In conclusion, VA may be affected by RT variations inside the macula in patients with SSc. Measuring RT with OCTA could be a useful predictor of early diagnosis.

1. Introduction

Systemic sclerosis (SSc) is a multisystem chronic autoimmune disorder characterised by immunological activation, extensive vasculopathy, and pervasive fibrosis with diverse clinical symptoms [1, 2]. SSc is defined as substantial vascular involvement that is not restricted to the microcirculation of the skin's periphery but can also be found in the lungs, kidneys, cardiac muscles, GIT, as well as the eyes [3, 4]. Microvasculature involvement is one of the early manifestations of SSc and may contribute to severe multiorgan failure through pathological alterations, such as endothelial damage, vessel walls mononuclear cell infiltration, and obliterative lesions [5] Those structural vascular alterations, in conjunction with persistent vasospasm, may result in insufficient blood flow, tissue damage, and capillary infarction.

Research papers increasingly discuss ocular symptoms among SSc patients [6, 7] and their prevalence as well as association with the underlying disease stage. The pathogenesis of ocular and related systems in patients with SSc is complicated and remains unclear [8]. The retina features microcirculation with immune privilege, a lack of adrenergic vasomotor innervation and resident fibroblasts. [9, 10] This structure appears to provide protection from SSc-related vasculopathy and fibrosis processes. However, many conflicting findings on retinal diseases in SSc have been documented in the literature. There was no correlation among SSc with retinopathy in some trials [11]. Ushiyama et al. [12] found that retinal abnormalities are frequently observed in patients with SSc (SSc 34% VS Control 8%), perhaps reflecting vascular pathological changes. Therefore, evaluation the effects of SSc on

retinal disease requires additional research with a larger patient population.

Due to fact that retinal and choroidal microvasculature is clearly vulnerable to systematic vascular changes, it may provide a useful means by which to monitor disease progression in patients with SSc [13]. Because retinal tissue has the maximum oxygen extraction per blood volume, choroidal and retinal thicknesses have been proposed as prospective inflammatory predictor for autoimmune complications besides a vascular component [14]. However, research on this role for retinal thickness has been limited. OCTA is a noninvasive imaging modality that offers morphologic and quantitative data about microvascular ocular alterations. OCTA generates angiographic high-quality and slab-segmented images using the motion contrast of erythrocytes over a stationary background [4, 15] A variety of OCTA-based studies have assessed choroidal microcirculation among SSc patients and controls; however, limited data are available on retinal thickness in these groups.

To date, rare studies have used OCTA as a potential tool to assist with early diagnosis and severity evaluation in SSc. This study attempted to examine the ocular health of SSc patients and compared the RT and VD of SSc patients and normal control using OCTA.

2. Materials and Methods

2.1. Subjects. This prospective cross-sectional study was conducted at the Ophthalmology and Rheumatology Department in the First Affiliated Hospital of Nanchang University (Nanchang, China) in 2021. The Rheumatology and Immunology outpatients sequentially recruited 16 patients (32 eyes) with SSc and no clinical signs of eye problems. The Centre for Ocular Diseases Clinical Research recruited healthy individuals. Data on age, sex, illness duration, autoantibody profile, and blood pressure were recorded for all subjects. Clinical examination and OCTA imaging were performed to ensure the lack of ocular abnormalities in these patients. One retina specialist assessed all patients' OTCA results with blind method.

2.2. Inclusion and Exclusion Criteria. SSc patients were required to satisfy the 2013 ACR/EULAR classification criteria for SSc [2]. Patients aged from 16 to 63 years without symptoms or evidence of retinal vasculitis, choroiditis, or optic neuritis were eligible to participate. In addition, hydroxychloroquine-induced chorioretinopathy was excluded for patient participation. The subsequent were further exclusion characteristics: (1) autoimmune illnesses apart from SSc; (2) systemic diseases, such as DM, grim hypertension systemic (over 179 mmHg systolic or over 109 mmHg diastolic), and ossia nerve systemic illness affecting the eyes (ossia nervus opticus); (3) choroidal or retinopathy disorder (e.g., arteriovenous disorder, glaucoma, or elevated IOP intraocular pressure); (4) history of trauma, ocular tumor, or surgery; (5) any contraindications, allergies, or local anesthesia/mydriatics intolerances; (6) complications which could impact fundus imaging; as well as (7) pregnancy or lactating women.

2.3. Ethical Considerations. This research complied with the Helsinki Declaration. Ethical review and approval were granted for this work by the board of Nanchang University, First Affiliated Hospital. Each participant voluntarily signed an informed consent form after reading and comprehending its contents.

2.4. Clinical Examinations. The following clinical tests and ocular investigations were performed for all participants: (1) immunological data as, anti-Scl-70 antibody, anti-SS-A anti-body, anti-SS-B anti-body, and ANA antibody were measured by indirect immunofluorescence assay; (2) evaluation of the patient's inflammatory status via C-reactive protein (CRP) level and erythrocyte sedimentation ratio (ESR) analyses; (3) assessment of the patient's mental state via HADS score; (4) OCTA; (5) ocular measurements, include IOP (Goldmann tonometry), VA (Snellen chart), spherical equivalent refractive error, the tear breakup time (BUT), Schirmer's test, tear meniscus height (TMH), and ocular staining score (OSS).

The protocol of BUT, Schirmer's test, TMH, and OSS were examined as we have previously described [16].

BUT: fluorescein sodium was applied evenly on the ocular surface, and the first tear point film rupture was observed under cobalt blue light, and the time for this to occur was recorded. Less than 10 s was considered positive.

Schirmer's test: after disinfecting the conjunctival sac, one end of a piece of filter paper measuring (5*35 mm was folded into a right angle and inserted into the conjunctival sac. Length of the wet region of the paper after 5 minutes was observed, and < 5 mm was considered positive.

TMH: this was measured under infrared light after a blink using Keratograph 5M software.

OSS: a complete evaluation was performed using corneal fluorescein staining in conjunction with conjunctival lissamine green staining. The cornea, the nasal conjunctiva, and the temporal conjunctiva were the three areas of the ocular surface that were taken into consideration for each eye. A score was given to the nasal and temporal conjunctiva based on the amount of spotty conjunctivitis in the palpebral fissure. A positive OSS index was that the score higher than or equal 3.

2.5. Optical Coherence Tomography Angiography. For OCTA imaging and displaying the retinal cross-section and microvasculature simultaneously, we employed system of RTVue Avanti XR (Optovue, CA). The OCTA protocol was as previously described [16]. We imaged for 3.9 seconds at a central of 840 nm wavelength and 45 nm bandwidth, while axial and horizontal resolutions were 5 mm and 22 μm, respectively, all along with a scanning speed of 70,000 A scans/s. Five angiographies were captured in the mode of 3 mm*3 mm scanning. In four volume scans, an overall of 933,120 A scans (2 for horizontal and vertical scans each) were obtained after four volume scans. Each eye had a 3 mm*3 mm en-face OCTA angiographic imaging. Following scanning, each retinal imaging was split into nine ETDRS subregions with (0.5, 1.5, and 3 mm in radius) circles, and RT was analysed. The nine subregions include outer superior (OS), inner superior (IS), outer nasal (ON), inner nasal (IN), outer inferior (OI), inner inferior

Table 1: Demographic and clinical data from SSc patients and normal controls.

	SSc (n = 16, 32 eyes)	Control (n = 16, 32 eyes)	p value
Age (y)	46.750 ± 11.358	49.500 ± 5.955	0.398[a]
Gender			
Female	12	14	0.654[b]
Duration of SSc (y)	3.100 ± 3.068	N/A	
ESR (mm/h)	23.484 ± 22.497	N/A	
CRP (10 mg/L)	4.723 ± 4.720	N/A	
ANA, n (%)	13 (81.250)	N/A	
Scl-70), n (%)	6 (37.500)	N/A	
Anti SSA/Ro, n (%)	4 (25.000)	N/A	
Anti SSB/La, n (%)	0 (0.000)	N/A	
Systolic blood pressure (mm Hg)	112.813 ± 14.625	124.438 ± 5.738	0.0060[a]
Diastolic blood pressure (mm Hg)	72.875 ± 13.386	82.938 ± 6.298	0.0107[a]
HADS	8.938 ± 2.839	2.813 ± 1.109	**< 0.0001[a]**

Note: bold values indicate $p < 0.05$; [a]independent t test; [b] chi-square test. Abbreviations: ANA: antinuclear antibody; anti-topo I (Scl-70): anti-DNA topoisomerase I; N/A: not applicable.

Table 2: Ocular and visual data from patients with SSc and healthy controls.

	SSc (n = 16, 32 eyes)	Control (n = 16, 32 eyes)	p value[a]
VA (logMAR)	0.644 ± 0.254	0.9 ± 0.134	**< 0.001**
Mean IOP (mm Hg)	15.656 ± 1.865	15.225 ± 1.689	**0.426**
BUT (s)	5.000 ± 1.218	13.906 ± 1.785	**< 0.001**
SIT (mm)	6.250 ± 0.762	12.938 ± 1.390	**< 0.001**
TMH (mm)	0.162 ± 0.028	0.581 ± 0.123	**< 0.001**

Note: bold values indicate $p < 0.05$. [a]p value was obtained using a generalized estimation equation (data from both eyes were included).

(II), outer temporal (OT), inner temporal (IT), and center (C). RT was considered as full thickness (from internal limiting membrane to retinal pigment epithelium), inner (from internal limiting membrane to inner plexiform layer) and outer (the difference between full RT and inner RT). The proportion of the region which showed vascular perfusion provided an estimate of VD, which was accomplished by generating 2D imaging en-face of superficial retina. Assign then distribute image block's value to each background (0) or perfusion (1). With the intention of calculating VD from macula centre to the edge of 3 mm × 3 mm brightness gradient image, average skeletal plate value was scaled by pixel size in the region of interest, which was 512 pixels/3 mm. We measured macular RT and SVD. In every case, we started by evaluating the subjects' right eye. The left-eye data was inverted to provide a mirror image of the right-eye data. One set of data per person was compiled by averaging the results from the left and right eyes.

2.6. Statistical Analysis. Data were processed utilizing SPSS 24.0 and reported as mean ± standard deviation. Using RStudio and GraphPad Prism version 8, we compared independent sample groups using the t-test, chi-square, and Fisher's exact tests (La Jolla, Ca, US). All types of RTs and SVDs were compared between groups using the generalised estimation equation. Linear correlation analyses were carried out across RT groups with SVD in each group. Multiple regression models, both univariate and multivariate, were performed to determine the associations between RT and ocular factors. To analyze SVD and RT thickness groups as diagnostic indicators for SSc, Receiver Operating Characteristic (ROC) curves were plotted. Significant statistical differences were defined as those ($p < 0.05$). Adjustments to p values for multiple comparisons were made using a false discovery rate (FDR).

3. Results

3.1. Subjects. Mean age was similar in the control group (49.500 ± 5.955 years) and SSc group (46.750 ± 11.358 years; $p = 0.398$). Mean time to diagnosis for SSc patients was 3.100 ± 3.068 years. SSc patients had significantly higher HADS scores compared to controls (8.938 ± 2.839) vs. 2.813 ± 1.109; $p < 0.0001$) (Table 1). The SSc group exhibited lower VA ($p < 0.001$) and shorter BUT than the control group (5.000 ± 1.218 s vs. 13.906 ± 1.785 s; $p < 0.001$), lower SIT score (6.250 ± 0.762 mm vs. 12.938 ± 1.390 mm; $p < 0.001$) and lower TMH (0.162 ± 0.028 vs. 0.581 ± 0.123 mm; $p < 0.001$) (Table 2).

3.2. Macular RT. Table 3 and Figure 1(f) display the subregional RT for the SSc and control groups. Following age, VA, IOP, and BP adjustments, inner RT was statistically reduced in SSc patient's group than in controls in OS ($p < 0.0001$), IS ($p < 0.001$), OT ($p = 0.006$), IT ($p = 0.033$), C regions ($p = 0.018$), and IN region ($p = 0.014$)

Table 3: Regional macular RT compared across patients with SSc and normal controls.

Location	SSc (n = 16, 32 eyes)	Control (n = 16, 32 eyes)	p value	FDR[a]
Macular inner retinal thickness (μm, mean ± SD)				
IS	104.781 ± 6.494	113.781 ± 5.482	< 0.001	**< 0.001**
OS	103.219 ± 8.385	111.000 ± 5.853	< 0.001	**< 0.0001**
IN	111.781 ± 6.514	115.781 ± 5.802	0.022	**0.014**
ON	122.531 ± 7.229	123.469 ± 4.280	0.610	0.195
II	112.156 ± 6.222	114.344 ± 5.445	0.204	0.075
OI	103.188 ± 6.963	104.813 ± 6.463	0.396	0.136
IT	101.844 ± 6.461	104.438 ± 4.614	0.078	**0.033**
OT	90.938 ± 5.465	94.781 ± 5.110	0.006	**0.006**
C	48.938 ± 6.283	52.344 ± 5.463	0.036	**0.018**
Macular outer retinal thickness (μm, mean ± SD)				
IS	218.906 ± 15.378	216.781 ± 5.723	0.533	0.708
OS	188.500 ± 12.083	193.250 ± 12.746	0.139	0.386
IN	217.813 ± 11.616	218.406 ± 12.745	0.863	0.797
ON	195.219 ± 15.737	195.063 ± 8.583	0.969	0.815
II	211.406 ± 13.671	211.813 ± 7.046	0.900	0.804
OI	180.969 ± 10.811	180.469 ± 12.959	0.876	0.799
IT	206.875 ± 7.606	214.094 ± 8.216	0.001	**0.005**
OT	179.344 ± 6.302	187.063 ± 10.895	0.003	**0.011**
C	192.594 ± 25.615	194.469 ± 15.046	0.691	0.758
Macular full retinal thickness (μm, mean ± SD)				
IS	323.688 ± 11.828	330.563 ± 7.746	0.016	**0.019**
OS	291.719 ± 11.450	304.250 ± 11.992	< 0.001	**< 0.001**
IN	329.594 ± 11.092	334.188 ± 15.135	0.212	0.198
ON	317.750 ± 11.144	318.531 ± 8.944	0.791	0.437
II	323.563 ± 10.485	326.156 ± 9.354	0.386	0.305
OI	284.156 ± 9.792	285.281 ± 13.187	0.708	0.446
IT	308.719 ± 12.822	318.531 ± 7.431	0.001	**0.001**
OT	270.281 ± 8.862	281.844 ± 11.043	< 0.001	**< 0.001**
C	241.531 ± 28.778	246.813 ± 16.585	0.312	0.216

Note: bold values indicate $p < 0.05$. [a] Generalized estimation equation models were applied to attain p values comparing mean inner, outer as well as full macular RT in SSc patients and healthy subjects. Models were adjusted for age, IOP, VA, and BP.

(Figure 1(c)). The remaining 3 inner retinal regions (ON, $p = 0.195$; II, $p = 0.075$; OI, $p = 0.136$) (Figure 1(c)) did not change significantly across groups. The outer RT in patients with SSc was statistically reduced than OT in controls ($p = 0.011$) and IT ($p = 0.005$) regions (Figure 1(d)). Full RT was statistically significant thinner in SSc than controls in IS ($p = 0.019$), OS ($p < 0.001$), IT ($p = 0.001$), and OT ($p < 0.001$) regions (Figure 1(b)). No additional differences between groups were found to be statistically significant ($p > 0.05$).

Macular RT was strongly correlated to diastolic BP in univariate analysis ($\beta = 0.176$, $p = 0.037$) but not with VA, age, mean IOP, or systolic blood pressure. The multivariate regression analysis resulted that systolic blood pressure ($\beta = -0.393$, $p = 0.001$) was inversely correlated to macular RT. Diastolic BP ($\beta = 0.347$, $p = 0.005$) and BUT ($\beta = 1.876$, $p = 0.044$) were significantly related to thinner macular RT (Table 4).

3.3. Superficial Macular Retinal VD. SVD at each retinal subregions in the healthy group and SSc patients are shown in Table 5, Figures 1(a) and 1(f) following age, IOP, VA, and BP adjustments. Patients with SSc had a significantly decreased SVD than healthy subjects in the IS, OS, ON, IT, and OT regions ($p \leq 0.001$) (Table 5, Figures 1(a) and 1(f)). In SSc patient's group, SVD was inversely associated to disease duration (−0.540) (Figure 2(d)).

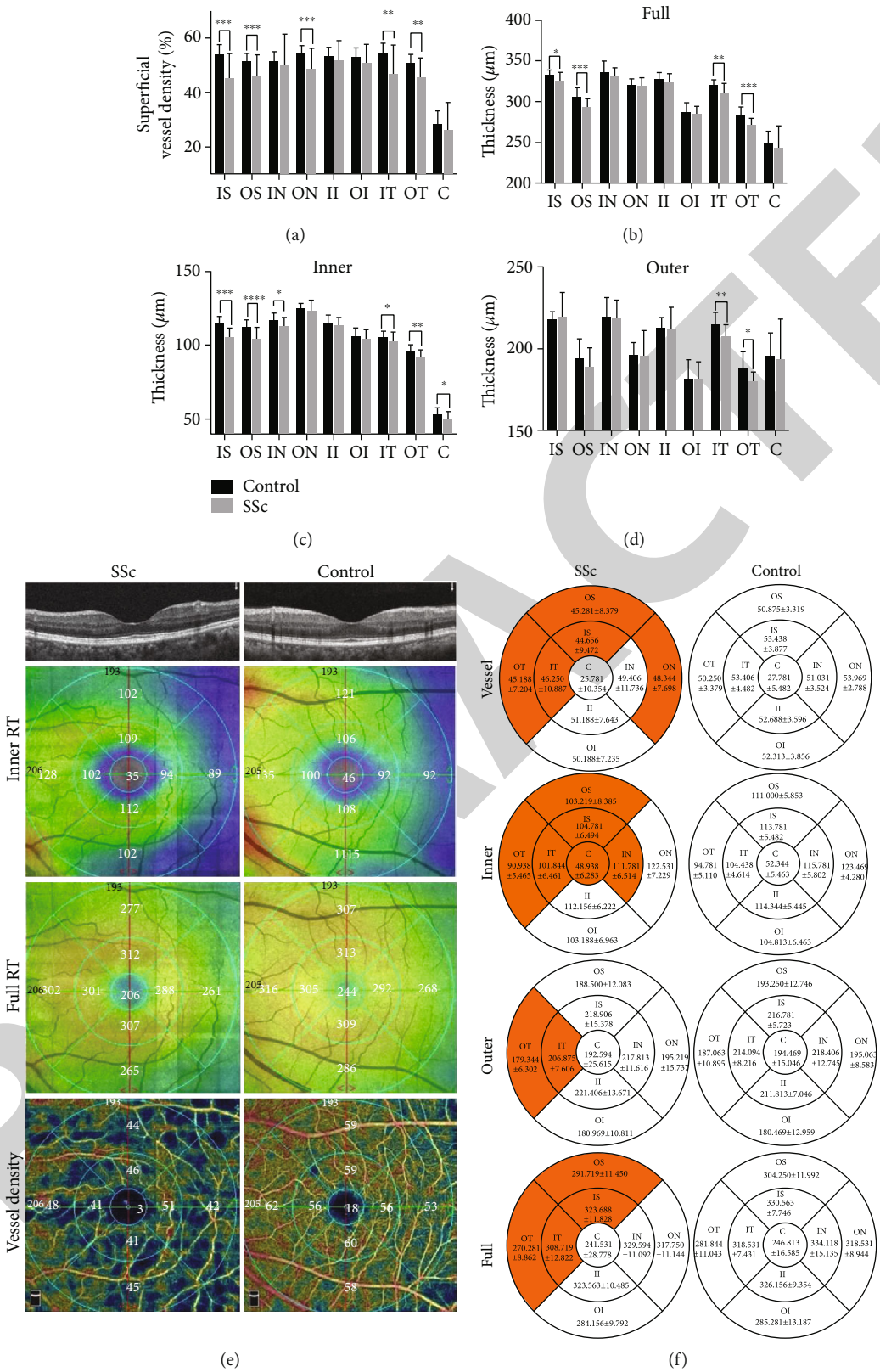

Figure 1: The RT and SVD analyses and OCTA images. (a) Regional analysis of SVD in the SSc and control groups. The vertical coordinate is SVD value; the horizontal coordinate is retinal subregions. (b–d) Regional analysis of three types of RT between SSc and control groups. The vertical axis represents RT values, whereas the horizontal axis represents retinal regions. (e) RT in a cross-sectional OCTA study of SSc and control group. ETDRS was used to evaluate the inner, full RT, and SVD. (f) Comparing the SSc and control groups in the nine subregions of SVD and three types of RT. ∗, $p < 0.05$; ∗∗, $p < 0.01$; ∗∗∗, $p < 0.001$; ∗∗∗∗, $p < 0.0001$.

Table 4: Macular RT and its correlation with demographic and ocular parameters in patients with SSc: a univariate and multivariate regression analyses.

Parameters	Univariate regression analysis regression coefficient ($\beta \pm$ SE)	p value[a]	Multivariate regression analysis Regression coefficient ($\beta \pm$ SE)	p value[a]
Age (y)	−0.008 ± 0.103	0.941	−0.127 ± 0.094	0.270
VA (logMAR)	0.094 ± 4.518	0.984	5.883 ± 4.299	0.368
Mean IOP (mm Hg)	0.038 ± 0.615	0.951	0.876 ± 0.618	0.310
Systolic blood pressure (mm Hg)	0.112 ± 0.076	0.155	−0.393 ± 0.106	**0.001**
Diastolic blood pressure (mm Hg)	0.176 ± 0.081	**0.037**	0.347 ± 0.111	**0.005**
BUTs	0.522 ± 0.937	0.582	1.876 ± 0.881	**0.044**
SIT (mm)	0.194 ± 1.505	0.898	−1.867 ± 1.189	0.129

Note: bold values indicate $p < 0.05$. [a]p value was obtained with generalized estimating equation.

Table 5: Regional SVD compared in patients with SSc and normal controls.

Region (%, mean ± SD)	SSc (n = 16, 32 eyes)	Control (n = 16, 32 eyes)	p value	FDR[a]
IS	44.656 ± 9.472	53.438 ± 3.877	< 0.001	< **0.001**
OS	45.281 ± 8.379	50.875 ± 3.319	0.001	< **0.001**
IN	49.406 ± 11.736	51.031 ± 3.524	0.456	0.105
ON	48.344 ± 7.698	53.969 ± 2.788	< 0.001	<0.001
II	51.188 ± 7.643	52.688 ± 3.596	0.291	0.073
OI	50.188 ± 7.235	52.313 ± 3.856	0.105	0.052
IT	46.250 ± 10.887	53.406 ± 4.482	0.001	**0.001**
OT	45.188 ± 7.204	50.250 ± 3.379	0.002	**0.001**
C	25.781 ± 10.354	27.781 ± 5.482	0.349	0.082

Note: bold values indicate $p < 0.05$. [a] Mean SVD was compared between Healthy and SSc patients using generalised estimating equation models, and p values were calculated.

3.4. ROC Curve Analysis of RT and SVD. OCTA data were analysed to assess the specificity and sensitivity of RT and SVD as diagnostic predictors of SSc-induced alterations (Figure 3). We found that IS, OS, ON, IT, and OT regions had significantly different RTs among the groups. AUC for SVD in the IS region was 0.827 (95% CI: 0.704 to 0.9500), and for the ON region, it was 0.752 (95% CI: 0.607–0.896), a diagnostic sensitivity for SVD of moderate to high for SSc (Figure 3(a)). Significant differences between groups were found in inner RT in the regions of IS, OS, IN, IT, OT, and C; outer RT in IT and OT; and full RT in IS, OS, IT, and OT. AUC for outer RT in the IS region was 0.874 (95% CI: 0.786 to 0.962), indicating moderate to high diagnostic sensitivity for SSc (Figure 3(d)).

3.5. Relationship between RT and SVD and Relationship between Disease Duration and HADS. SSc patients with inner RT was positively related to SVD in the OT region ($r = 0.36$) (Figures 2(a) and 2(b)), implying that decreased SVD is related to retinal thinning in SSc. Patients with SSc who had their condition progress over a longer period of time had increased HADS index (0.8467) (Figure 2(d)). A lower SVD was associated with longer disease duration (−0.540) in the SSc group, as we have already mentioned (Figure 2(d)).

4. Discussion

This study demonstrates that patients with SSc had significantly decreased VA, RT, and retinal VD, in addition to significant relationships among these parameters using OCTA. In our study, we found the SSc patients had poor visual acuity and dry eye (shorter BUT, lower SIT score and lower TMH) consistent with some previous studies. [17] Two case-control studies showed that fibrosis of the adjacent conjunctiva and lacrimal gland might induce tear production decreased in SSc [18, 19]. Moreover, they showed that SSc patients are significantly more likely to experience dry eye symptoms. In contrast to these findings, Wangkaew et al. revealed no statistical difference between SSc patients and healthy subjects after adjusting for the use of xerogenic drugs and smoking, suggesting that the utilization of drugs with anticholinergic side-effects and smoking may also be associated with higher dry eye symptom scores in SSc patients. [20, 21] Keratoconjunctivitis, skin changes of the eyelid, uveitis, episcleritis, weakening of the extraocular muscles, scleritis, glaucoma, peripheral ulcerative keratitis, enophthalmos, and cataract are some of the other clinical symptoms. One-third of SSc patients had retinal abnormalities on fundus examination, according to a cross-sectional investigation evaluating retinal involvement [12].

Although its pathophysiology is poorly understood, it is widely acknowledged that SSc begins in the microcirculation network. Raynaud's phenomenon occurs at the initial stage of SSc in about 95% of patients and may guide diagnosis if accompanied by capillaroscopy abnormalities. [22, 23] Capillaroscopy is a noninvasive imaging technique that explores microcirculatory involvement and may show specific signs of the disease in patients who have Raynaud's

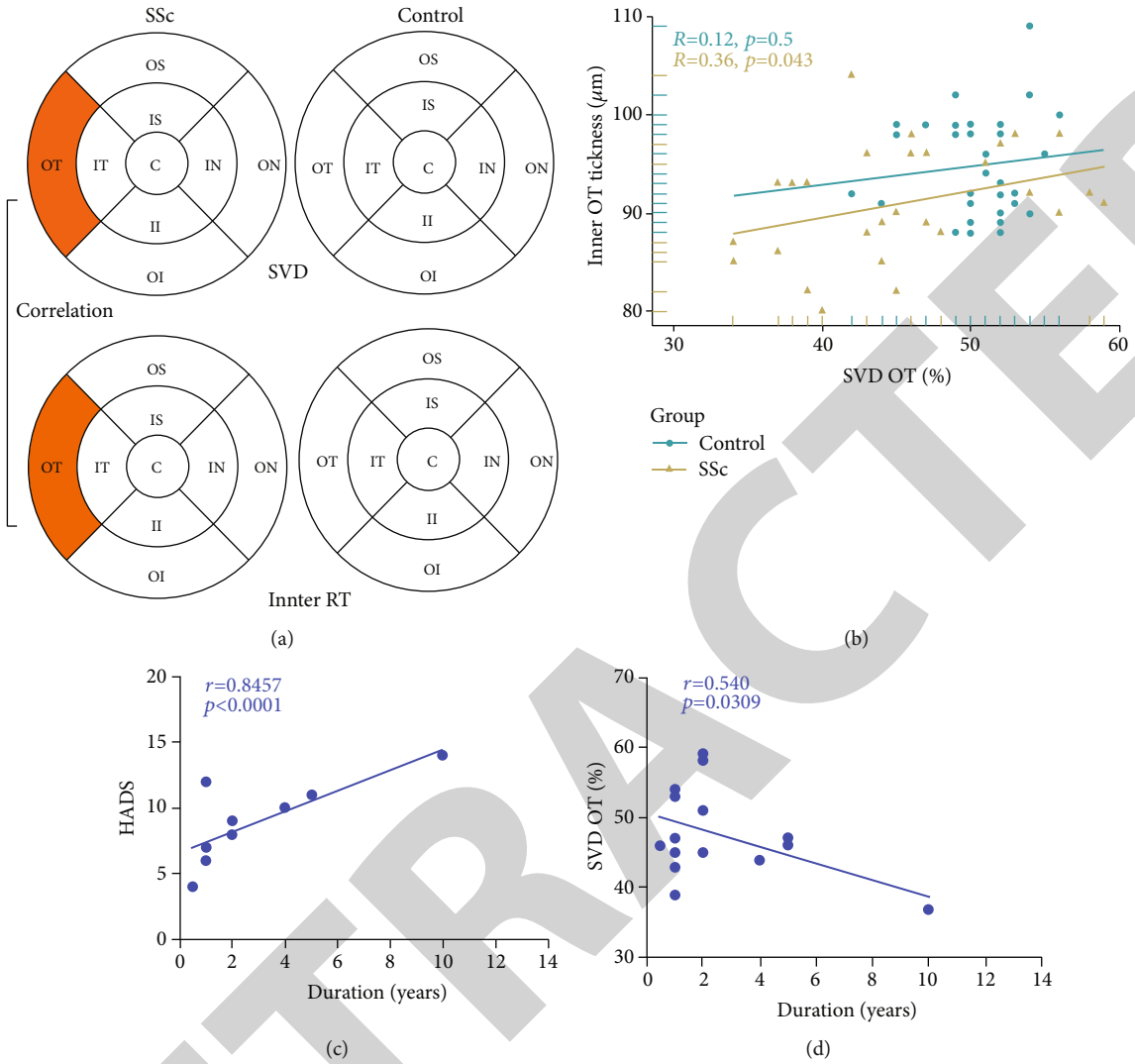

Figure 2: Relationship between RT and SVD in SSc patients and healthy controls and association between disease duration and both HADS and SVD. (a and b) In patients with SSc, SVD was actively linked to inner RT in the OT region (r = 0.36; p = 0.043). (c) A significant correlation was found between disease duration and HADS (r = 0.8457, p < 0.0001). (d) Disease duration was inversely related to SVD in the region of OT. (r = −0.540, p = 0.0309).

phenomenon but no skin sclerosis. To date, capillaroscopy has been considered part of the EULAR/ACR standards for SSc and may provide useful information about prognosis for SSc patients. [2, 24] Maricq and Cutolo capillaroscopic classification system may be useful in recognizing patients at different phases of illness. [25, 26] Over time, the capillaroscopic pattern in SSc patients evolved from destruction of giant capillaries to that of capillary beds [27]. Furthermore, capillaroscopy may be used to detect a window of opportunity for treatment in patients who progress from giant capillary to capillary bed destruction. However, retinal blood vessels involved may differ qualitatively from nailfold capillaries. [12] In the evaluation of SSc, retinal vascular, ocular, and visual factors are frequently neglected. While there have been investigations looking at the choroidal and retinal vascular features in SSc [13, 28, 29], further detailed investigations at varying retinal and choroid depths using OCTA are required.

Vasculopathy are the most important features of SSc, not only because they are almost always present, but also provide clues to early diagnosis, which long before the appearance of nonvascular symptoms. [22, 23] Because retinal vasculature indicates systemic arteriolar and capillary pathology in SSc, early diagnosis of ocular microcirculation involvement is crucial. The different layers of retina acquire nutrition from different vessel: outer layer acquire from choroidal vessels, the inner layer acquire from the central retinal blood vessels, and the macular region acquire from choroidal capillaries. The posterior eye is one of the tissues in the body that has the highest metabolic activity. As a consequence, it is exceedingly vulnerable to capillary injury [30, 31]. Once the vasculopathy happened in the retina, the pathology of the retinal region will also be changed, which might affect the whole choroidal and retinal vascular network. Our research revealed that the retinal SVD is significantly diminished in all layers among SSc patients. The

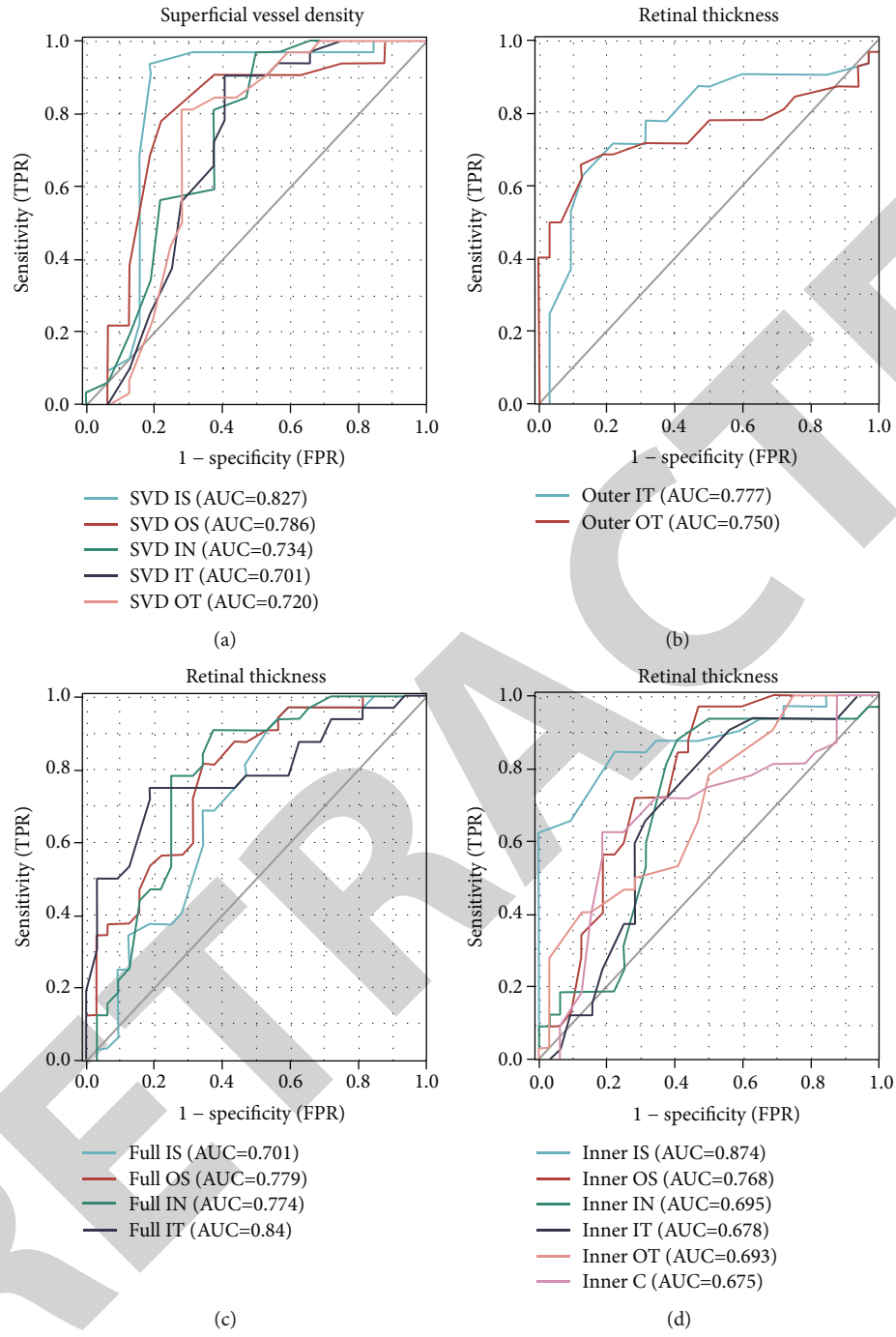

Figure 3: ROC curve analysis of RT and SVD. (a) The area under the ROC curve for SVD was 0.827 (95% CI: 0.704 to 0.9500) in IS, 0.827 in OS (95% CI: 0.704 to 0.950), 0.734 in ON (95% CI: 0.607 to 0.862), 0.701 in IT (95% CI: 0.564 to 0.837), and 0.720 in OT (95% CI: 0.583 −0.856). (b) The area under the ROC curve for outer RT was 0.777 (95% CI: 0.656 to 0.899) for IT and 0.750 for OT (95% CI: 0.619 to 0.880). (c) The area under the ROC curve for full RT was 0.701 (95% CI: 0.569 to 0.833) for IS, 0.779 for OS (95% CI: 0.666 to 0.892), 0.774 for IT (95% CI: 0.654 to 0.894), and 0.784 for OT (95% CI: 0.669–0.900). (d) The area under the ROC curve for inner RT was 0.874 (95% CI: 0.786 to 0.962) for IS, 0.768 for Inner OS (95% CI: 0.648–0.888), 0.695 for IN (95% CI: 0.648 to 0.888), 0.678 for IT (95% CI: 0.540–0.816), 0.693 for OT (95% CI: 0.565 to 0.822), and 0.675 for C (95% CI: 0.536–0.813).

thickness of the inner RT had a positive correlation with the SVD (Figure 4). Studies have found the changes of microcirculation may develop long before clinically detectable retinopathy. Similarly, we speculate that subclinical alteration also exists in SSc patients.

SSc mainly targets small arteries and capillaries by decreasing their density and obliterating them. [32] The retinal and choroidal vasculature would be perfect for observing pervasive arteriolar and capillary pathology in SSc, making the early diagnosis of changes to ocular microcirculation crucial. Rommel

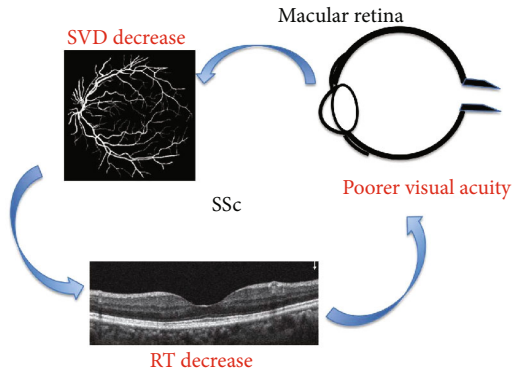

Figure 4: Relationship between SVD, RT, and visual in SSc patient. The decrease of superficial retinal vascular density might induce related area of retinal thickness decreased, and then resulted poorer vision at last.

et al. [13] found in SSc group that the perfusion of the retinal and choroidal was significantly decreased. This suggests that retinal or choroidal perfusion is involved in early stages of the disease and eventually impacts vascular dysfunction in both tissues, suggesting that retinal and choroidal examinations should be considered immediately after SSc diagnosis to detect early alterations. In our research, RT was found to be lowered in all retinal regions of SSc patients by ETDRS partition method, including the IS, OS as well as IT area of inner retina and OT and IT area of outer retina, in addition to OT and IT area of full-thickness retina. To our knowledge, this is first report of retinal thickness evaluation in SSc using OCTA.

Our investigation of the ROC curve for SVD and inner RT in the IS region revealed a potential diagnosis method for early detection of retinal alterations in SSc. Early diagnosis and evaluation are essential for effective therapy and a favourable prognosis. SSc is a heterogeneous disease that may progress to fatal complications after several months or may remain limited to sclerodactyly and Raynaud's phenomenon. The detection of an increased risk of complications in scleroderma is important to recognize patients at risk of progression to severe complications. OCTA is a noninvasive and an easy technology that offers information on the perfusion of the intraocular vascular network. Alteration in microcirculation may precede clinically retinopathy in people with SSc; hence, OCTA is a good approach for distinguishing healthy eyes from those affected by SSc.

The RT assessed by OCTA may aid in the imaging diagnosis of SSc, however additional research is required for future clinical application. Given the importance of this study's findings, more analyses of data from a larger number of participants with greater clinical diversity will be required to confirm our findings. Moreover, we should differentiate the patient suffered from limited form of SSc or diffused form of SSc, which showed different severity, clinical manifestations, complications, prognosis, and survival.

5. Conclusion

We utilised OCTA to improve our understanding of RT and SVD in SSc patients. The results suggested that the inner, outer, and total RT were thinner in SSc patients, whereas the SVD was reduced in the IS, OS, ON, OT, and IT regions. In addition, a positive correlation was detected between changes in RT and SVD. Thus, OCTA may aid in the imaging-assisted diagnosis of SSc.

Data Availability

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

Ethical Approval

The studies involving human participants were reviewed and approved by the Medical Ethics of the First Affiliated Hospital of Nanchang University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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.

Authors' Contributions

Rui Wu and Yi Shao have contributed equally to this work.

Acknowledgments

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Retraction

Retracted: Analysis of Effect of Six Sigma Method Combined with CI Strategy on Improving of Nursing Quality in Outpatient Infusion Rooms

BioMed Research International

Received 20 June 2023; Accepted 20 June 2023; Published 21 June 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] X. Shen, J. Wei, Y. Zhang, and Y. Zhang, "Analysis of Effect of Six Sigma Method Combined with CI Strategy on Improving of Nursing Quality in Outpatient Infusion Rooms," *BioMed Research International*, vol. 2022, Article ID 8975435, 8 pages, 2022.

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Research Article

Analysis of Effect of Six Sigma Method Combined with CI Strategy on Improving of Nursing Quality in Outpatient Infusion Rooms

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Objective. The infusion room is the last part of an outpatient visit, with high patient density, large staff mobility, and a wide variety of conditions. In addition, most patients are accompanied by their families during infusion, and nursing staff in infusion rooms have to face more trivial and miscellaneous tasks than nursing staff in other treatment departments, which are more complex. The purpose of this research is to explore the impact of the Six Sigma method and CI strategy on the quality of nursing management in infusion rooms, so as to provide reference for clinical research. *Methods*. A total of 2142 patients treated in our outpatient infusion rooms from June 2019 to June 2020 was included into this retrospective analysis. Of these, 1105 patients admitted before 2020 received routine care management services and were considered as the control group. Another 1037 patients were admitted after 2020 and received the Six Sigma method combined with CI strategic care management and were considered as the research group. The incidence of adverse events during treatment was counted in both groups, and patients' compliance behavior and psychology were investigated. After treatment, patients' evaluation of the quality of nursing and their satisfaction with the nursing were investigated. *Results*. The incidence of adverse events during infusion in the research group was dramatically lower than that in the control group, while the compliance behavior scores were higher ($P < 0.05$). In addition, SAS and SDS in the research group were lower than those in the control group, while the quality of nursing were higher ($P < 0.05$). It was also clear that the research group had 93.39% satisfaction with nursing, which was also higher than the control group ($P < 0.05$). *Conclusion*. Implementation of infusion room nursing management according to the Six Sigma method with CI strategic plan can avoid adverse events and improve infusion nursing satisfaction. It also helps reduce the incidence of dispute events.

1. Introduction

The infusion room is the last part of an outpatient visit, with high patient density, large staff mobility, and a wide variety of conditions. In addition, most patients are accompanied by their families during infusion, and nursing staff in infusion rooms have to face more trivial and miscellaneous tasks than nursing staff in other treatment departments, which are more complex [1]. As a result, nursing in infusion rooms is more intensive and disorganized [2]. Surveys have shown that in tertiary hospitals, the average daily outpatient infusion room receives more than about 300 patients alone. With the addition of patients' accompanying persons or family members, the average daily population flow in the infusion room is basically at 500-800 visits/day [3]. At the same time, patients are characterized by limited mobility, organic discomfort, and emotional agitation during infusion. Accompanying family members are prone to adverse emotions due to the limited things they can undertake, which makes it further difficult to carry out nursing work [4]. Infusion room nursing has the risk of different degrees and aspects of adverse events that affect the quality of nursing under multiple factors, and nursing management is an effective way to improve the quality and efficiency of nursing [5].

Nursing service strategies in outpatient infusion rooms need to meet both broad applicability and must be time-effective and can be completed within a limited working time [6]. Among the nursing management programs, the Six Sigma method is considered a near perfect quality management program, proposed for Bill Smith of Motorola [7].

This management scheme applied to nursing management can clearly point out the problems in nursing and develop appropriate solutions [8]. Recently, Six Sigma has also been gradually gaining attention in clinical healthcare services and has now achieved excellent results in clinical departments such as the operating room and ophthalmology [9, 10]. Corporate Identity (CI) strategy is mostly used in "corporate image" management, but with the awakening of hospitals to their own brand and image awareness and attention, some studies have also incorporated CI strategy ideas into nursing management and achieved more desirable results; For example, Hardy et al. proposed that the CI strategy is the best management choice for the future clinical radiology department [11, 12]; Becze stated that the CI strategy will be a necessary measure for the future hospital [13]. We believe that the Six Sigma method and CI strategy are equally effective in improving the overall quality of nursing and patient treatment experience in outpatient infusion rooms and reducing the occurrence of doctor-patient disputes, but there are no studies at home or abroad to confirm this view.

Since 2020, our hospital has been carrying out the nursing management of the Six Sigma method and CI strategic thinking in infusion rooms, and sufficient cases have been accumulated so far. So, a retrospective analysis will be performed. Our purpose is to find a management solution suitable for outpatient infusion rooms, which can improve the quality of nursing services while reducing the pressure of nursing work. This has extremely important reference significance for outpatient infusion rooms in all hospitals around the world in the future.

2. Materials and Methods

2.1. General Data. The infusion rooms in our hospital were regarded as the study site, and patients receiving infusion therapy were included as subjects. They were divided into the control group (1105 cases, included from June to December 2019) and the research group (1037 cases, included from January to June 2020) based on the time of inclusion. In the control group, there were 539 males (48.78%) and 566 females (51.22%), with an average age of 41.92 ± 15.37 years. In the research group, there were 507 males (48.89%) and 530 females (51.11%), with an average age of 42.06 ± 16.12 years. Among them, patients in the control group received conventional infusion room nursing management, and the research group received the Six Sigma method combined with CI strategic nursing management. This study has been approved by the Ethics Committee of our hospital, and all research subjects signed the informed consent form.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria are as follows: (1) receiving infusion therapy in infusion rooms after a visit to our hospital; (2) being watched by father or mother, partner, or child; (3) Age: 18-75 years old; (4) basic reading and writing skills; and (5) signed informed consent forms. Exclusion criteria are as follows: (1) receiving nursing interventions from nondesignated caregivers, (2) combined audiovisual dysfunction, (3) not having basic reading and writing skills, and (4) no family or caregiver care.

2.3. Methods. Nursing services are completed by the same nursing team in our hospital, and all nurses have 3-5 years of work experience. Control group: routine nursing management was implemented. Nursing staff are required to carefully check identification information, prescription, and drug information before performing infusion operations, to develop infusion nursing operation procedures, and to link the quality of infusion room nursing to nurse performance, etc. Research group: Six Sigma method in conjunction with CI strategic nursing management was performed. Combining the definition, measurement, analysis, improvement, and control phases of the Six Sigma method with the mind identification (MI), behavioral identity (BI), and visual identity (VI) of the CI strategy, this research nursing management program was developed: (1) Definition phase: the proportion of adverse events of patients in infusion nursing and their satisfaction were seen as criteria to assess the quality of nursing management, to reduce the incidence of adverse events in infusion and increase satisfaction and improve the quality of nursing management. (2) Analysis phase: synthesizing our previous nursing experience with relevant literature [13–15], we concluded that the main reasons for adverse reactions and dissatisfaction with nursing expressed by patients during infusion can be divided into two areas. On the one hand, the performance of nursing staff does not meet the clinical requirements, such as not paying attention to the hygienic environment or having a lazy mentality leading to the lack of classification of medical and domestic waste, the lack of skill in infusion operation leading to repeated punctures and irregular fixation of dressings, and the low cooperation between nurses leading to long waiting time for infusion for patients. On the other hand, patients and their accompanying family members have insufficient knowledge of infusion rooms and the requirements related to infusion treatment, such as lack of knowledge of garbage sorting leading to difficulties in sanitary management of the rooms, and precautions after infusion bringing about needle dislodgement and serious bleeding back. Therefore, the focus of implementing quality of nursing management for patients in the 2020 group can be determined to include both nursing staff management and patient cognitive management. (3) Improvement phase: CI strategies were integrated into this phase. ① Build professional beliefs for nursing staff through culture building. Create a good nursing atmosphere, such as posting slogans in the infusion rooms with the themes of "Respect for Life" and "High-quality Nursing." Regularly organize nursing staff to carry out cultural performances with the theme of "ethics of nursing behavior" and encourage nursing staff to promote nursing cultural quality by adapting songs, creating skits, writing stand-up comedy, etc. in conjunction with their own clinical work experience. ② Implement nursing behavior management for nursing staff. First, professional nursing skills training was implemented regularly for nursing staff to improve their professional competence. In the process of training, nurses should improve their awareness of self-protection,

especially when separating used needles to avoid needlestick injuries. Then, we formulate the duties of nursing staff in infusion rooms, including the hygienic management of infusion rooms (such as waste classification, ventilation management, and infrastructure disinfection), standardization of the infusion care process, and the preservation program for disposable sterile medical supplies. Subsequently, a code of ethical conduct for nursing staff was written, stipulating that nursing staff should use honorific form and be gentle when dealing with patients and their families, and should not show perfunctory emotions in response to repeated inquiries from patients. Meantime, nursing staff were trained in communication skills so that they could implement infusion-related health education to patients as briefly, quickly, and effectively as possible (e.g., no excessive movement of the limb on the receiving side during infusion, personal garbage needs to be disposed of in a fixed garbage can, no loud noises are allowed during infusion unless necessary, and nursing staff should be informed immediately of any discomfort). ③ Standardize the visual image of nursing staff. Regularly issue new work clothes to nursing staff to ensure that they are well dressed and clean. Issue each caregiver a badge with his or her name and require it to be worn daily. We also standardize the accessories and makeup of nursing staff so that their external appearance remains gentle and approachable. (5) Control stage: develop quality assessment indexes according to the nursing program, clarify the work requirements for nursing staff at all levels, regularly inspect the work of nursing staff, and link the inspection results to their performance.

2.4. Outcome Measures

(1) The occurrence of adverse events such as inadequate sanitary management, inadequate management of medical items, infusion operation errors and unsuccessful completion of infusion in the infusion rooms during the study period was counted, and the incidence of adverse events was calculated

(2) Compliance behavior: before the end of treatment, the compliance behavior of patients and family members during infusion was assessed by a departmental compliance questionnaire distributed by nurses [16]. It includes 4 items of wandering infusion, patient hygiene behavior, family hygiene behavior, and family caregiving behavior. Each item has 25 points out of 100, the higher the score, the higher the degree of compliance behavior

(3) Psychology: after treatment, patients' psychology was assessed using the Self-Rating Scale for Anxiety (SAS) and Depression (SDS) [17], the scoring results are from 0 to 100 points, with higher scores indicating more severe negative feelings of anxiety and depression

(4) Nursing quality evaluation: a survey was conducted using a nursing quality questionnaire [18]. It contained four aspects: technical level, infusion environment, etiquette service, and psychological guidance, each of which was scored out of 10. The total score was calculated; the higher the score, the higher the nursing quality

(5) Nursing satisfaction: a self-administered nursing satisfaction questionnaire was developed [19], which assessed six items including infusion room environment, nursing intervention during waiting for infusion, service attitude, infusion technique level, communication, postinfusion precautions explanation, and overall satisfaction; each item was set as three options of very satisfied, satisfied, and dissatisfied. In the meantime, patients were asked to indicate the reason for dissatisfaction after selecting the dissatisfaction option. Total satisfaction rate = (very satisfied + satisfied)/total × 100%. Both quality of care and satisfaction surveys were conducted when patients completed treatment and were ready to leave the hospital

2.5. Statistical Analysis. Data were entered into SPSS 22.0, and the counting data such as the incidence of adverse events, nursing satisfaction rate, and gender were expressed by (n (%)) with a χ^2 test. Age was expressed as $\bar{x} \pm s$, t-test was performed, and statistical differences were represented as $P < 0.05$.

3. Results

3.1. Comparison of General Data. Comparing the general data of gender, age, and marital status between the two groups, we found that the differences in gender, age, marital status, and primary caregiver were not statistically remarkable ($P > 0.05$, Table 1), confirming comparability between both groups.

3.2. Comparison of Incidence of Adverse Events between Both Groups. Subsequently, the total rate of adverse events in the research group was only 6.56%, which was dramatically lower compared to the control group (13.48%) ($P < 0.001$). It was also seen that the incidence of adverse events such as inadequate hygiene management, improper management of medical items, infusion operation errors, and unsuccessful completion of infusion were all lower in the research group than in the control group ($P < 0.05$, Table 2).

3.3. Comparison of Compliance Behavior Scores between Both Groups. The results of compliance behavior scores in both groups denoted that the total score of the research group (23.14 ± 2.65) was higher than that of the control group (17.15 ± 3.91) ($P < 0.05$, Figure 1(a)). It was also seen that the research group also had higher score results than the control group in all domains of wandering infusion, patient hygiene behavior, family hygiene behavior, and family caregiving behavior ($P < 0.05$, Figures 1(b)–1(e)).

3.4. Comparison of Psychology between Both Groups. The SAS score of the research group was 37.07 ± 17.88, which was lower than that of the control group ($P < 0.05$,

Table 1: Comparison of general data between both groups ($\bar{x} \pm s/n$ (%)).

Groups	Cases	Gender		Age (year)	Marital status				Primary caregiver		
		Male	Female		Unmarried	Married	Divorced	Widowed	Man and wife	Parents	Children
Control group	1105	539 (48.78)	566 (51.22)	41.92 ± 15.37	230 (20.81)	571 (51.67)	149 (13.48)	155 (14.03)	514 (46.52)	377 (34.12)	214 (19.37)
Research group	1037	507 (48.89)	530 (51.11)	42.06 ± 16.12	225 (21.70)	519 (50.05)	128 (12.34)	165 (15.91)	495 (47.73)	371 (35.78)	171 (16.49)
t/χ^2		0.003		0.206	0.249	0.566	0.618	1494	0.319	2.971	3.003
P		0.958		0.837	0.618	0.452	0.432	0.222	0.572	0.082	0.083

Table 2: Comparison of incidence of adverse events between both groups (n (%)).

Adverse events	Performance	Control group ($n = 1105$)	Research group ($n = 1037$)	χ^2	P
Inadequate hygiene management	Uncategorized garbage	13 (1.18)	6 (0.58)		
	Incomplete cleaning and disinfection records	22 (1.99)	13 (1.25)		
	Total	35 (3.17)	19 (1.83)	3.881	0.049
Improper management of medical items	Expired sterile infusion items	3 (0.27)	0 (0.00)		
	Contamination of sterile infusion items	2 (0.18)	0 (0.00)		
	Total	5 (0.45)	0(0.00)	4.682	0.030
Infusion operation errors	Incorrect patient information verification	3 (0.27)	0 (0.00)		
	Wrong configuration of drug solution	3 (0.27)	0 (0.00)		
	Repeated punctures	11 (1.00)	5 (0.48)		
	Drug extravasation	9 (0.81)	4 (0.39)		
	Irregular fixation of dressing	26 (2.35)	14 (1.35)		
	Total	52 (4.71)	23 (2.22)	9.800	0.002
Unsuccessful completion of infusion	Needle blockage	10 (0.90)	3 (0.29)		
	Localized redness and swelling at the puncture site	8 (0.72)	3 (0.29)		
	Severe hemorrhage	31 (2.81)	18 (1.74)		
	Needle dislodged	8 (0.72)	2 (0.19)		
	Total	57 (5.16)	26 (2.51)	10.095	0.001
Total		149 (13.48)	68 (6.56)	28.192	<0.001

Figure 2(a)). Besides, the SDS score in the research group was 31.79 ± 17.44, which was also dramatically lower than that in the control group ($P < 0.05$, Figure 2(b)).

3.5. Comparison of Quality of Nursing Evaluation between Both Groups. The ratings of nursing staff technical level, infusion environment, etiquette service, and psychological guidance in the research group were 9.15 ± 0.72, 9.13 ± 0.65, 8.86 ± 0.86, and 8.76 ± 1.23, respectively. Compared with the control group, the evaluation scores of technical level, infusion environment, etiquette service, and psychological guidance were higher in the research group ($P < 0.05$, Figures 3(a)–3(d)). The research group was also higher than the control group when compared with the total quality of nursing evaluation score of both groups ($P < 0.05$, Figure 3(e)).

3.6. Comparison of Nursing Satisfaction between Both Groups. The nursing satisfaction survey of both groups manifested that the total satisfaction rate of the research group was 93.39%, which was higher than that of the control group (90.21%) ($P = 0.017$, Table 3).

4. Discussion

Six Sigma is one of the quality management methods, which was first applied in the quality management of manufacturing companies and gradually expanded to the quality management of the service industry through subsequent development [20]. Nursing interventions are among the service interventions. Research has shown that adding the Six Sigma management model to the management of hospital service quality allows for an increase in the scientific nature

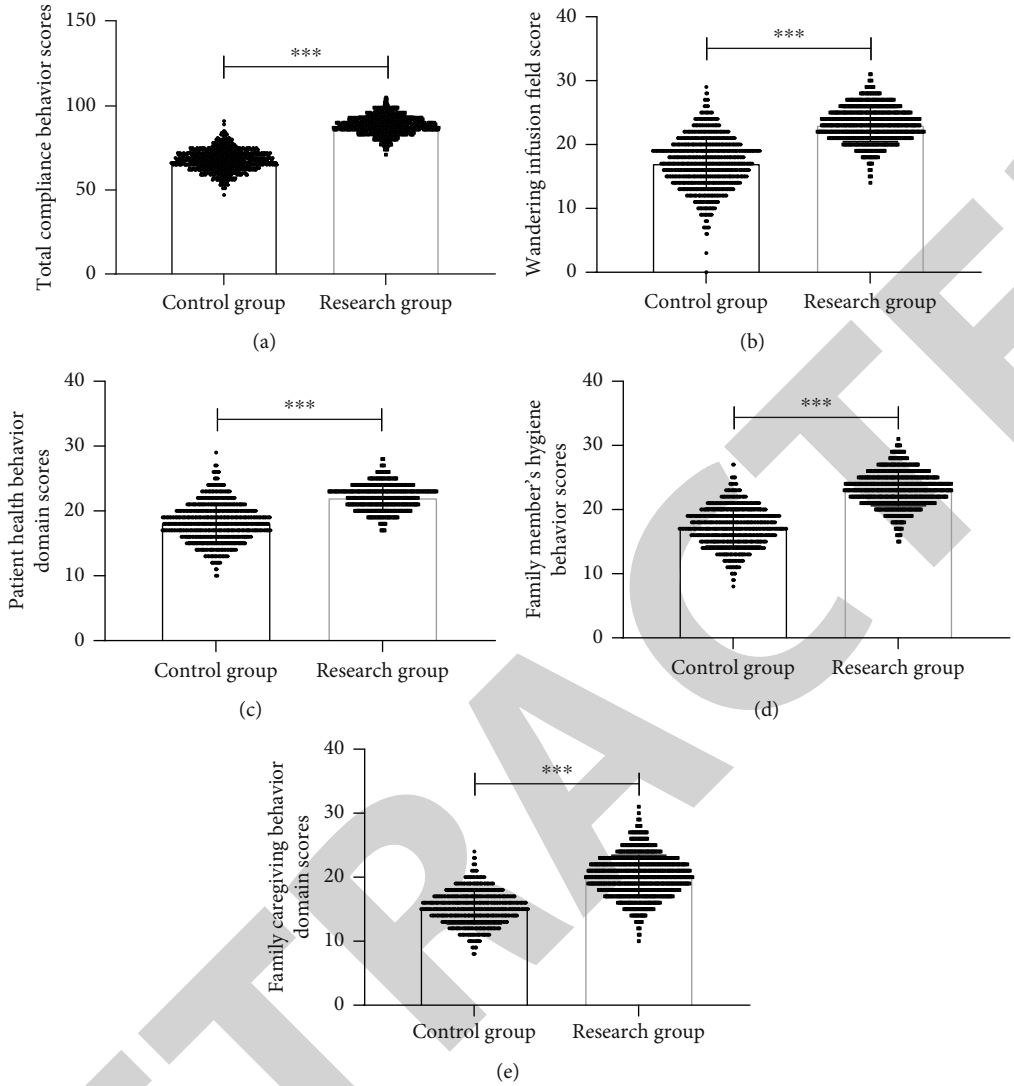

Figure 1: Comparison of compliance behavior scores between both groups. (a) Comparison of total compliance behavior scores. (b) Comparison of wandering infusion field scores. (c) Comparison of patient health behavior domain scores. (d) Comparison of family members' hygiene behavior scores. (e) Comparison of family caregiving behavior domain scores. $^{***}P < 0.001$.

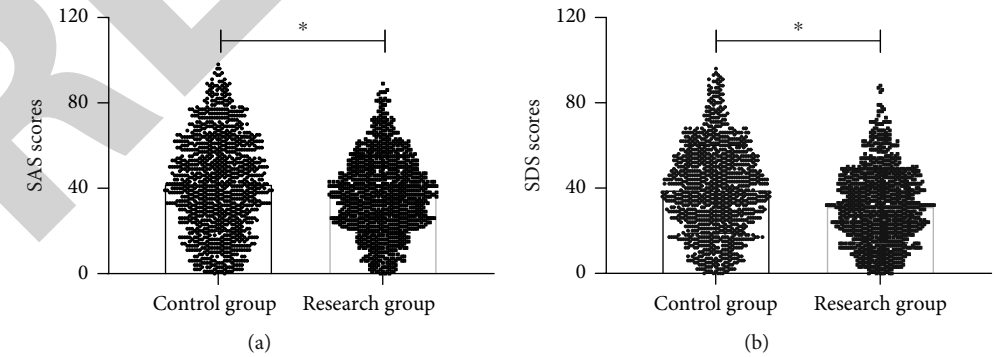

Figure 2: Comparison of mental scores between both groups. (a) Comparison of SAS score results. (b) Comparison of SDS score results. $^{*}P < 0.05$.

of hospital care management and an increase in patient satisfaction [21]. Previous studies have shown that performing Six Sigma quality of nursing management in the labor and delivery office has been shown to promote standardized writing of nursing documents and cognitive education of nursing knowledge [22].

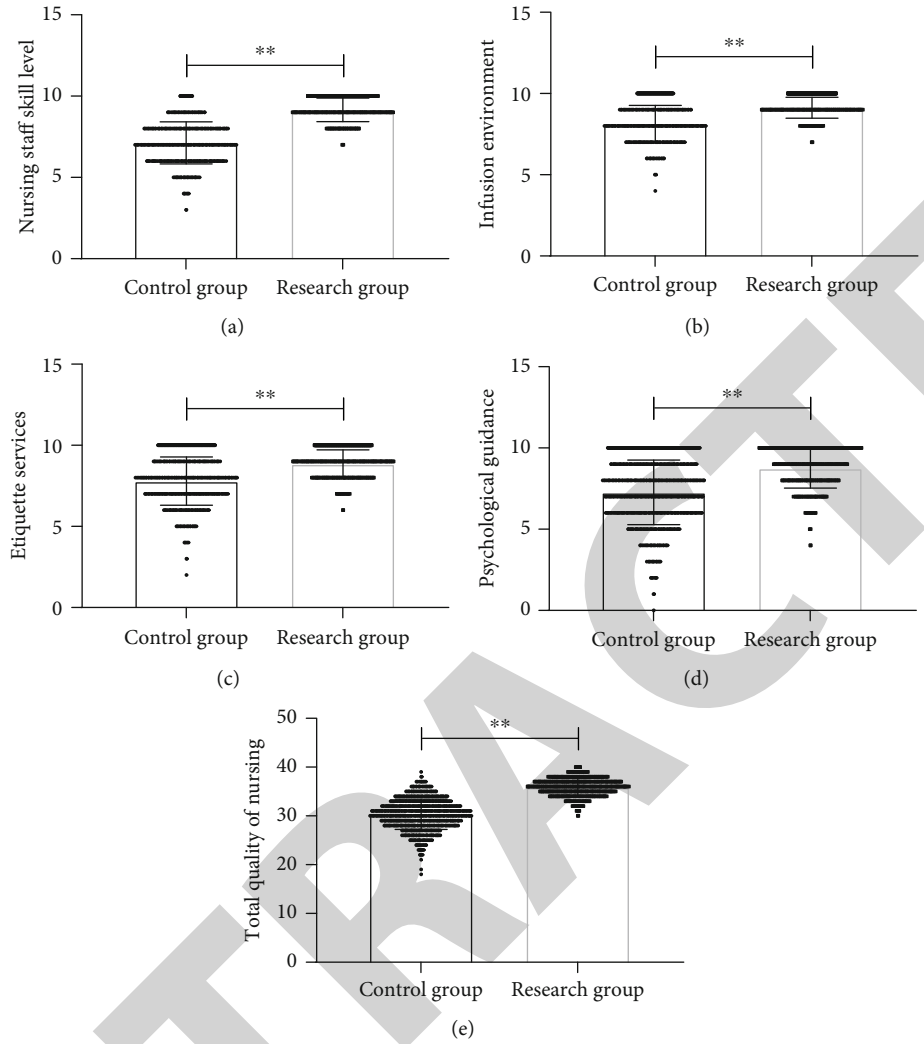

Figure 3: Comparison of quality of nursing evaluation between both groups. (a) Comparison of nursing staff skill level evaluation results. (b) Comparison of infusion environment evaluation results. (c) Comparison of etiquette services evaluation results. (d) Comparison of psychological guidance evaluation results. (e) Comparison of total quality of nursing evaluation scores. $^{**}P < 0.01$.

Table 3: Comparison of both groups' satisfaction with nursing (n (%)).

Groups	Cases	Very satisfied	Satisfied	Dissatisfied	Total satisfaction rate
Control group	1083	226 (20.87)	751 (69.34)	106 (9.79)	977 (90.21)
Research group	998	298 (29.86)	634 (63.53)	66 (6.61)	932 (93.39)
χ^2					5.661
P					0.017

The infusion room is a separate clinic for intravenous treatment in the hospital, and the work is mainly carried out by nursing staff, so the quality of nursing is the main reflection of the quality of management in the room. In the case of emergency infusion rooms, the implementation of nursing management in conjunction with the Six Sigma method can reduce the risk of dispute events while improving patient satisfaction [23]. CI strategy is mostly applied to the construction of corporate culture, through the planning and improvement of corporate image, to achieve the ultimate goal of deepening the quality image of the company into the minds of the public [24]. Previous studies related to the integration of CI strategies into nursing quality management (especially nursing quality management in infusion rooms) are fewer, which researchers believe is related to the fact that most researchers have focused more on nursing operations and nursing technology in their studies to the neglect of nursing environment and nursing culture construction [25]. Therefore, in this study, while applying the Six Sigma method to improve the quality of nursing

management in infusion rooms, CI strategic thinking was incorporated into it in the hope that the quality of nursing in infusion rooms of our hospital could be optimized in terms of both actual nursing work and nursing thinking.

This study demonstrated that the incidence of adverse events such as inadequate hygienic management during infusion, improper management of medical items, infusion operation errors, and unsuccessful completion of infusion were lower in the research group than in the control group. It is evident that the implementation of the new care management policy has improved the safety of care in all aspects and the improvement is holistic in nature. There are reasons as follows: (1) To solve the problem completely, we need to identify the root causes of the problems. The Six Sigma management process, inquiring about nursing adverse events and analyzing the causative factors as a key step, has a directive effect on the direction of subsequent nursing and also allows for more targeted nursing interventions [26]. (2) CI strategic thinking is not a fetter and supervision of nursing staff, but a correct guidance of nursing concepts and ideas. Positive, conscientious, and dedicated nursing thinking can increase the patience of nursing staff for their own work and the acceptance of patients and their families. In turn, the nursing staff will be able to think more clearly in the boring, busy, and messy infusion room nursing work [27]. Moreover, we also found that the compliance behavior of the research group was dramatically improved, while the poor psychology was improved. Research has noted that most patients feel they are not being given enough attention due to the large number of people in infusion rooms, the noisy environment, and the high turnover of staff [28]. At the same time, patients generally exhibit resistance and rejection of health care workers due to the pain caused by the disease [29]. This not only greatly increases the incidence of doctor-patient disputes but also will seriously affect nursing treatment. And the results of this experiment revealed that the use of the Six Sigma method and CI strategic thinking for nursing management can effectively compensate for this shortcoming, reduce patients' resistance to health care workers, and improve treatment acceptance. It was seen that patients in the research group rated the quality of nursing and were more satisfied with it than the control group. There are reasons as follows: (1) A reduction in the incidence of adverse events reduces the tension of patients and their families and leads to an increase in their satisfaction. (2) The first step in six sigma is to set goals. The goal in this study was to improve patient satisfaction with nursing, and the motivation of nursing staff was improved by linking quality of nursing to salary performance after clarifying the goals of nursing management [30]. (3) The CI strategy implements planning and management of the nursing staff's external appearance and internal temperament, making it easier for patients to accept the nursing staff and follow their advice. An increase in nursing satisfaction increases patients' trust in nursing staff and improves their compliance with nursing operations, so patients and their families show increased performance in support of nursing.

At present, the Six Sigma method in nursing management has received some attention and application, but CI strategic thinking is still relatively rare, which still deserves further exploration. Furthermore, the basis for the grouping in this study was related to different approaches to nursing management on the one hand and to time years on the other, which may also produce potential factors affecting the results. Thus, we still need to follow up with a clinical randomized controlled trial to further confirm the effectiveness of the application of the Six Sigma method with the CI strategic plan to implement infusion room nursing management. In addition, in modern infusion room nursing management, we need to pay attention not only to the performance and operational skills of nursing staff but also to the construction of the nursing environment. We can further optimize the environment of infusion rooms to enhance the treatment experience of patients.

5. Conclusion

Implementation of infusion room nursing management based on the Six Sigma method with CI strategic plan can avoid adverse events and improve infusion nursing satisfaction. It can help reduce the incidence of dispute events.

Data Availability

The data used in the article is 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 a potential conflict of interest.

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Retraction

Retracted: Effect of Cold Fluid Compensatory Swallowing Combined with Balloon Dilation on the Treatment of Poststroke Cricopharyngeal Achalasia: A Pilot Randomized Controlled Trial

BioMed Research International

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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] X. Li, L. Jin, C. Gu, W. Zhang, X. Zhou, and X. You, "Effect of Cold Fluid Compensatory Swallowing Combined with Balloon Dilation on the Treatment of Poststroke Cricopharyngeal Achalasia: A Pilot Randomized Controlled Trial," *BioMed Research International*, vol. 2022, Article ID 4171561, 7 pages, 2022.

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Research Article

Effect of Cold Fluid Compensatory Swallowing Combined with Balloon Dilation on the Treatment of Poststroke Cricopharyngeal Achalasia: A Pilot Randomized Controlled Trial

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Objective. This study is aimed at comparing the treatment efficacy between catheter balloon dilation combined with cold fluid compensatory swallowing training and catheter balloon dilation alone on poststroke cricopharyngeal achalasia (CPA). *Methods*. We conducted a single-blind, randomized controlled trial (RCT). Poststroke patients with CPA were divided into two groups: the control group (treated with catheter balloon dilation) and the trial group (catheter balloon dilation combined with cold fluid compensatory swallowing). Videofluoroscopic swallowing study (VFSS) was performed, and functional oral intake scale (FOIS) was used to evaluate and compare the swallowing function of patients in the 2 groups before and after intervention. Posttreatment VAS pain scores and recovery time were also measured. *Results*. VFSS and FOIS scores in the two groups were improved after treatment ($P < 0.05$). In the trial group, VFSS scores in the pharyngeal phase and aspiration degree were significantly higher compared with the control group ($P < 0.05$) but not in the oral phase ($P > 0.05$). The difference in FOIS scores and patients' recovery time from intervention to eating mushy food between the trial and control groups was significant ($P < 0.05$), but not the VAS scores ($P > 0.05$). *Conclusion*. The catheter balloon dilation combined with cold fluid compensatory swallowing was superior to catheter balloon dilation alone in terms of relieving dysphagia and reducing aspiration in patients with CPA following stroke. Long-term efficacy should be followed up with more objective and quantitative indicators in future studies.

1. Introduction

The upper esophageal sphincter (UES), mainly comprised of cricopharyngeus muscle (CPM), is the gateway to the esophagus. CPM remains tightly closed to prevent air from entering the stomach and food reflux in the resting state. During swallowing, the CPM relaxes to allow the bolus to pass [1]. Cricopharyngeal achalasia (CPA) is characterized by incomplete relaxation of UES or lack of coordination of the UES opening with pharyngeal contractions [2]. It occurs when the CPM fails to relax during deglutition, and patients with CPA present symptoms such as swallowing dysfunction, dehydration, aspiration, choke and malnutrition, nasopharyngeal regurgitation, and respiratory illnesses, which seriously affect the life quality of patients [3, 4].

CPA is a typical dysphagia associated with stroke [5]. Lateral medullary lesion has been identified as an independent predictor for CPA [6]. Among patients suffering from brainstem stroke, the incidence of accompanying CPA is as high as 50% [7]. Effective protocols are needed for dysphagia management to avoid severe clinical complications and reduce morbidity and mortality of poststroke patients. Catheter balloon dilation is widely applied in clinic poststroke CPA treatment. The possible mechanism of the balloon dilatation for CPA treatment might be that the sensory input from the inflated balloon promotes the motor responses of

the swallowing central pattern generator [8]. Balloon dilatation has the advantages of noninvasiveness, easy operation, and minor side effects [9, 10]. However, repeated catheterization and balloon pulling in balloon dilation may cause local mucosal edema and pain, resulting in poor tolerance and coordination [11]. Yuan and Zhang have reported the rehabilitation compliance of patients with dysphagia and cricopharyngeal dysfunction and proposed that balloon dilation therapy is more effective in patients with good adherence [12]. CPM can respond to oropharyngeal, esophageal, and neurohormonal triggers through complex control networks. Thus, even minor stimuli may change the behavior of CPM [6]. For example, transcranial magnetic stimulation on the motor cortex can produce motor evoked potential on the CPA and induce UES contraction [13]. Air and water stimulation induces lower esophageal sphincter relaxation accompanied with UES contractile reflex [14]. Ice packs have been used to reduce swelling and relieve pain. Studies have shown that ice stimulation can significantly shorten the swallowing reflex time, trigger swallowing movement, and enhance oropharyngeal muscular coordination [15]. It mainly increases sensory input to enhance the sensitivity of swallowing reflex by stimulating the soft palate and pharynx to sharpen the sensitivity of local nerve sensation and reconstructing the neurological network [16]. Therefore, it is indicated that ice stimulation may improve the motor and sensory activities of the cricopharyngeal muscle and promote the swallowing reflex. In addition, ice stimulation can reduce the incidence of aspiration, thereby improving patients' attention to feeding [17]. Studies [18, 19] have confirmed that ice water balloon dilatation can improve swallowing function and alleviate the adverse reactions caused by balloon dilation, which is of clinical significance.

However, there is insufficient evidence for the clinical efficacy of cold fluid compensatory swallowing. In this study, we aimed to explore the therapeutic efficacy of cold fluid compensatory swallowing combined with balloon dilation on swallowing function and quality of life of stroke patients with CPA. We hypothesized that combination with cold fluid compensatory swallowing could improve the swallowing function of patients compared with balloon dilation treatment alone. The findings of our study may provide novel strategy for the management of poststroke CPA.

2. Methods

2.1. Study Design and Subjects. This single-blind randomized trial recruited stroke patients treated at the Rehabilitation Department of in Hangzhou No. 128 Hospital, China, from December 2019 to February 2021. The inclusion criteria were as follows: (1) patients aged 18-80 years old, (2) stroke patients who met the national diagnostic criteria of cerebrovascular diseases through cranial CT or MRI [20], (3) videofluoroscopic swallowing study [21] (VFSS) confirmed achalasia of the cricopharyngeal muscle, and (4) Chinese version of Mini-Mental State Examination (MMSE) [22, 23] score ≥ 24. The exclusion criteria were as follows: (1) patients who underwent transnasal balloon dilatation; (2) unstable vital signs, failure of essential organs, and pregnant or lactating women; (3) previous abnormal structures of the oral cavity, pharynx, and esophagus; and (4) recent treatments or presence of previous or current conditions that might impact the results of the trial. This study was approved by the Clinical Research ethics committee of Hangzhou No. 128 hospital, China (no. 20200107-04). Informed consent was obtained from each patient. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2200061770).

2.2. Intervention. According to the computer-generated randomization sequence, the included cases were randomly divided into the trial group (patients underwent catheter balloon dilation combined with cold fluid compensatory swallowing) and the control group (patients underwent catheter balloon dilation). One nurse generated the random allocation sequence, enrolled participants, and then assigned participants to interventions. The allocation sequence was concealed in numbered sealed opaque envelopes. The physicians and occupational therapists were blind to treatment allocation. Under the guidance of speech-language therapists, both groups completed routine swallowing function training [24], low-frequency electrical stimulation [24], and catheter balloon dilatation [8]. Regular swallowing function training included basic, direct, and compensatory training for 30 minutes per day, 5 days per week.

Trial group: patients held a urethral catheter (14Fr) in the mouth and actively swallowed it. When it is difficult to swallow the catheter, the rehabilitation nurse pushed the catheter appropriately, observed the response of patients, and then performed catheter balloon dilatation [8]. The process was repeated ten times, about 30 minutes each time, three times a week. After dilatation, patients continued to take ice water compensatory swallowing training [25]. They drank ice water with a long handle spoon at 4°C for 1 ml each time and swallowed with the head down and exerted force as instructed for about 15 minutes. The nurse affirmed the successful swallowing of patients.

Control group: after undergoing catheter balloon dilatation as the trial group, patients were given dexamethasone, chymotrypsin, and gentamycin nebulization to prevent mucosal edema and reduce mucus secretion.

2.3. Outcomes. All participants were initially evaluated for the severity of swallowing disorder with VFSS and FOIS before and after resuming oral feeding and after four weeks of treatment. One occupational therapist was trained to evaluate patients' VAS scores and average hospital stay after treatment.

2.4. Primary Endpoints. Videofluoroscopic swallowing study (VFSS) [21] evaluation: VFSS is the gold standard to diagnose and evaluate the swallowing function of patients with dysphagia. Philips Digital Gastrointestinal Machine was used for fluoroscopy acquisition. The video images were recorded with lateral projection and stored digitally at a speed of 30 frames per second. The swallow consistency order was thick-liquid, semisolid, solid, and thin-liquid. Based on angiography, the VFSS scores were assessed at three phases: oral phase (0-3 points), swallowing phase (0-

3 points), and aspiration degree (0-4 points). For the oral phase, 0 point indicates nonswallow or swallow by gravity; 1 point indicates that no bolus formation, only flow of disperse food; 2 points indicate inadequate swallow with some remaining food in oral cavity; 3 points indicate a normal complete swallow at one time. For the swallowing phase, 0 point indicates no laryngeal elevation, closure of epiglottis and palatine arches, and inadequate swallow reflex; 1 point indicates large residue in pyriform sinus, 2 points indicate small amount of residue that can be repeatedly swallowed; 3 points indicates the adequate swallow. For the aspiration degree, 0 point indicates large aspiration without choke; 1 point indicates large aspiration with choke; 2 points indicate small amount of aspiration without choke; 3 points indicate small amount of aspiration with choke; 4 points indicate no aspiration. The VFSS scale covered 13 items, with a total score of 10 points. The higher the score was, the better the rehabilitation effect on swallowing function would be.

Functional oral intake scale (FOIS) [26]: according to the patients' oral feeding situation, the patients' swallowing function was evaluated by FOIS scoring into 7 grades from I to VII, corresponding to 1 to 7 points: I, nothing by mouth; II, tube feeding, with minimal attempts of food; and fluid; III, tube feeding, with consistent intake of food and fluid; IV, a total oral diet with a single consistency; V, a total oral diet with multiple consistencies that were specially prepared or compensated; VI, a total oral diet with multiple consistencies without special preparation, but with specific food limitation; and VII, a total oral diet with no restrictions. The FOIS score ≥ 3 was regarded as significant improvement.

2.5. Secondary Endpoints. Visual analogue scale (VAS) [27, 28]: VAS is a continuous scale self-completed by the respondent. It is usually comprised of a horizontal or vertical line at 10 cm long marked with verbal descriptors for extreme at both ends. Herein, we used a numeric version of VAS. The patients were asked with an introductory question and select a number ranging from 0 to 10 integers that best matched their pain intensity. It is an 11-point numeric scale representing different levels of pain, where 0 meant no pain (one extreme) and 10 meant extreme pain (the other extreme). The higher the score was, the more severe the pain patients suffered. We used VAS scores and visual evaluation to evaluate the adverse events, including mucosal edema, bleeding, and pain. Recovery time referred to the period from the first day of intervention to the day when the patient started to eat mushy food.

2.6. Sample Size. The sample size was calculated using the G∗Power 3.1.9 program based on a previous study [8]. The effect size of the repeated-measures analysis of variance was 0.3, with a power of 0.95 and a significance level of 0.05, using two groups and three rounds of measurements. The minimum sample size was 16 per group. A total of 36 participants were selected, with 18 participants in each group, accounting for a predicted dropout rate of 20%.

2.7. Statistical Analysis. Statistical analyses were performed using IBM SPSS 25.0. The measurement data were expressed as the mean ± standard deviation (SD). Independent t-test was used to compare numerical parameters between two groups. Independent sample t-test was used for intergroup comparison, and paired sample t-test was used for intragroup comparison. Statistical significance was set at $P < 0.05$.

3. Results

In this study, we evaluated the effect of cold fluid compensatory swallowing combined with balloon dilation compared with catheter balloon dilation alone on the treatment of poststroke CPA patients using a randomized controlled trial. We found that the trial group presented higher efficacy to relieve dysphagia and aspiration in the pharyngeal phase and aspiration degree compared with the control group, improving the swallowing function and promoting the recovery of patients with CPA post stroke.

3.1. Participants. Following the inclusion criteria and exclusion criteria, 36 patients were included. The study flowchart is presented in Figure 1.

The clinical characteristics of patients enrolled in this study were shown in Table 1. There was no significant difference in general data, such as gender, age, stroke duration, stroke type, lesion location, and degree of dysphagia and pain, between the two groups. One patient in the trial group dropped out for personal reasons.

3.2. VFSS and FOIS Scores. VFSS and FOIS scores in the two groups were both elevated after treatment (both $P < 0.05$) (Tables 2 and 3). Compared with the control group, VFSS scores were significantly increased in the pharyngeal phase and aspiration phase (both $P < 0.05$), but not in the oral phase ($P > 0.05$) in the trial group. FOIS scores in the trial group were higher than those in the control group and showed significant increase in the trail group after the treatment ($P < 0.05$).

3.3. Recovery Outcome. After intervention, 16 patients in both groups recovered and began to eat food, and 3 patients still could not eat even the mushy food. The differences in patients' recovery time from eating meals between the trial and control groups were significant, and patients in the trial group had shorter recovery time compared with the control group (both $P < 0.05$), whereas VAS score showed no significant difference between the two groups ($P > 0.05$) (Table 3).

4. Discussion

This study indicated significant differences in VFSS scores of swallowing period, degree of aspiration, and FOIS scores between catheter balloon dilation combined with cold fluid compensatory swallowing training and catheter balloon dilation alone for the treatment of poststroke cricopharyngeal achalasia patients ($P < 0.05$). The combination treatment can improve swallowing function and reduce pulmonary infection, which was consistent with the research by Zhuang et al. [18]. Compared with the previous study, we used both VFSS and FOIS scoring systems to evaluate the swallowing

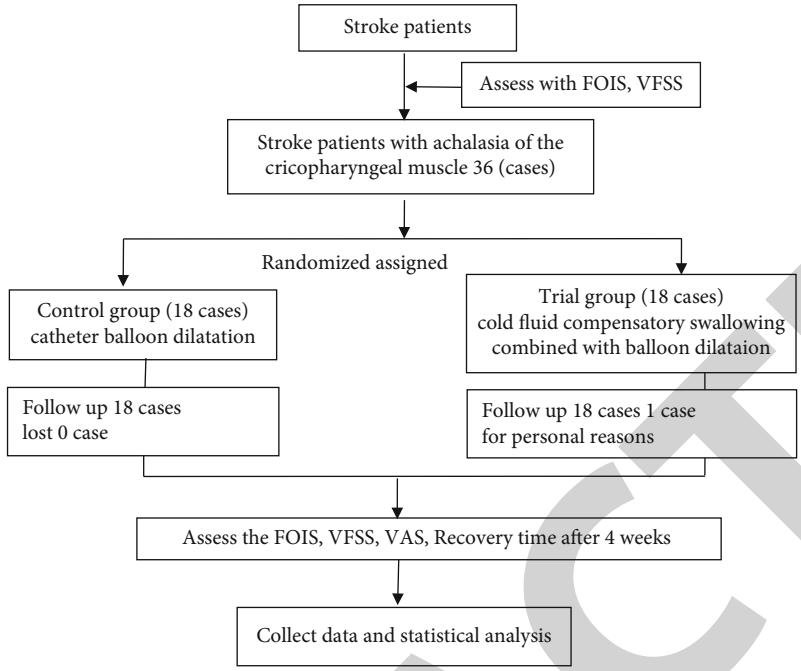

Figure 1: The study flowchart.

Table 1: Clinical characteristics of patients.

	Control group ($n = 18$)	Trial group ($n = 18$)	P value
Gender (M/F)	12/6	10/8	
Age (years)	62.22 ± 10.75	64.94 ± 10.22	0.442
Diagnosis			
Infarction	12	11	
Hemorrhage	6	7	
Time from onset (days)	45.83 ± 14.24	44.89 ± 15.73	0.851
Location			
Brain stem	10	12	
Combine	8	6	
Achalasia			
Complete	9	7	
Incomplete	9	11	
History			
Hypertension	17	16	
Diabetes	11	15	
Coronary heart disease	3	1	

function of patients. The effects were compared before and after treatments as well as between the control and trial groups to achieve a valid conclusion. Catheter balloon dilatation is widely used in the treatment of dysphagia caused by CPA [10]. During swallowing, the expanded balloon stretches the CPM to promote its opening, stimulates the CPM with a certain sense of tactile and pressure, and induces reflex swallowing through the superior laryngeal nerve to regulate the excitability of the brainstem swallowing center [8]. There are various sensory receptors in the mouth and pharynx. Sensory input plays a critical role in the initiation and regulation of swallowing [29]. After balloon dilatation, the patients in the trial group swallowed cold liquids with their heads down to consolidate the therapeutic effect of balloon dilatation on the swallowing muscle groups. The rehabilitation specialist nurse observed the patient's response, provided timely guidance, and gave positive affirmation and feedback. Studies [30, 31] have revealed that repeated ice stimulation increases the excitability of the cortical swallowing motor pathway, which is beneficial to rebuild the neural function network between the cortex and the medulla and restores the cortical regulation of the brainstem swallowing center. Drinking ice water can shorten the pharyngeal reaction time, prolong the laryngeal elevation time, and accelerate the laryngeal closure speed [30, 31]. Pharyngeal cold stimulation can effectively improve the sensitivity of the soft palate and pharynx, make swallowing easier, attract patients' attention on feeding and swallowing, and reduce aspiration. Li et al. [32] have found that patients who receive ice stimulation training experience less adverse events (e.g., aspiration, choking, and aspiration pneumonia) compared with the control group, and the difference was statistically significant. Compared with the previous studies, we combined the ice stimulation and catheter balloon dilation for the treatment of poststroke patients with CPA. We found ice stimulation improved the treatment efficacy compared with the catheter balloon dilation alone, which relieved dysphagia and aspiration in the pharyngeal phase and aspiration degree and promoted the recovery of swallow function of patients.

Table 2: Comparison of VFSS scores between two groups.

VFSS	Group	Pretherapy	Posttherapy	95% confidence interval of the difference		*P* value
The oral phase	Control group	2.44 ± 0.51	2.61 ± 0.50	Low lever	High lever	
	Trial group	2.18 ± 0.53	2.35 ± 0.61	-0.124	0.640	0.178
Pharyngeal phase	Control group	1.50 ± 0.51	2.06 ± 0.54[a]	-0.877	-0.071	0.023
	Trial group	1.41 ± 0.50	2.53 ± 0.62[ab]			
Aspiration phase	Control group	2.56 ± 0.51	3.33 ± 0.48[a]	-0.701	-0.044	0.027
	Trial group	2.82 ± 0.53	3.71 ± 0.47[ab]			
Total	Control group	6.44 ± 1.04	8.39 ± 0.78[a]	-0.745	0.700	0.949
	Trial group	6.82 ± 1.01	8.41 ± 1.28[a]			

Table 3: Comparisons of FOIS and VAS scores and recovery time between two groups.

	Group	Pretherapy	Posttherapy	95% confidence interval of the difference		*P* value
FOIS	Control group	1.72 ± 0.67	4.39 ± 0.98[a]	Low lever	High lever	
	Trial group	1.82 ± 0.73	5.18 ± 1.07[ab]	-1.496	-0.079	0.030
VAS	Control group		0.61 ± 0.70	-0.255	0.654	0.379
	Trial group		0.41 ± 0.62			
Recovery time (d)	Control group		26.13 ± 2.53	0.063	4.187	0.043
	Trial group		24.00 ± 3.14[b]			

Note: intragroup comparison before and after treatment, [a]$P < 0.05$; compared with the control group after treatment, [b]$P < 0.05$. d: days.

Our study also showed significant differences in patients' recovery time from intervention to eating meals between the trial and control groups ($P < 0.05$), but VAS scores showed no difference between the two groups ($P > 0.05$). The reason might be that patients in the control group were given dexamethasone, chymotrypsin, and gentamycin nebulization after dilatation, preventing mucosal edema and reducing mucus secretion. The pain of patients in both groups was controlled. Successful experience can improve patients' self-efficacy [33], which makes patients more actively coordinated. Our study enables patients to continuously practice near-physiological swallowing, enhancing patients' self-confidence by successfully drinking cold liquids and making them more cooperated with active swallowing catheter insertion before balloon dilation. Active swallowing catheter insertion can also help repeatedly train the muscles, improving their strength and coordination of swallowing muscle groups [34]. Swallowing catheter placement consolidates and improves the role of catheter balloon dilatation in treating CPA and promotes the recovery of patients' swallowing function. Yang et al. [16] compare the efficacy of ice water balloon dilatation with regular temperature balloon dilatation. They find that the differences in average treatment times, average hospital stay, and average treatment cost between the two groups are noticeable. Ice water balloon dilatation is more effective ($P < 0.05$), which is in line with the findings by Sun and Wang [35]. One study has reported [18] that ice water alleviated and controlled pharyngeal pain, congestion, and edema caused by balloon expansion. We found that in the trial group, intervention relieved patients' discomfort and shorten the dysphagia treatment time. Compared with the previous studies, we conducted a randomized controlled trial to explore the effect of cold fluid compensatory swallowing combined with balloon dilation on the treatment of poststroke CPA patients. We used not only FOIS scores but also the gold standards methods such as VFSS to evaluate the swallow function recovery of patients. Ice stimulation has been demonstrated to promote the relaxation of CPA, which may effectively improve the treatment effect of catheter balloon dilation and accelerate the recovery of patients.

This study also showed no significant difference in VFSS scores between the two groups in the oral phase ($P > 0.05$) that might be related to the fact that the oral problems of the included patients were not prominent, and the retardation of the cricopharyngeal muscle mainly caused dysphagia. Moreover, this study still had some limitations. First, this was a single-blind trial with small sample size, and there was a lack of long-term efficacy follow-up. Second, our study used the VFSS and FOIS scores to clinically evaluate the swallowing function, which might be affected by subjective factors. We plan to evaluate swallowing process with more objective and quantitative indicators in future studies. Third, the adverse events, including mucosal edema, bleeding, and

pain, were assessed through visual evaluation and VAS scores.

In conclusion, catheter balloon dilatation combined with ice water compensatory swallowing training may effectively improve the swallowing function and reduce aspiration of patients with CPA after stroke, relieve patients' throat pain, and shorten the treatment time. The findings of our study may provide a novel strategy for the management of post-stroke CPA. In the future, we can further carry out the multicenter, large sample, long-term double-blind, randomized controlled research, to explore the relevant underlying mechanism, improve the training and treatment scheme, and provide a scientific and standardized reference basis for clinical treatment of poststroke CPA. Moreover, the evaluation systems should be optimized, and long-term treatment efficacy and recovery will be further explored in the future research.

Data Availability

The datasets used and analyzed in the current research would be available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xiangwei Li and Linna Jin contributed equally to this work.

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Retraction

Retracted: Clinical Analysis of 85 Cases of External Auditory Canal Cholesteatoma Surgery under Specialized Endoscopy

BioMed Research International

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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] Y. Guo, M. Qian, J. Li, J. Xu, H. Chen, and H. Zhang, "Clinical Analysis of 85 Cases of External Auditory Canal Cholesteatoma Surgery under Specialized Endoscopy," *BioMed Research International*, vol. 2022, Article ID 9190241, 9 pages, 2022.

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Research Article

Clinical Analysis of 85 Cases of External Auditory Canal Cholesteatoma Surgery under Specialized Endoscopy

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Objective. To investigate the clinical characteristics, surgical experience, and surgical outcomes of external auditory canal cholesteatoma (EACC) surgery under endoscopic otolaryngoscopy. *Methods.* A retrospective analysis of 85 EACC cases admitted to the Department of Otolaryngology, Renji Hospital, Shanghai Jiaotong University School of Medicine, from January 2016 to February 2021 was performed, followed by retrospective analysis of clinical data to explore the feasibility and clinical characteristics of all-oral endoscopic EACC surgery. A total of 85 EACC patients (90 ears) with a mean age of 49.93 ± 14.87 years were included in the study. According to Udayabhanu staging, 43 ears (47.78%) were stage I, 40 ears (44.44%) were stage II, and 7 ears (7.78%) were stage III. All patients underwent transendoscopic surgery. *Results.* 79 ears (87.78%) underwent endoscopic EACC resection alone (+external auditory canal tumor resection/tympanostomy tube insertion), 9 ears (10%) underwent endoscopic EACC resection+tympanostomy+tympanoplasty, 1 ear (1.11%) underwent endoscopic EACC resection +tympanoplasty, and 2 ears (2.22%) underwent EACC resection+otolaryngotomy+tympanoplasty+auditory chain reconstruction endoscopically. Of these, 7 ears (7.78%) underwent auricular cartilage-chondroplasty and 2 ears (2.22%) underwent auricular cartilage membrane repair. All patients were reviewed at 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year postoperatively. One patient with stage II external auditory atresia had a recurrence after 6 months and underwent endoscopic ear surgery (ESS) again. One patient with stage 2 atresia recurred after 1 year and again underwent endoscopic ear surgery. The rest of the patients recovered well after the surgery, and the grafts healed well. *Conclusion.* EACC surgery through the external ear canal under a dedicated endoscope is a safe, reliable, and effective method. Patients with stage I and II external auditory canal cholesteatoma surgery under endoscopy have a rapid postoperative recovery with significant hearing improvement, and stage IIIA patients can also achieve good results under strict evaluation of indications.

1. Introduction

External auditory canal cholesteatoma (EACC) is a cystic mass of skin debris and cholesterol crystals that obstructs the external auditory canal and is not a true tumor with osteoplastic properties. It is an uncommon, benign disease of unclear etiology and pathogenesis. EACC has been reported as a result of external ear canal trauma, chronic inflammation, narrowing of the ear canal, or spontaneous occurrence [1, 2]. Patients with EACC often complain of unilateral ear leakage and otalgia. Unilateral hearing impairment is rarely reported [3, 4]. Patients with EACC initially have limited lesions, mainly present in the external auditory canal, with no obvious symptoms, but when the lesions develop progressively, invading the tympanic membrane into the tympanic chamber and even more into the mastoid process, the facial nerve and extratemporal bone structures are destroyed, and facial nerve palsy and vagal fistulae will inevitably appear. And advanced infiltration of the skull base can cause meningitis or intracranial abscesses [5, 6].

The initial presentation of EACC relies on simple examinations such as frontoscopy and endoscopy, which do not reveal the full extent of the disease [7, 8]. High-resolution temporal bone CT can clearly show the lesion, such as whether it invades the facial nerve or the jugular venous bulb [9, 10]. Shin et al. classified EACC into four types based on the CT of the temporal bone and its clinical features: stage I: lesions limited to the external auditory canal; stage II: lesions invading the tympanic membrane and then protruding into the middle

ear; stage III: lesions not limited to the auditory canal and invading the mastoid process; stage IV: lesions not only invading the temporal bone but also involving its adjacent parts [11, 12] (Figure 1).

The principles of treatment for EACC are to completely remove the lesion, maintain normal structure and function, restore the normal epithelial migration ability of the external auditory canal, and maintain the integrity of the tympanic membrane and auditory chain as much as possible. The specific surgical approach should be determined by the extent of the lesion and the specific intraoperative situation. Shin's staging not only evaluates the preoperative site and extent of EACC invasion but also provides a basis for the operator to choose the appropriate surgical approach. Due to the physiological curvature of the external auditory canal or scar stenosis, some relatively hidden lesions (e.g., tympanic cavity and mastoid process) are not clearly identified during microscopic surgery, and there are certain blind spots in the field of view. In contrast, microscopic surgery, in order to remove the hidden lesions present in a wide range of lesions and to preserve important structures, is inevitably achieved at the cost of destroying more bony structures; however, this cost, although we now have many reconstruction methods to repair the relevant structures, is still fraught with difficulties, and the repair does not guarantee the integrity of the original anatomical structures [13, 14].

Based on this, this paper retrospectively analyzed 85 cases of EACC admitted to the Department of Otolaryngology, School of Otolaryngology, Shanghai Jiao Tong University, from January 2016 to February 2021, followed by a retrospective analysis of clinical data to investigate the feasibility and clinical characteristics of total oral endoscopic EACC surgery. A total of 85 EACC patients (90 ears) with a mean age of 49.93 ± 14.87 years were included in the study. According to Udayabhanu staging, 43 ears (47.78%) were stage I, 40 ears (44.44%) were stage II, and 7 ears (7.78%) were stage III. All patients underwent transendoscopic surgery, to explore the different stages of endoscopic otolaryngoscopy surgical approach and efficacy of EACC.

2. Materials and Methods

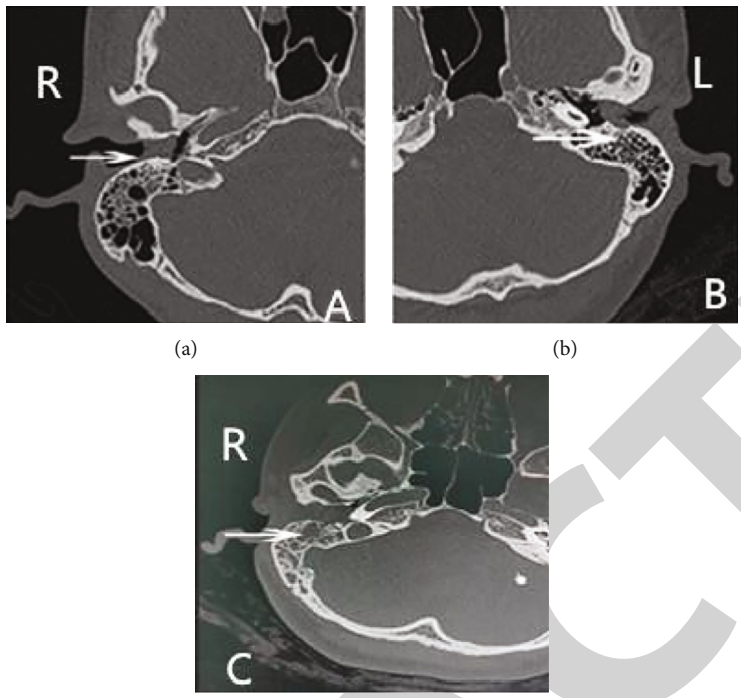
2.1. General Clinical Data. General data of cases: a total of 85 (90 ears) EACC cases were included in this study. There were 31 males and 54 females, aged 14-93 years, with age of 50 ± 15 years. The distribution was more concentrated in the two age groups of 14~33 years and 53~71 years. The disease course ranged from 1 week to 30 years, with an average of 31 ± 13 months. Among them, 80 had monaural disease and 5 had binaural disease. 52 ears were left and 38 ears were right. 83 ears (92%) were acquired primary and 7 ears (8%) were secondary. It was secondary to an external auditory canal mass in 2 ears, secondary to external auditory canal atresia in 1 ear, and secondary to radiotherapy for nasopharyngeal carcinoma in 4 ears. The chief complaints were ear stuffiness in 54 patients, earache in 48 patients, hearing loss in 55 patients, tinnitus in 12 patients, ear discharge in 15 patients, ear bleeding in 5 patients, ear itching in 6 patients, and mouth opening pain in 4 patients. None of the patients had vertigo or facial paralysis. 53 patients had experienced one or more external auditory canal irrigations in the outpatient clinic. Otoendoscopy showed granulation in the external auditory canal in 17 cases and a mass in the external auditory canal in 2 cases. All patients underwent middle ear and mastoid CT, and 29 patients (32 ears) underwent pure tone threshold audiometry before surgery. Hearing subjects were normal in 5 ears, conductive deafness in 10 ears, mixed deafness in 12 ears, and sensorineural deafness in 5 ears.

The same skilled otosurgeon performed all the procedures on the study subjects. The hospital medical ethics committee has approved this clinical study, and all patients and their families have given informed consent and signed the informed consent form.

2.1.1. Inclusion Criteria. (1) Medical history is consistent with the clinical presentation of external auditory cholesteatoma. (2) Age is 18-60 years. (3) There is no previous history of otitis media surgery. (4) On examination, visual or endoscopic examination showed white, gray, or brown soft tissue masses and granules in the external auditory canal. (5) On ancillary examination, high-resolution CT of the temporal bone showed soft tissue masses in the external auditory canal with or without destruction of the external auditory canal wall and/or mastoid, destruction of the tympanic chamber, and destruction of the bone wall mainly in the external auditory canal. (6) On audiometry, pure tone audiometry showed conductive deafness or mixed deafness. (7) Pathological diagnosis is external auditory canal cholesteatoma.

2.1.2. Exclusion Criteria. Exclusion criteria are as follows: (1) significant narrowing and malformation of the external auditory canal; (2) benign and malignant tumors and tuberculosis of the external auditory canal; (3) mental disorders, cognitive and consciousness disorders; (4) serious underlying diseases with poor control (e.g., diabetes, coagulation disorders, and malignant tumors); (5) pregnant or preparing for pregnancy, lactating; and (6) unable to cooperate with the evaluation.

2.2. Research Methods. All patients underwent otoendoscopy, CT of the middle ear and mastoid, and otoendoscopic surgical treatment. According to the extent of lesion invasion in EACC, Udayabhanu staging was adopted [15]. Stage I: the lesion is confined to the external auditory canal without bone destruction; stage II: there is bone destruction with or without middle ear involvement, but does not involve adjacent structures (including temporomandibular joint, mastoid process, jugular bulb, facial nerve bone canal, and dura mater); stage IIIA: those with bone destruction and involvement of adjacent structures, but no complications; stage IIIB: those with other complications at the same time. In this study, 43 ears were in stage I, 40 ears were in stage II, and 7 ears were in stage IIIA according to the Udayabhanu stage. There were 31 ears with otitis externa, 4 ears with secretory otitis media, 10 ears with tympanic membrane



(a) (b) (c)

Figure 1: CT images of the Shin stages of EACC. Note: (a) stage I: soft tissue shadow in the right external auditory canal, the lesion is confined to the external auditory canal without bone destruction; (b) stage II: soft tissue shadow in the left external auditory canal invades the tympanic membrane into the middle ear cavity and destroys the bone of the external auditory canal wall; (c) stage III: soft tissue shadow in the right external auditory canal, not only destroys the bone of the external auditory canal but further invades the small bone of the middle ear cavity and involves the mastoid.

perforation, and 1 ear with external auditory canal atresia; see Table 1.

2.3. Treatments. All patients underwent ESS under local or general anesthesia. Among them, 64 patients (67 ears) underwent local anesthesia surgery (39 ears in stage I, 24 ears in stage II, and 4 ears in stage IIIA) and 21 patients (23 ears) underwent general anesthesia surgery (4 ears in stage I, 16 ears in stage II, and 3 ears in stage IIIA). Intraoperative diagnosis combined with CT and intraoperative findings showed destruction of the bone wall of the external auditory canal in 47 ears (40 ears in stage II and 7 ears in stage IIIA). Among them, 31 had destruction of the posterior wall of the ear, 28 had destruction of the inferior wall of the ear, 26 had destruction of the anterior wall of the ear, and 19 had destruction of the parietal wall of the ear. There were 19 ears with annular destruction of the bone wall of the external auditory canal, 29 ears with thin invagination of the tympanic membrane, 10 ears with perforation of the tympanic membrane, and 4 ears with destruction of the ossicular chain. It involved the horizontal and vertical segments of the facial nerve canal in 1 ear, the temporomandibular joint in 5 ears, and the mastoid process in 1 ear. 74 ears underwent exclusively otoendoscopic resection of EACC, 2 ears underwent otoendoscopic resection of EACC+resection of external auditory canal mass, 3 ears underwent otoendoscopic resection of EACC+tympanoplasty, 9 ears underwent otoendoscopic resection of EACC+tympanoplasty+tympanoplasty, 1 ear underwent otoendoscopic resection of EACC+tympanoplasty, and 2 ears underwent otoendoscopic resection of EACC+atticotomy+tympanoplasty+ossicular chain reconstruction (PORP 1 ear, autologous ossicles 1 ear).

Among them, 7 ears were repaired with tragus cartilage-perichondrium and 2 ears were repaired with tragus perichondrium.

2.4. Procedures

(1) Local anesthesia and preoperative preparation: patients with local block anesthesia of the external auditory canal combined with external auditory canal mass underwent tumor resection

(2) Exploration and resection of cholesteatoma: for impacted significant cholesteatoma, the volume was first reduced from the center of the lesion and then the dissection was performed between the cholesteatoma capsule and the external auditory canal skin until the pocket was completely removed

(3) Thorough cleaning of the epithelium: sequential cleaning of the epithelium at the "pit" of bone destruction, the epithelium around the tympanic ring, and the epithelium and granulation on the surface of the tympanic membrane. The tympanic membrane was checked for integrity. There was pinpoint perforation or small perforation of the

Table 1: Clinical data and result analysis of 85 cases (90 ears) of EACC.

—	—	Number of samples	Percentage
Patients	Cases	85	—
—	Ears	90	—
Sex	—	—	—
—	Male	31	36%
—	Female	54	64%
Age	—	—	—
—	Minimum	14	—
—	Maximum	93	—
Sides	—	—	—
—	Left	52 (ears)	58%
—	Right	38 (ears)	42%
Monaural	—	—	—
Binaural	Monaural	80 (ears)	94%
—	Binaural	5 (ears)	6%
Acquired primary/secondary	—	—	—
—	Primary	83 (ears)	92%
—	Secondary	7 (ears)	8%
Secondary disease	—	—	—
—	External auditory canal tumor	2 (ears)	2%
—	Atresia of external auditory canal	1 (ear)	1%
—	After radiotherapy for nasopharyngeal carcinoma	4 (ears)	4%
Clinical features	—	—	—
—	Ear stuffiness	54	64%
—	Ear pain	48	567%
—	Hearing loss	55	65%
—	Tinnitus	12	14%
—	Ear discharge	15	18%
—	Ear bleeding	5	6%
—	Ear itching	6	7%
—	Ear mouth opening pain	4	5%
Hearing condition	—	—	—
—	Normal	5 (ears)	6%
—	Conductive deafness	10 (ears)	11%
—	Mixed deafness	12 (ears)	13%
—	Sensorineural hearing loss	5 (ears)	6%
Udayabhanu stage			
—	I	43 (ears)	48%
—	II	40 (ears)	44%
—	IIIA	7 (ears)	8%
—	IIIB	0	0
Combined with other diseases of middle ear and external ear	—	—	—
—	Otitis externa	31 (ears)	34%
—	Secretory otitis media	4 (ears)	4%
—	Tympanic membrane perforation	10 (ears)	11%
—	Atresia of external auditory canal	1 (ear)	1%
Anesthesia	—	—	—

Table 1: Continued.

—	—	Number of samples	Percentage
—	Local	64 (67 ears)	75% (74%)
—	General	21 (23 ears)	25% (26%)
Ossicular chain reconstruction	—	—	—
—	No	88 (ears)	98%
—	PORP	1 (ear)	1%
—	TOPR	0 (ear)	0
—	Autogenous ossicles	1 (ear)	1%

tympanic membrane with exudation, and preoperative CT showed no significant abnormality of the tympanum, which was not repaired at the same time. Tympanic exploration was performed while moderate or large perforation of the tympanic membrane or preoperative CT revealed tympanic soft tissue shadows

(4) Exploration of the tympanum: an external auditory canal skin tympanic membrane flap was done and the exploration tympanum was lifted. If there was cholesteatoma epithelium in the tympanic cavity, incision and exploration of the lateral wall of the attic were performed. If the ossicular chain is interrupted/destroyed, the corresponding reconstruction is performed. For patients with attic incision, the tragus cartilage-perichondrium was used to repair the residual tympanic membrane, while for patients with tympanic membrane perforation, the tragus perichondrium was used to repair the residual tympanic membrane

(5) Reconstruction of the ossicular chain: there was ossicular chain destruction for corresponding artificial ossicular chain reconstruction

3. Results

All patients in this study had no statistical differences in general data indicators such as age of onset, side, and gender and were balanced and comparable, and the clinical characteristics are shown in Table 1. All patients were pathologically confirmed to have EACC after surgery. Referring to the typology of foreign scholars Naim [3, 8] and domestic scholars Huang Hongming [16], a total of 85 patients with EACC (90 ears) were included in this study, with a mean age 49.93 ± 14.87 years. According to Udayabhanu staging, 43 ears (47.78%) were stage I, 40 ears (44.44%) were stage II, and 7 ears (7.78%) were stage III. All patients were discharged the day after surgery and were reviewed regularly at 1 week, 2 weeks, 1 month, 3 months, and 6 months postoperatively. All patients were followed up regularly for 12 to 68 months. One patient with EACC stage II and external auditory atresia recurred 6 months after surgery and underwent endoscopic tympanoplasty+tympanoplasty+auditory chain reconstruction again. Eight months after the second surgery, the localized lesion in the external auditory canal recurred again and an endoscopic removal of EACC was performed, which has been recurrence-free for 12 months. One patient with stage II disease recurred 12 months after surgery and again underwent endoscopic resection of the EACC and has been recurrence-free for 9 months. The rest of the patients have been followed up with no recurrence.

4. Discussion

4.1. Endoscopic Options for Different Stages of EACC. Udayabhanu proposed the following staging criteria for EACC: stage I lesions are limited to the external auditory canal without bone destruction, stage II lesions are those with bone destruction with or without middle ear involvement but without the involvement of adjacent structures (including the temporomandibular joint, mastoid process, jugular venous bulb, facial nerve canal, and dura mater), stage IIIA lesions are those with bone destruction and involvement of adjacent structures without complications, and stage IIIB lesions are those with a combination of other complications [17]. Unlike the classical Holt staging, which includes the area of invasion of the middle and upper tympanic chambers, which are the areas of predominance for endoscopic surgery, stage III of Holt staging is relatively broad. Compared with Holt's staging criteria, stage II patients have a larger scope (e.g., superior tympanic chamber), and for the current endoscopic management of superior tympanic cholesteatoma [18], stage II patients of Udayabhanu can be completely resolved, and some stage IIIA patients are also feasible for endoscopic surgery after comprehensive evaluation, but strict indications need to be mastered, and timely replacement of the posterior auricular approach with microscopic mastoid surgery should be prepared. There is preparation of the posterior auricular access microscopic mastoid surgery. In the three stage IIIA patients in this study, one case did not invade the temporomandibular joint, so the operation was performed in the same way as in stage II patient; two patients with invasion of the mastoid cavity required mastoid opening, and endoscopic mastoid opening was chosen because the mastoid in these two cases was of the plate-barrier type, and the mastoid air space only had a small cavity, so it was not necessary to remove a large amount of bone in a small space, and the patient was prepared to change the microscope at any time. In patients with

good mastoid pneumatization and lesions involving most of the mastoid airspace or even the mastoid tip, endoscopic opening of the mastoid is not recommended. In the current literature, it is recommended to perform external auditory canal formation after removal of cholesteatoma in adults with EACC [19], because the external auditory canal of patients with EACC is mostly in the shape of a "flask" with a large inner and small outer surface after removal of cholesteatoma, which may cause postoperative narrowing and recurrence of the external auditory canal. In the present study, there was no recurrence in any of the cases, and only one case of membranous atresia, which was recanalized after repeated cautery with silver nitrate.

4.2. Case Characteristics. The clinical incidence of EACC is low, and the first diagnosis in the outpatient clinic is less confirmed. In this study, 53 patients (62%) experienced at least one outpatient irrigation treatment with impacted cerumen as the first diagnosis, which may be related to cerumen accumulation on the keratinocyte surface in some patients with cholesteatoma. The maximum number of rinses was 5, which may be related to insufficient experience in diagnosis and treatment in lower community hospitals. Given the different incidence ratio between men and women, reports vary in the literature. There were 31 males (36%) and 54 females (64%) in this study. Both the age of onset and the course of the disease present a polarization. There were more adolescent patients and elderly patients and more patients with disease duration of less than 1 month and more than 10 years. It may be due to the narrower external auditory canal in younger patients and decreased epithelial migration and poor hygiene in older patients. 45 (53%) patients had an onset time of no more than 1 month and were mostly accompanied by ear stuffy ear pain, which was associated with acute infection or periostitis of the external auditory canal caused after irrigation stimulation. Nine (11%) patients had an onset time of more than 10 years, which was considered to be related to the fact that the patients did not return after anti-infective treatment in the acute phase and their willingness to seek treatment decreased. Acquired primary in 83 ears (92%), secondary in 7 ears (8%), secondary to external auditory canal mass in 2 ears, secondary to external auditory canal atresia in 1 ear, and secondary to nasopharyngeal carcinoma after radiotherapy in 4 ears. The relationship between a history of radiotherapy for NPC and the incidence of EACC has rarely been mentioned in previous literature. In fact, we found that EACC patients with a history of radiotherapy for nasopharyngeal carcinoma were mostly associated with secretory otitis media, which was associated with radiation damage to the cilia of the middle ear mucosal epithelium and decreased self-cleaning ability of the external auditory canal skin; see Figure 2.

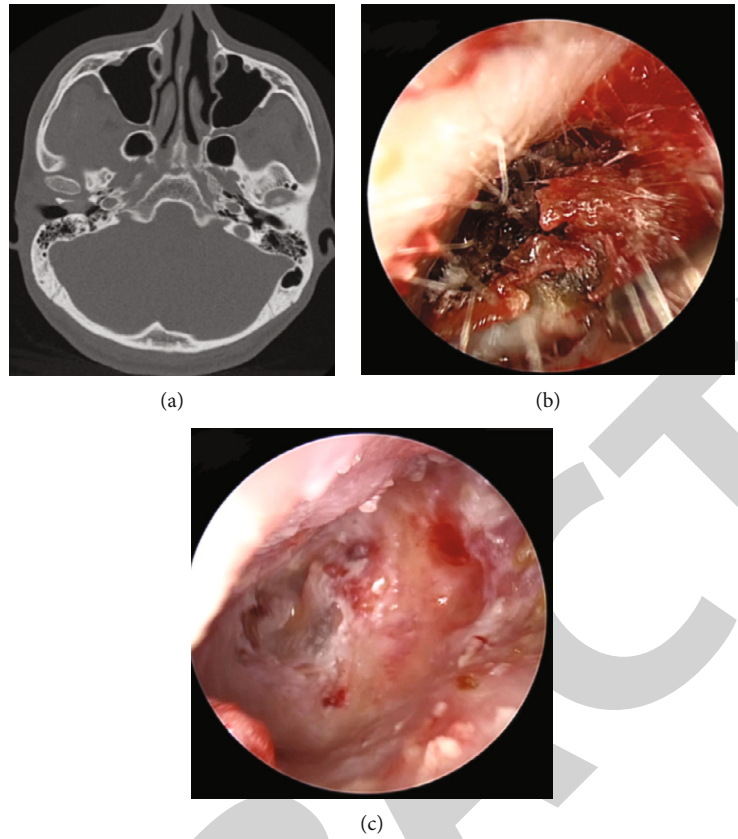
4.3. Extent of Disease and Direction of Invasion. CT of EACC showed soft tissue shadows in the external auditory canal with/without bone destruction, with/without middle ear involvement. It has been reported in the literature that its growth direction shows an "inward roll" property characterized by outside-in, which is distinguished from inside-out of middle ear cholesteatoma. EACC may involve the attic and tympanic sinuses inward or the mastoid posteriorly. In this study, the posterior wall was the most destroyed in statistics, which is more consistent with literature reports.

There are two main directions of external auditory canal cholesteatoma invasion. The tympanic membrane is compressed inward, resulting in thin, invaginated, loss of elasticity, and even perforation of the tympanic membrane. If some patients have repeated irrigation or coinfection, it can also cause acute inflammation or even perforation of the tympanic membrane. In this study, 10 ears (12%) had perforation. The cholesteatoma epithelium enters the attic and tympanic sinuses through perforation and destroys structures such as the ossicular chain, which can involve the horizontal segment of the facial nerve canal. The other is the mastoid posteriorly, involving the vertical segment of facial nerve canal; see Figure 3.

For middle ear cholesteatoma, the facial nerve is most commonly involved in the horizontal and conical segments. For EACC, the most commonly affected facial nerve is the vertical segment, as it can invade the mastoid process. Four ears had secretory otitis media in this study. After EACC destroys the external auditory canal, the wall will block the mastoid air cells, poor drainage causes mastoid effusion, and nasopharyngeal carcinoma radiotherapy complicated by secretory otitis media is much common. Endoscopic surgery does not involve bone grinding in the mastoid region and cannot expose the entire course of the facial nerve canal, so endoscopic surgery should pay attention to avoid injury in patients with EACC involving the mastoid process, especially those with bone destruction in the mastoid segment of the facial nerve canal suggested by preoperative CT.

4.4. Selection of Surgical Plan and Skills

4.4.1. Selection of Anesthesia. 64 patients (67 ears: 39 ears in stage I, 24 ears in stage II, and 4 ears in stage IIIA) were operated on with local anesthesia. 21 patients (23 ears: 4 ears in stage I, 16 ears in stage II, and 3 ears in stage IIIA) were operated on with general anesthesia. In this study, we found that stage I and II can be completely operated with local anesthesia, while some stage II and IIIA patients involving attic chiseling were recommended for general anesthesia surgery. For patients with external auditory canal cholesteatoma, the effect of local block anesthesia of the external auditory canal was inferior to that of tympanic membrane repair under local anesthesia because they have experienced repeated ear canal irrigation, combined otitis externa, and external auditory canal periostitis in the outpatient clinic. Most of the patients with tympanic membrane repair under local anesthesia had no pain. In external auditory canal cholesteatoma surgery under local anesthesia, about 20% of patients complain of pain during surgery, which was mostly tolerable. Only one 91-year-old female patient complained of intolerable ear pain. For such patients, in addition to local block anesthesia of the external auditory canal, local block anesthesia of the posterior auricular sulcus and temporomandibular joint fossa can be added, and attention should be paid to the direction and depth of needle insertion to



(a) (b) (c)

Figure 2: Excision of external auditory canal cholesteatoma in patients with EACC stage II. Note: (a) CT in patients with EACC stage II revealed destruction of the bone wall of the external auditory canal and no involvement of the middle ear; (b) cerumen and white cholesteatoma epithelium in the external auditory canal were observed under an otoendoscope; (c) ear endoscopy after external auditory canal cholesteatoma removal surgery in patients shows intact and thin tympanic membrane and enlargement of the bone wall of the external auditory canal.

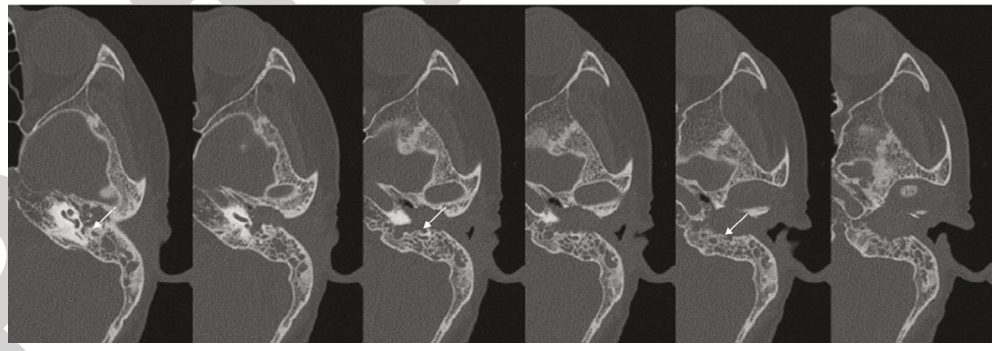


Figure 3: CT of EACC stage III patients (white arrow: the vertical segment of the facial nerve is destroyed and exposed).

implement injection to avoid causing transient facial paralysis [20]. During the operation, the patient's mood can be soothed by communicating with the patient, encouraging positively, and playing music. In this study, 4 juvenile patients (3 under general anesthesia and 1 under local anesthesia) were enrolled. General anesthesia is recommended for minor patients to avoid emotional stress, pain, and inability to cooperate to complete the operation or psychological shadow. For stage IIIA and IIIB patients, general anesthesia is recommended for surgery, due to the possibility of conversion to microscopic open surgery during surgery.

4.4.2. Surgical Options. In stage I patients with EACC, otoendoscopic resection of external auditory canal cholesteatoma was performed, and those with external auditory canal tumors also underwent resection of external auditory canal tumors. Patients with EACC stage II and secretory otitis media underwent otoendoscopic resection of external

auditory canal cholesteatoma+tympanic membrane. There are not many reports on this in the previous literature, considering that the patients with personal history of nasopharyngeal carcinoma in this study were caused by decreased epithelial self-cleaning ability due to radiotherapy. For patients with EACC stage II~III, otoendoscopic resection of external auditory canal cholesteatoma+tympanic exploration+tympanoplasty (+ossicular chain reconstruction) was performed.

In EACC stage III, even if mastoid was involved, most were cholesteatoma invasion and obstructive inflammation. Mastoid inflammation can improve spontaneously after thorough epithelial cleaning and unobstructed drainage. Not many cases of this have been reported. There are a large number of domestic reports on EACC [21], especially stage III. However, the number of reported cases of stage III ESS is less [22].

4.4.3. Recurrence. There were a total of 2 patients with recurrence in this study.

One of the patients with recurrence had atresia of the external auditory canal, and the first operation was performed under otoendoscope to chisel the atretic bone, clean the external auditory canal and tympanic cholesteatoma epithelium, and perform tympanoplasty. The patient's own ear canal was narrow and recurred again after surgery; thus, epithelial debridement under local anesthesia was performed. The principle of surgical treatment of EACC is complete removal of the lesion, followed by reconstruction of the external auditory canal structure to restore epithelial self-cleaning ability. Patients with recurrent cholesteatoma in the literature are mostly associated with external auditory canal stenosis or atresia, and microscopic external auditory meatoplasty is recommended. If some narrow lesions of the external auditory canal are present for more than 1/2 week, external auditory canal skin grafting is considered [23]. Therefore, ESS has limitations for the treatment of patients with external auditory canal stenosis.

4.5. Advantages of Endoscopic EACC Surgery. For stage I and II EACC patients with invasion of the external auditory canal bone and tympanic membrane, endoscopic surgery is the best choice, and with the increasing use of endoscopy in middle ear surgery, it has the advantages of aesthetics, faster postoperative recovery, smaller visual field blindness, and more direct surgical access compared to traditional microsurgery with posterior or internal ear incisions [24]. In the present study, six patients with invasion of the tympanic cavity had no significant exudation after removal of the ear canal filling 14 days after surgery, and the tympanic membrane and external auditory canal skin grew well 1 month after surgery. For patients with stage IIIA invasion of the mastoid, it takes about 3 months for the dry ear to open after microscopic mastoid root treatment with posterior ear access, and there is no improvement or decrease in hearing [25]. In this study, there was no significant exudation after removal of the ear canal filling at 14 days in stage IIIA patients, and the tympanic membrane and external ear canal skin grew well at 1 month after surgery, and the average postoperative air-conduction hearing improved and the air-bone conduction difference decreased significantly.

In conclusion, patients with stage I and II external auditory canal cholesteatoma recovered quickly after endoscopic surgery and had significantly improved hearing, and the air-bone conduction difference was significantly reduced or disappeared, while stage IIIA patients could also achieve good results under strict evaluation of indications, but should be prepared to change microscopic surgery at any time. However, the sample size of this study was small, a more comprehensive understanding of the use of endoscopy in patients with stage III external auditory canal cholesteatoma is lacking, and a larger sample is needed to evaluate the effectiveness of staged treatment.

5. Conclusion

Although it is a nongenuine tumor, it is biologically aggressive, easily destroying bone and eroding adjacent structures. The preoperative imaging (temporal bone resolution CT) is an important clinical guide for otologists to assess the extent of lesion destruction, diagnose EACC, guide clinical staging, and select the appropriate surgical approach. Patients with stage I and II EACC can be completely managed endoscopically, and most patients can even tolerate local anesthesia, and patients with disrupted auditory chain can undergo simultaneous or two-stage reconstruction. Some stage IIIA EACC patients can be operated endoscopically and require simultaneous tympanoplasty+tympanoplasty (+auditory chain reconstruction). Some stage IIIA and IIIB cases require microscopic management or combined surgery with laparoscopy. ESS has limitations in cases with external auditory canal stenosis, and microscopic external auditory meatoplasty is recommended.

Data Availability

The figures and tables used to support the findings of this study are included in the article.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Retraction

Retracted: Efficacy of Balloon Guide Catheter-Assisted Thrombus Repair in Stroke Treatment: A Retrospective Survey in China

BioMed Research International

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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] Q. Li, T. Zhou, Y. He et al., "Efficacy of Balloon Guide Catheter-Assisted Thrombus Repair in Stroke Treatment: A Retrospective Survey in China," *BioMed Research International*, vol. 2022, Article ID 4278048, 7 pages, 2022.

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Research Article

Efficacy of Balloon Guide Catheter-Assisted Thrombus Repair in Stroke Treatment: A Retrospective Survey in China

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Background. The first-pass (FP) effect, defined by successful cerebral reperfusion from a single pass of an endovascular stentriever, was associated with shorter procedural times and possible improved outcomes in patients with ischemic stroke secondary to large vessel occlusion. The adjunctive use of balloon guide catheter (BGC) may increase the rates of the first-pass effect. In this retrospective study we examined the impact of BGC on the first-pass effect in acute stroke patients. *Methods*. We included patients with acute ischemic stroke with large vessel occlusion treated by endovascular thrombectomy from 2018 to 2019. We categorized the cases into BGC and non-BGC groups. Differences in time metrics and outcomes were compared. *Result*. One hundred and thirty-two patients were included, and sixty-two were in BGC group (47.0%). The median procedural time was shorter (83.0 minutes vs 120.0 minutes, $P = 0.000$), and FP rate was higher in BGC group (58.1% vs 32.9%, $P = 0.004$) compared with non-BGC group. Proportion of modified Thrombolysis in Cerebral Infarction (mMTICI) 3 was higher (66.1% vs 37.1%, $P = 0.001$), and modified Rankin Scale (mRS) 0 to 2 was higher (59.7% vs 41.4%, $P = 0.036$) in BGC group compared with non-BGC group. In addition, BGC was associated with successful reperfusion odds ratio, 0.383; 95% confidence interval: 0.174-0.847; $P = 0.018$). The FP rate of BGC in the distal ICA was higher than that in the proximal ICA (87.5% vs 39.5%, $P = 0.000$), and the good clinical outcome rate at 90 days in the distal ICA was also higher than that in the proximal ICA (91.7% vs 39.5%, $P = 0.000$). *Conclusion*. We showed that BGC shortened the procedural time and increased the rate of the successful FP. We recommend that BGC could be considered the preferred technique for endovascular intervention in stroke.

1. Introduction

Stroke is the leading cause of death among the elderly, with 2.5 million new cases occurring in China each year [1]. Acute ischemic stroke is the main pathological type of stroke caused by cerebral ischemia, leading to the dysfunction and degeneration of cerebrovascular components. At present, some effective treatments for acute ischemic stroke (including thrombolysis, endovascular revascularization, acute ischemic stroke reperfusion, etc.) have significantly improved the survival rate of acute ischemic stroke, but the reduction in mortality has also increased the number of survivors with complications after stroke [2].

Endovascular treatment of large vessel occlusion is superior to intravenous thrombolysis alone in patients with acute ischemic stroke secondary to large vessel occlusion within 24 hours ictal onset [3–9]. Endovascular treatment encompasses a range of techniques including lone stentriever with balloon guide catheter (BGC), contact aspiration, and combined stentriever with contact aspiration. BGC applied endovascular treatment for acute ischemic stroke can block blood flow during thrombus removal to prevent distal

embolization [10]. A recent meta-analysis of studies showed that the use of BGC improved the grade of reperfusion and clinical outcomes in patients who had a stent retriever as their preferred treatment modality [11]. Endovascular thrombectomy is a new treatment for cerebral infarction in recent years, including stent thrombectomy and thrombectomy. In this procedure, a small catheter is entered through an artery (usually the femoral artery) and removed along with the clot at the site of the brain stem. Thrombectomy has shown benefit and safety in patients with less severe brain damage due to a smaller area of brain cell death (ischemic core) [12]. Hesse et al. [13] showed the improved reperfusion in combined stent retriever thrombectomy with aspiration compared with either stent thrombectomy or contact aspiration alone. This led to a preference in some endovascular centers for clot retrieval by the placement of stentriever within the target thrombus in addition to aspiration by a distal access catheter [14]. However, the results from Aspiration versus Stent Retriever study (ASTER) suggested that the stent retriever had a higher first-pass (FP) rate compared with aspiration technique (31.3% vs 26.3%) [15]. An alternative would be the deployment of BGC together with stentrieval which would involve proximal blood flow temporary blocking technique during mechanical thrombectomy [16–18]. FP rate of BGC in endovascular treatment was 63% [19], in addition to shorter procedural time [18]. Although the results of BGC were investigated in the Western stroke population, it was never reported in Chinese patients, leading to uncertainty of efficacy in this population.

In this study, we performed a retrospective study to investigate the effectiveness of BGC-assisted clot retrieval in Chinese stroke patients.

2. Materials and Methods

2.1. Study Setting. A total of 132 patients with anterior circulation ischemic stroke within 24 hours of stroke ictal onset were retrospectively screened to be included in our study. All patients were admitted to either Henan Provincial People's Hospital or Nanyang Central Hospital or Zhengzhou Central Hospital Affiliated to Zhengzhou University from January 2018 to November 2019. All patients signed the informed consent. Inclusion criteria for endovascular therapy (EV) were as follows: 18-85 years old; National Institutes of Health Stroke Scale (NIHSS) ≥ 6; brain CT hypo intensity $< 1/3$ of the infarcted area; modified Rankin Scale (mRS) ≤ 2; occlusion of intracranial internal carotid artery and/or middle cerebral artery M1 segment. Exclusion criteria were as follows: intracranial hemorrhage identified by CT or MR; life expectancy less than 3 months; pregnancy; or contrast agent allergy. The decision to allocate to BGC vs no-BGC was at the physicians' discretion. In addition, those who met the criterion of intravenous thrombolysis were treated by recombinant tissue plasminogen activator (rt-PA) followed by EV.

2.2. Description of EV Procedure

2.2.1. BGC Procedure. In this group, 64 patients underwent revascularization treatment using BGC proximal blood flow control technique combined with stentriever and aspiration. According to the patients' level of consciousness and degree of cooperation, local anesthesia or general anesthesia was selected. Seldinger technique was used for puncture through the right femoral artery [20]. A short vascular access sheath (8F) was placed. 8F BGC was placed in the proximal segment of the internal carotid artery (ICA) or the distal segment of the ICA, and a 5F Navien catheter (Medtronic Corporation, 710 Medtronic Pkwy NE, Minneapolis, MN 55432, USA) was placed at the C1 level of the ICA. Aided by a 0.36 mm (0.014 inches) microguidewire, the intracranial segment of ICA or the horizontal segment occlusion of the middle cerebral artery (MCA) was accessed with a microcatheter to visualize the distal and proximal ends of the embolus. After the stentriever was placed within the embolus, 5F Navien was delivered to the proximal end of the M1 segment of the MCA or distal ICA. After the stentriever was placed within the thrombus for approximately 5 min, the BGC was inflated to arrest blood flow. Irrigation of the guide catheter by isotonic saline was stopped. Double negative suction pressure was applied to the BGC and the Navien catheter, followed by stentrieval. Angiography was performed to assess angiographic outcomes.

2.2.2. Non-BGC Procedure. In the non-BGC group ($n = 70$), the 8F balloon guiding catheter was replaced by an 8F MPA1 guiding catheter (Cordis Corporation, 14201 NW 60th Ave, Hialeah, FL 33014, USA), and the remaining endovascular techniques were the same as the BGC group.

After recanalization by the above methods, balloon angioplasty and stent implantation were performed for patients with severe stenosis or occlusion of ICA or the horizontal segment of MCA [21]. Postoperative treatment included oral aspirin 100 mg daily and clopidogrel 75 mg daily at the physicians' discretion.

2.3. Evaluation Method. Modified Thrombolysis in cerebral infarction scale (mMTICI) was used to evaluate reperfusion. MTICI grade 0 to 2a indicated failed reperfusion, while MTICI grade 2b or 3 indicated successful reperfusion. NIHSS was used to evaluate neurological function, with scores ranging from 0 to 42. The modified Rankin Score (mRS) was used to evaluate postoperative 90-day clinical outcome. mRS score ≤ 2 indicated a good outcome, while mRS score ≥ 3 indicated a poor outcome [17]. Brain CT examination, 24 hours after the procedure, was used to identify postprocedure intracerebral hemorrhage. According to the European Cooperative Acute Stroke Study (ECASS) II criteria, intracerebral hemorrhage would be classified as nonsymptomatic or symptomatic intracerebral hemorrhage [22].

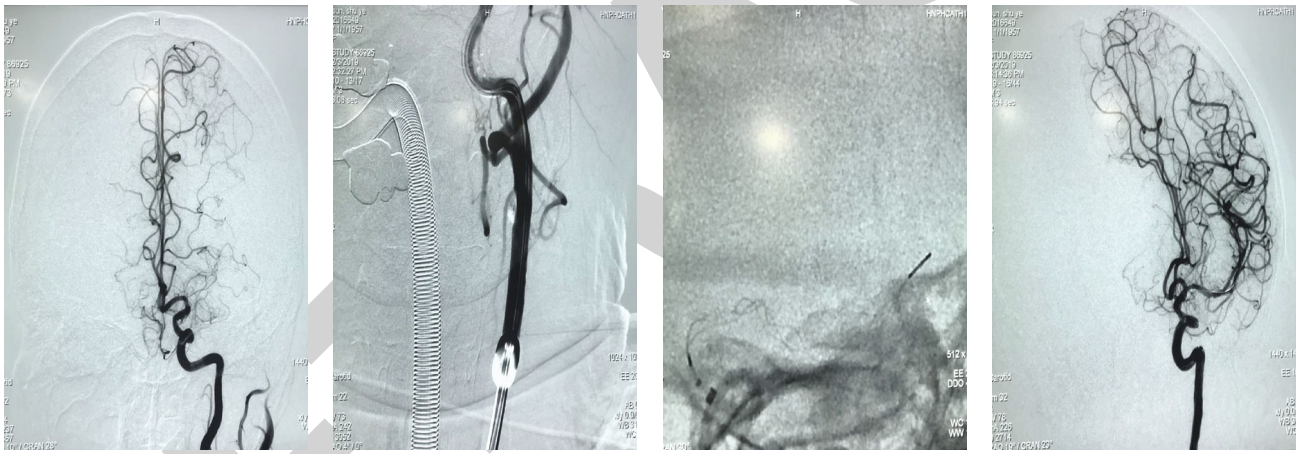
2.4. Follow-Up Method. Outpatient follow up was conducted 90 days after EV, and patients who could not attend the clinic were followed up by telephone interviews.

2.5. Statistical Analysis. SPSS 21.0 was used for statistical processing. Measurement data were expressed as median and interquartile range (IQR), and t-test was used for comparison between groups. Classification variables were described by frequency or percentage, and nonparametric

Table 1: Baseline characteristics.

	Non-BGC group ($n = 70$)	BGC group ($n = 62$)	Total ($n = 132$)	t/F/Z	P value
Age, M(IQR), year	65 (55.6, 72.3)	64 (54.8,70.0)	64 (55.3, 70.8)	0.997	0.321
Gender/male, n (%)	39 (55.7)	38 (61.3)	77 (58.3)	0.421	0.597
Hypertension, n (%)	38 (54.3)	33 (53.2)	71 (53.8)	0.015	1.000
Diabetes, n (%)	19 (27.1)	17 (27.4)	36 (27.3)	0.001	1.000
Hyperlipidemia, n (%)	11 (15.7)	9 (14.5)	20 (15.2)	0.037	1.000
Atrial fibrillation, n (%)	9 (12.9)	9 (14.5)	18 (13.6)	0.077	0.805
NIHSS on admission, M (IQR)	16.0 (11.8, 18.0)	15.5 (11.0, 18.0)	16.0 (11.0, 18.0)	0.408	0.684
Time to ED, M (IQR), (min)	486.0 (297.0, 724.5)	480.0 (284.3, 724.5)	480.0 (288.0, 720.0)	0.176	0.861
ASPECT, n (%)					
<7	9 (12.9)	12 (19.4)	21 (15.9)	1.038	0.347
≥7	61 (87.1)	50 (80.6)	111 (84.1)		
Occlusion sites, n (%)					
ICA + M1	42 (60.0)	36 (58.1)	78 (59.1)	0.051	0.860
M1	28 (40.0)	26 (41.9)	54 (40.9)		
Intravenous tPA, n (%)	12 (17.1)	16 (25.8)	28 (21.2)	1.477	0.287

ED: emergency department; t: t test, F: fisher test; Z: ranksum test; BGC: balloon guided catheter; NIHSS: national institutes of health stroke scale; ASPECT: alberta stroke program early CT score.



(a) (b) (c) (d)

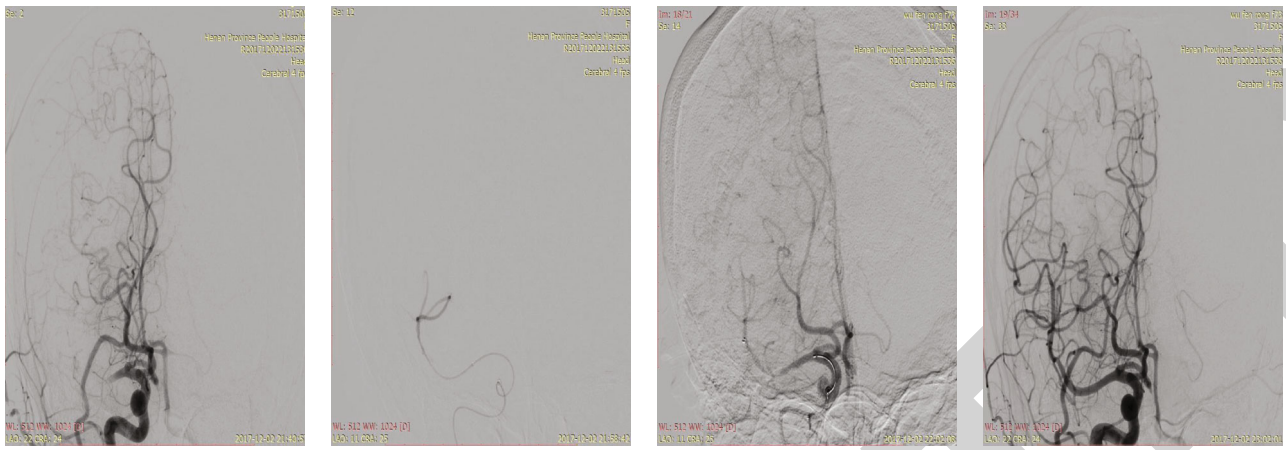
Figure 1: Digital subtraction angiography (DSA) of a 67-year-old woman with middle cerebral artery M1 segment occlusion undergoing endovascular therapy using a balloon guide catheter (BGC). (a) Left middle cerebral artery occlusion on DSA. (b) BGC balloon being inflated to control the blood flow temporarily. (c) The stentriever of Trevo is released at the occluded segment, and Navien is placed at the proximal of the occluded segment. (d) Modified Thrombolysis in Cerebral Infarction (mMTICI) 3 after withdrawing the stentriever.

test was used. The multivariate logistic regression model was performed to investigate the association between independent variables, and outcomes. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline Characteristics. One hundred and thirty-two patients were included in the study, 62 patients in the BGC group and 70 patients in the non-BGC group. The median age was 64 years, and 77 of the patients (58.3%) were men. The baseline characteristics for age, male gender, hypertension, diabetes, hyperlipidemia, atrial fibrillation, NIHSS score, time to ED, ASPECT, intravenous rt-PA, and arterial occlusion sites in the BGC and non-BGC groups were not significantly different between the groups (Table 1, $P > 0.05$). Intravenous rt-PA was used in 25.8% (16 of 62) and 17.1% (12 of 70) of patients in the BGC and non-BGC groups, respectively ($P = 0.287$). Two examples of thrombectomies performed with BGC and non-BGC were presented in Figures 1 and 2.

3.2. Procedural Outcomes. The median procedural time was significantly shorter in the BGC group than in the non-BGC group (83.0 minutes vs 120.0 minutes, $P = 0.000$). The FP rate with the BGC was significantly higher than that



(a) (b) (c) (d)

Figure 2: Digital subtraction angiography (DSA) of a 70-year-old man with middle cerebral artery M1 segment occlusion illustrates endovascular therapy using the MPA1 Guiding Catheter. (a) Right middle cerebral artery occlusion on DSA. (b) Angiograms of the distal vessel of occlusion segment. (c) The stentriever is released at the occluded segment, and Navien is placed at the proximal of the occluded segment. (d) Modified Thrombolysis in Cerebral Infarction (mMTICI) 3 after withdrawing the stentriever.

Table 2: Procedural outcomes.

	Non-BGC group ($n = 70$)	BGC group ($n = 62$)	Total ($n = 132$)	t/F/Z	P value
Procedure time, M (IQR), (min)	120.0 (93.8, 165.0)	83.0 (50.8, 128.3)	113.0 (72.0, 149.5)	4.612	0.000**
Stent implantation, n (%)	24 (34.3)	31 (50.0)	55 (41.7)	3.340	0.079
Using of tirofiban, n (%)	44 (62.9)	45 (72.6)	89 (67.4)	1.415	0.267
FP, n (%)	23 (32.9)	36 (58.1)	59 (44.7)	8.452	0.004**
mTICI-3, n(%)	26 (37.1)	41 (66.1)	67 (50.8)	11.052	0.001**
mTICI–2b-3, n (%)	64 (91.4)	57 (91.9)	121 (91.7)	0.011	1.000
Nonsymptomatic cerebral hemorrhage, n (%)	4 (5.7)	4 (6.5)	8 (6.1)	0.031	1.000
Symptomatic cerebral hemorrhage, n (%)	10 (14.3)	10 (16.1)	20 (15.2)	0.087	0.811
SAH, n (%)	1 (1.4)	3 (4.8)	4 (3.0)	1.301	0.341
Embolism, n (%)	15 (21.4)	7 (11.3)	22 (16.7)	2.433	0.161
Cerebral hernia, n (%)	2 (2.9)	4 (6.5)	6 (4.5)	0.979	0.419
Mortality, n (%)	6 (8.6)	8 (12.9)	14 (10.6)	0.651	0.573
90d-mRS (0-2), n (%)	29 (41.4)	37 (59.7)	66 (50.0)	4.380	0.036*

*$P < 0.05$, ** <0.01, t: t test; F: fisher test; Z: ranksum test; mRS: modified rankin scale; mTICI: modified thrombolysis in cerebral infarction scale; BGC: balloon guided catheter.

with non-BGC (58.1% vs 32.9%, $P = 0.004$). The rate of MTICI grade 3 was higher in the BGC group (66.1% vs 37.1%, $P = 0.001$).

The incidences of nonsymptomatic hemorrhage, symptomatic hemorrhage, subarachnoid hemorrhage, and embolism and cerebral hernia were not significantly different between the two groups. The proportion of 90-day mRS of score 0 to 2 was higher in the BGC group than in the non-BGC group (59.7% vs 41.4%, $P = 0.036$). The mortality was not significantly different between the 2 groups (Table 2).

We performed binary logistic regression analysis which showed that BGC was associated with successful reperfusion odds ratio, 0.383; 95% confidence interval: 0.174-0.847; $P = 0.018$, Table 3).

The FP rate of BGC in the distal ICA was higher than that in the proximal ICA (87.5% vs 39.5%, $P = 0.000$), and the good clinical outcome rate at 90 days in the distal ICA was also higher than that in the proximal ICA (91.7% vs 39.5%, $P = 0.000$). There were no statistically significant differences between the two groups in procedural time, MTICI, stent implantation, symptomatic hemorrhage, embolization, and cerebral hernia (Table 4, $P > 0.05$).

4. Discussion

In our retrospective study, we showed that BGC proximal blood flow control technique for thrombectomy of large vessel occlusion led to shorter procedural time and higher rates of FP recanalization.

The proximal blood flow blocking technique with balloon guided catheter was invented by Massari et al. [23], Massachusetts medical school in the United States of

Table 3: Binary logistics regression analysis of independent variables and clinical outcome (mRS ≤ 2).

	β	S.E	Wals	Sig.	OR	95% CI
Age	0.009	0.016	0.339	0.561	1.009	0.978-1.041
mTICI	0.223	0.299	0.557	0.455	1.250	0.696-2.243
NIHSS on admission	-0.311	0.313	0.991	0.319	0.733	0.397-1.352
BGC VS non-BGC	-0.959	0.404	5.620	0.018*	0.383	0.174-0.847

mRS: modified rankin scale; mTICI: modified thrombolysis in cerebral infarction scale; NIHSS: national institutes of health stroke scale.

Table 4: Comparison of the results between the distal and proximal BGC groups.

	Proximal ICA ($n = 38$)	Distal ICA ($n = 24$)	Total ($n = 62$)	P value
FP, n (%)	15 (39.5)	21 (87.5)	36 (58.1)	0.000**
Procedural time(min), M (IQR)	95.0 (72.0,136.5)	78.0 (50.0,128.3)	83.0 (50.8, 128.3)	0.980
Stent implantation, n (%)	19 (50.0)	12 (50.0)	31 (50.0)	0.799
mTICI 2b-3, n (%)	34 (89.5)	23 (95.8)	57 (91.9)	0.337
Symptomatic hemorrhage, n (%)	8 (21.1)	2 (8.3)	10 (16.1)	0.291
Embolization, n (%)	6 (15.8)	1 (4.2)	7 (11.3)	0.232
Cerebral hernia, n (%)	4 (10.5)	0 (0.0)	4 (6.5)	0.151
90d-mRS (0-2), n (%)	15 (39.5)	22 (91.7)	37 (59.7)	0.000**

** $P < 0.005$, ICA: internal carotid artery; mRS: modified rankin scale.

America. The purpose of this technique was to improve the rate of successful reperfusion, FP rate and to reduce distal nontarget embolization. Previous studies have shown that successful reperfusion can be achieved in more than half of the patients by BGC-assisted thrombectomy [24, 25]. It was shown that fusion between stentriever and thrombus was improved compared with conventional techniques. Compared with the stent thrombectomy alone, BGC-assisted thrombectomy shortened procedure time by on average 11 minutes [26, 27]. In addition, proximal blood flow blockade by BGC reduced the incidence of distal micro-emboli [16, 18, 28]. However, due to the lack of access to BGC, there was no published study on the safety and effectiveness of BGC in China.

Velasco et al. [18] have performed a meta-analysis on the clinical outcomes of stroke patients treated with balloon guided catheter control. The study showed that the proportion of mRS 0 to 2 was 59.7% for patients treated with BGC at 90 days, and the mortality rate was 13.7%. In our study, we found that the clinical outcome in the BGC group at 90 days was 59.7%; the mortality rate was 12.9%, and the rate of MTICI grade 3 was 66.1%. These findings were in line with the results of the meta-analysis. Our study also showed that the procedure time of BGC group was significantly shorter than that of non-BGC group. This was also consistent with the study by Nguyen et al. [17], whereby BGC median procedural time was 120 minutes. In addition, our study also showed no statistical significance in mortality, symptomatic hemorrhage, embolism, cerebral hernia, and subarachnoid hemorrhage between the two groups. This provided reassurance of the safety and effectiveness of BGC proximal blood flow control in the treatment of cerebral infarction caused by large vessel occlusion.

In this study, it was found that BGC was associated with successful reperfusion odds ratio; the 95% confidence interval was 0.174-0.847. Besides, the FP rate of BGC at the distal ICA was higher than that at the proximal ICA, and the good clinical outcome rate at 90 days was also higher than that at the proximal ICA. Velasco et al. [29] found that the FP rate of BGC located at the distal ICA was 70%, while that at the proximal ICA was only 43%, which was consistent with the results of this study. The reason may be that when BGC is placed at the distal ICA, there are no obvious collateral vessels, which can effectively control forward flow, increase the rate of the FP, and have a good clinical outcome. However, in procedural time, stent implantation, MTICI, symptomatic hemorrhage, and embolization and cerebral hernia, there was no statistical significance between the two groups, which was inconsistent with previous studies. This may be due to the bias caused by the small sample size, which needs to be confirmed by larger, prospective clinical studies.

Nonetheless, there are some limitations to this study. This was a retrospective design, and it has a small sample size. Therefore, it is not free of selection bias. In addition, prevention of embolus escape is one of the most important functions of balloon guiding catheter. But the study did not prove the difference in embolus escape between BGC group and non-BGC group.

5. Conclusions

Mechanical thrombectomy assisted by BGC blocking anterograde blood flow is an effective method for acute anterior circulation large vessel occlusive stroke. The procedure time was significantly shortened when using BCG. It can increase the FP rate and complete recanalization rates of occluded

vessels without increasing the risk of hemorrhagic transformation. And it makes a better clinical outcome at 90-day.

Abbreviations

BGC: Balloon guide catheter
FP: First-pass
mMTICI: Modified thrombolysis in cerebral infarction
mRS: Modified rankin scale
ASTER: Aspiration versus stent retriever study
EV: Endovascular therapy
NIHSS: Health stroke scale
rt-PA: Recombinant tissue plasminogen activator
ICA: Internal carotid artery
MCA: Middle cerebral artery
ECASS: European cooperative acute stroke study
IQR: Interquartile range.

Data Availability

The datasets used and analyzed in the current study would be available from the corresponding author upon request.

Ethical Approval

This study was approved by the Human Research Ethical Committee of the Henan Provincial People's Hospital.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Retraction

Retracted: Influence of P(VDF-TrFE) Membranes with Different Surface Potentials on the Activity and Angiogenic Function of Human Umbilical Vein Endothelial Cells

BioMed Research International

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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] Y. Xu, M. Cheng, P. Zhu, S. Yang, C. Lai, and S. Xu, "Influence of P(VDF-TrFE) Membranes with Different Surface Potentials on the Activity and Angiogenic Function of Human Umbilical Vein Endothelial Cells," *BioMed Research International*, vol. 2022, Article ID 5693994, 12 pages, 2022.

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Research Article

Influence of P(VDF-TrFE) Membranes with Different Surface Potentials on the Activity and Angiogenic Function of Human Umbilical Vein Endothelial Cells

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During bone tissue regeneration, neovascularization is critical, and the formation of a blood supply network is crucial for bone growth stimulation and remodeling. Previous studies suggest that bioelectric signals facilitate the process of angiogenesis. Owing to their biomimetic electroactivity, piezoelectric membranes have garnered substantial interest in the field of guided bone regeneration. Nevertheless, the knowledge of their influence due to varying surface potentials on the progression of angiogenesis remains ambiguous. Therefore, we proposed the preparation of an electroactive material, P(VDF-TrFE), and investigated its effects on the activity and angiogenic functions of human umbilical vein endothelial cells (HUVECs). The HUVECs were directly cultured on P(VDF-TrFE) membranes with different surface potentials. Subsequently, cell viability, proliferation, migration, tube formation, and expressions of related factors were assessed through appropriate assays. Our results revealed that the negative surface potential groups exerted differential effects on the modulation of angiogenesis *in vitro*. The P(VDF-TrFE) membranes with negative surface potential exhibited the greatest effect on cellular behaviors, including proliferation, migration, tube formation, and promotion of angiogenesis by releasing key factors such as VEGF-A and CD31. Overall, these results indicated that the surface potential of piezoelectric P(VDF-TrFE) membranes could exert differential effects on angiogenesis *in vitro*. We present a novel approach for designing bioactive materials for guided bone regeneration.

1. Introduction

Guided bone regeneration (GBR), a standard therapeutic procedure, combines bone augmentation with a barrier membrane for the repair of maxillofacial bone defects [1]. The GBR barrier membrane preserves the spatial integrity of the graft filler and inhibits the invasion of the gingival fibrous tissues in the bone healing region, thus facilitating bone regeneration. Thus far, bioinert GBR barrier membranes have been utilized in several contexts in clinical settings, including the treatment of alveolar bone defects caused due to periodontitis, malignancies, and maxillofacial trauma [2, 3]. Owing to the biological processes underlying GBR therapy and the novel concept of bioactive materials, bioactive barrier membranes can stimulate the formation and regeneration of new bone.

Angiogenesis is a key component in bone growth and remodeling [4]. In addition to delivering nutrients, growth factors, hormones, cytokines, and chemokines to bone tissues and eliminating waste products, the bone vasculature also serves as a communication network between the bone and nearby tissues [5, 6]. Given the close spatial and temporal association between bone formation and vascularization, a barrier membrane with proangiogenic activity is a promising strategy for improving bone regeneration and repair.

Endogenous electrical signals promote tissue regeneration and reconstruction (C. [7, 8]; Z. [9, 10]). Previous studies show that external electrical stimulation modulates or promotes angiogenesis through relevant cellular behaviors (M. [11]; H. [12]). Furthermore, the application of electroactive biomaterials as mediators of electrical signals to promote angiogenesis has been reported previously ([13]; W. [14]). The application of this method in clinical settings is restricted due to its inefficiency and discomfort. Inherently, electroactive biomaterial implantation is a potential

technique for localized electrical stimulation to address the above problem. Piezoelectric materials are smart materials that can produce electrical activity due to deformations or an external electric field [15]. This characteristic allows the delivery of electrical stimuli without external power. These piezoelectric polymers have been tested *in vitro* and *in vivo* for tissue regeneration owing to their biomimetic electroactivity ([16]; Y. [17]).

Previous studies have focused on the cytotoxicity and biocompatibility of piezoelectric polymers [18, 19]. However, studies on cell-biomaterial interactions are essential for the evaluation of their utility. Cellular phenomena related to biomaterials include cell adhesion, spreading, and proliferation [20]. Cell adhesion to the matrix is the initial and key process in tissue engineering as it affects subsequent cell behaviors and viability [21]. The adhesion of cells to the surface of biomaterials is the main factor regulating their biocompatibility. The surface properties of biomaterials can guide complex processes underlying cell adhesion, and the functionalization of the surface can control both cell morphology and responses [22]. Initial cell adhesion, determined by electrostatic forces, is crucial for cell communication and tissue development. The surface charge and potential determine the number, type, and degree of refolding of absorbed proteins and the subsequent cell adhesion processes [23]. Accumulating evidence on cell-matrix interfaces and the rapid development of tissue engineering has prompted our study on the surface potential in detail for different types of biological materials (W. [24]). Each cell type has unique properties, including the actual cellular responses to surface charge [25]. Such specific properties allow the designing and adaptation of biomaterial surfaces for specific applications. However, the influence of piezoelectric materials on cellular angiogenesis remains largely unclear. Moreover, to improve the development of piezoelectric GBR membranes, it is critical to determine whether their differential surface potential characteristics affect cell behavior.

This work aimed to contribute to our understanding of the effects of different surface potentials on the cellular behavior and angiogenesis processes of human umbilical vein endothelial cells (HUVECs) *in vitro*. Owing to its high electrical activity, physicochemical properties, and good biocompatibility, the P(VDF-TrFE) membrane was chosen as the experimental material in this study. Furthermore, P(VDF-TrFE) membranes with different surface potentials were synthesized, and their effects on the function of HUVECs were assessed.

2. Materials and Methods

2.1. Fabrication and Characterization of P(VDF-TrFE) Membranes. The P(VDF-TrFE) membranes were synthesized as described previously [26]. Briefly, 3 grams of powdered P(VDF-TrFE) polymer (Arkema, Paris, France) was dissolved in 20 milliliters of N,N-dimethylformamide (Aladdin, Shanghai, China) and dissolved at 60 °C. Subsequently, the solution was deposited on a titanium substrate and dried at 80 °C to allow the evaporation of the solvent, followed by isothermal crystallization. The P(VDF-TrFE) membranes were poled with a direct current electric field (6 kV/cm, 60 min, at 120 °C). The samples were divided into three groups based on their surface potential, "nonpoled", " negative (poled -)", and " positive (poled +)."

Scanning electron microscopy (SEM; Gemini 300, Zeiss, Germany) was performed to observe the surface morphology. The water contact angles of the samples were tested using a contact angle goniometer (ZhongChen Co., Ltd, Shanghai, China). X-ray diffraction (XRD, Ultima VI, Shimadzu, Kyoto, Japan) and Fourier transform infrared spectroscopy (FTIR, Bruker Optik GmbH, Ettlingen, Germany) analyses were also performed to determine the influence of polarization on the crystal structures. Subsequently, the relative surface potential of the poled P(VDF-TrFE) membranes was assessed by Kelvin probe force microscopy (KPFM, AFM, Brucker Icon, Billerica, USA). The P(VDF-TrFE) membrane without polarization ("nonpoled") was the control group.

2.2. Cellular Responses to P(VDF-TrFE) Membranes with Differential Surface Potentials

2.2.1. Cell Culture. HUVECs were cultured in Dulbecco's modified eagle medium (DMEM) with high glucose (Thermo Fisher Scientific, USA) supplemented with 10% fetal bovine serum (FBS, ExCell Bio Company, Shanghai, China) and 1% penicillin-streptomycin solution (Thermo Fisher Scientific, USA) under standard growth conditions (5% CO_2, 37 °C, and humidified sterile environment). Cells were then digested with trypsin-EDTA (0.25%) (Thermo Fisher Scientific, USA) for subsequent steps.

2.2.2. The Direct Contact Test. The samples were sterilized by immersing in 75% ethanol overnight and exposed to UV light for 1 h before the experiment. The direct contact test was evaluated through two biological assays for cell membrane integrity and morphology (KGAF001, KeyGEN BioTECH, China) and cell proliferation (CCK-8, Dojindo, Japan). Cells without samples were used as the control. The cells were seeded onto a 24-well plate at a density of 1.25×10^4 cells/cm_2. After 24 h of incubation, the wells were rinsed twice in phosphate buffer solution (PBS, Thermo Fisher Scientific, USA). The cells were incubated in dark for 30 minutes with a 1 mL working solution (containing 4 μM calcein and 8 μM propidium iodide in 10 mL of PBS). The samples were then examined under a fluorescence microscope (Optiphot-2, Nikon Corporation, Tokyo, Japan). For the determination of proliferative ability, cells were seeded in the samples at a density of 5×10^4 cells/cm_2. After incubation for 24 h and 72 h, the medium was replaced with a medium containing 10% CCK-8 solution and incubated for another 2 h. Next, 100 μL of the medium per well was transferred to a 96-well plate. The absorbance was measured at 450 nm using a microplate reader (ELX808, Bio-Tek, USA).

2.2.3. Cell Migration. The cell scratch and wound healing assay was performed to evaluate the effect of differential surface potentials on cell migration. The cells were seeded onto different samples in a 6-well plate at a density of 1×10^4

cells/cm_2. The scratch was made using a sterile pipette tip when the cell confluency reached 90%. The scratch width of every group was kept consistent at nearly 2 mm. After incubation for 6 h, 12 h, and 24 h, cells were examined under an optical microscope (DM4000, Leica, German). Images were quantitatively assessed using ImageJ 1.51.

2.2.4. Tube Formation Assay. The tube formation assay was performed to determine the effect of surface potentials on the angiogenesis of HUVECs *in vitro*. The sterilized pipette tips were pre-chilled to − 20 °C, and the Matrix gel (BD Biosciences, Bedford, MA, USA) was thawed overnight at 4 °C. After preparation, the liquefied matrix gel was carefully aspirated using the pre-chilled tips and evenly coated on the 48-well plate; care was exercised to not let in air bubbles. All steps were carried out on the ice to prevent the solidification of the Matrix gel at high temperatures. To guarantee consistency in Matrix gelation, the 48-well plates were placed in an incubator at 37 °C with 5% CO_2 for 30 minutes. HUVECs following different treatments during co-culture were digested, centrifuged, and resuspended in 1 ml of the medium while waiting for the matrix gel to harden. Subsequently, 1 mL of the cell suspension was added to each well of the 48-well plate with solidified matrix at a density of 1×10^5cells/cm^2 (making sure to thoroughly mix the addition by blowing with a pistol tip before adding). After the procedure, the 48-well plate was incubated at 37 °C with 5% CO_2 for 4–6 h to detect tube development in HUVECs. The tubes were observed under a microscope.

2.2.5. Effects of P(VDF-TrFE) Membranes with Differential Surface Potentials on Gene Expression. After 48 h of co-culture with the samples, total RNA was isolated from HUVECs using AG RNAex Pro reagent (AG21101, Accurate Biotechnology, Hunan, China). The amount and purity of the RNA were measured on a Nanodrop 100 spectrophotometer. The Evo M-MLV RT Kit with gDNA Clean was utilized to remove genomic DNA for qRT-PCR. Subsequently, reverse transcription was conducted. The SYBR Green Premix Pro Taq HS qPCR Kit (AG11701, Accurate Biotechnology, Hunan, China) was used to perform qRT-PCR following the manufacturer's protocol. The expressions of genes of interest, including vascular endothelial growth factor A (VEGF-A) and platelet endothelial cell adhesion molecule-1 (CD31), were quantified. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a normalization control. The primer sequences used in the study are listed in Table 1.

2.2.6. Effects of P(VDF-TrFE) Membranes with Differential Surface Potentials on Protein Expression. In 6-well plates, cells were co-cultured with the samples for 48 h. Total proteins were extracted from the cells using a RIPA lysis buffer (P0013, Beyotime Biotechnology, China). According to standard protocols, protein extracts were resolved by 8% SDS-PAGE and transferred onto PVDF membranes (Bio-Rad, Hercules, USA). PVDF membranes were blocked for 1 h with BSA containing 5% non-fat dry milk. Subsequently, PVDF membranes were incubated overnight at 4 °C with primary antibodies (GAPDH (1 : 1,000, Boster, China), VEGF-A (1 : 1,000, Proteintech, China), and CD31 (1 : 1,000, Proteintech, China)) followed by incubation with secondary anti-rabbit or anti-mouse IgG (1: 2000) for 1 h after washing them twice in TBST. The membranes were treated with an enhanced chemiluminescent agent to detect the protein bands (ECL, Pierce, USA). The Image Lab 4.1 software was used to analyze the data (Bio-Rad Laboratories, Hercules, CA, USA).

2.3. Statistical Analysis. Biological results were determined following three independent experiments. All data sets were analyzed using the GraphPad PRISM Version 9.00 software (GraphPad Software, Inc., USA). Considering the different polarization procedures and time as independent factors, a two-way analysis of variance (ANOVA) was used to evaluate the numerical data, followed by Tukey's multiple comparison post hoc test for differential polarization treatments at the same time point. Wherever applicable, one-way ANOVA was used to analyze data from three or more groups, followed by Dunnett's multiple comparison post hoc test. Statistical significance was defined at P value < 0.05.

3. Results

3.1. Characterization of P(VDF-TrFE) Membranes. A direct current field was used to pole the P (VDF-TrFE) membranes used in this study, following which FTIR and XRD analyses were performed to determine the β-phase content in the materials. Compared to the nonpoled group, both poled groups exhibited typical β-phase FTIR peaks (840 cm^{-1} and 1400 cm^{-1}) (Figure 1(a)). XRD analysis (Figure 1(b)) showed that the poled groups exhibited a prominent peak at approximately 20° relative to the nonpoled group, indicating an abundance of β-phase content. Overall, the content of the β-phase increased following negative and positive polarization.

As shown in Figure 2(a), SEM images reveal that the surface of P(VDF-TrFE) membranes was smooth, with no obvious fractures or defects, suggesting that polarization did not change or damage the surface morphology; no significant differences in the surface morphology among the groups was observed. The surface water contact angles (Figure 2(b)) of the P(VDF-TrFE) membranes after polarization were less than 90°, and no significant differences were found among groups, demonstrating that polarization did not change the wettability of the material surface.

The surface potentials of P(VDF-TrFE) membranes were characterized by AFM. As shown in Figure 3, the surface potential of the negative group is -2.11 ± 0.10 V; it is $+2.59 \pm 0.90$ V for the positive group and -0.551 ± 0.245 V for the nonpoled group. These results indicated that the surface potentials of the P(VDF-TrFE) membranes changed after polarization. The differentially poled groups developed different surface potentials.

3.2. HUVECs in the Direct Contact with P(VDF-TrFE) Membrane. As shown in Figure 4(a), live-dead assay was performed to assess the influence of direct contact of

Table 1: Real-time PCR Primer sequences.

Genes	Forward primer sequences(5′-3′)	Reverse primer sequences(5′-3′)
GAPDH	GGAGTCCACTGGCGTCTTCA	GTCATGAGTCCTTCCACGATACC
VEGF-A	AGGGCAGAATCATCACGAAGT	AGGGTCTCGATTGGATGGCA
CD31	GGGAAGATGGTCGTGATCCTT	TCTGGGGTGGTCTCGATTTTA

HUVECs with the differentially poled P(VDF-TrFE) membranes. After 24 h of direct contact incubation, fluorescence images of HUVECs co-cultured in different groups were analyzed (Figure 4(a)). Most cells showed spindle-shaped morphology (green fluorescence), and only a few dead cells (red fluorescence) were observed in all poled groups. Cells in the nonpoled group showed a good-shaped morphology with no significant differences from those in the control group. Therefore, P(VDF-TrFE) membranes with differential surface potentials did not negatively affect the viability of HUVECs.

The CCK-8 assay was performed to further elucidate the effects of differentially poled P(VDF-TrFE) membranes on cell proliferation ($F(3, 48) = 3.107$, $p = 0.0350$). Figure 4(b) illustrates the relative proliferation of cells incubated for 24 and 72 h. The results showed that after 24 h, the negative group and the control group exhibited similar proliferation levels with no statistically significant differences. At 72 h, the negative group showed the highest level of proliferation as compared to the other groups, and the difference was statistically significant (nonpoled: $p < 0.0001$; control: $p < 0.0001$).

3.3. Effects of P(VDF-TrFE) Membranes with Differential Surface Potentials on Cell Migration. The results of the P(VDF-TrFE) membranes with differential surface potentials on cell migration are summarized in Figure 5. A two-way ANOVA test suggested that the effects of differentially poled P(VDF-TrFE) membrane over time on cell migration were significant ($F(9, 36) = 7.438$, $p < 0.0001$). As shown in Figure 5(a), the initial scratch width in all groups was consistent at nearly 2 mm. After 6 h, the scratch area decreased slightly in all groups. No statistically significant differences were observed at this time point. Relative to the control group, the wound area left unhealed in the poled groups ($p = 0.0005$) and nonpoled groups ($p = 0.0271$) at the 12 h time point also decreased significantly. At 24 h, the negative group and nonpoled group showed a significant reduction in the wound area left unhealed as compared to the control group (poled - groups: $p = 0.0003$; nonpoled group: $p = 0.0180$). Wound closure was not 100% at the end of 24 h. Wound closure in the control, nonpoled, positive, and negative groups were $52.19 \pm 3.629\%$, $69.76 \pm 6.211\%$, $67.27 \pm 7.181\%$, and $85.90 \pm 1.331\%$, respectively. Taken together, these results suggested that the membrane with negative surface potential significantly enhanced the migration of HUVECs.

3.4. Effects of P(VDF-TrFE) Membranes with Differential Surface Potentials on Tube Formation. Tube formation is critical in angiogenic processes. The possible impacts of varying surface potentials on HUVEC tube formation *in vitro* were investigated by a tube formation assay (Figure 6). After incubation for 6 h, sturdy and elongated tube-like structures developed when HUVECs were incubated in Matrigel pre-coated 48-well plates. The length of the main stem of the formed tubules was quantified using the Image J software ($F = 7.024$, $p = 0.0125$). Unsurprisingly, negative group promoted tube formation, whereby the length of the main segment was significantly greater than those in the control and positive groups (poled +: $p = 0.0059$; control: $p = 0.0311$). These results demonstrated the potential of the membrane with negative surface potential to promote tube formation *in vitro*.

3.5. Effects of P(VDF-TrFE) Membranes with Differential Surface Potentials on Angiogenesis-Related Factor Expression. In this study, the expressions of the angiogenesis factors, VEGF-A and CD31, were analyzed by qRT-PCR (Figure 7) and western blotting. The statistical differences among the groups were confirmed using one-way ANOVA (VEGF-A: $F(3, 32) = 5.473$, $p = 0.0038$; CD31: $F(3, 44) = 4.732$, $p = 0.0060$). Dunnett's multiple comparisons test revealed that the negative group showed the highest level of VEGF-A expression as compared to the positive group ($p = 0.0081$), nonpoled group ($p = 0.0125$), and control group ($p = 0.0032$). The gene expression of CD31 exhibited similar trends. The gene expression of CD31 in the negative group was significantly higher relative to those in the others (poled + group: $p = 0.0248$; nonpoled group: $p = 0.0057$; control group: $p = 0.0090$). To further confirm the effects of differential surface potential membranes on angiogenesis, the levels of protein expression of CD31 and VEGF-A were determined by western blotting (Figure 8). According to quantitative data analysis, the trend of VEGF-A protein expression was consistent with those of the corresponding mRNA levels. The level of VEGF-A expression in the negative group increased significantly (control: $p = 0.0395$; poled +: $p = 0.0251$; nonpoled: $p = 0.0075$), which implied that the membrane with negative surface potential promoted the secretion of VEGF-A.

4. Discussion

In this study, piezoelectric P(VDF-TrFE) was poled by direct current fields, thereby generating differential surface potentials in these materials. The FTIR and XRD results showed that the β-phase content increased, consistent with the findings of a previous study. Cell behavior can be influenced by the surface morphology and wettability of biomaterials [20]. Previous studies suggest that the surface contact angle and surface topography affect the cell's attachment and

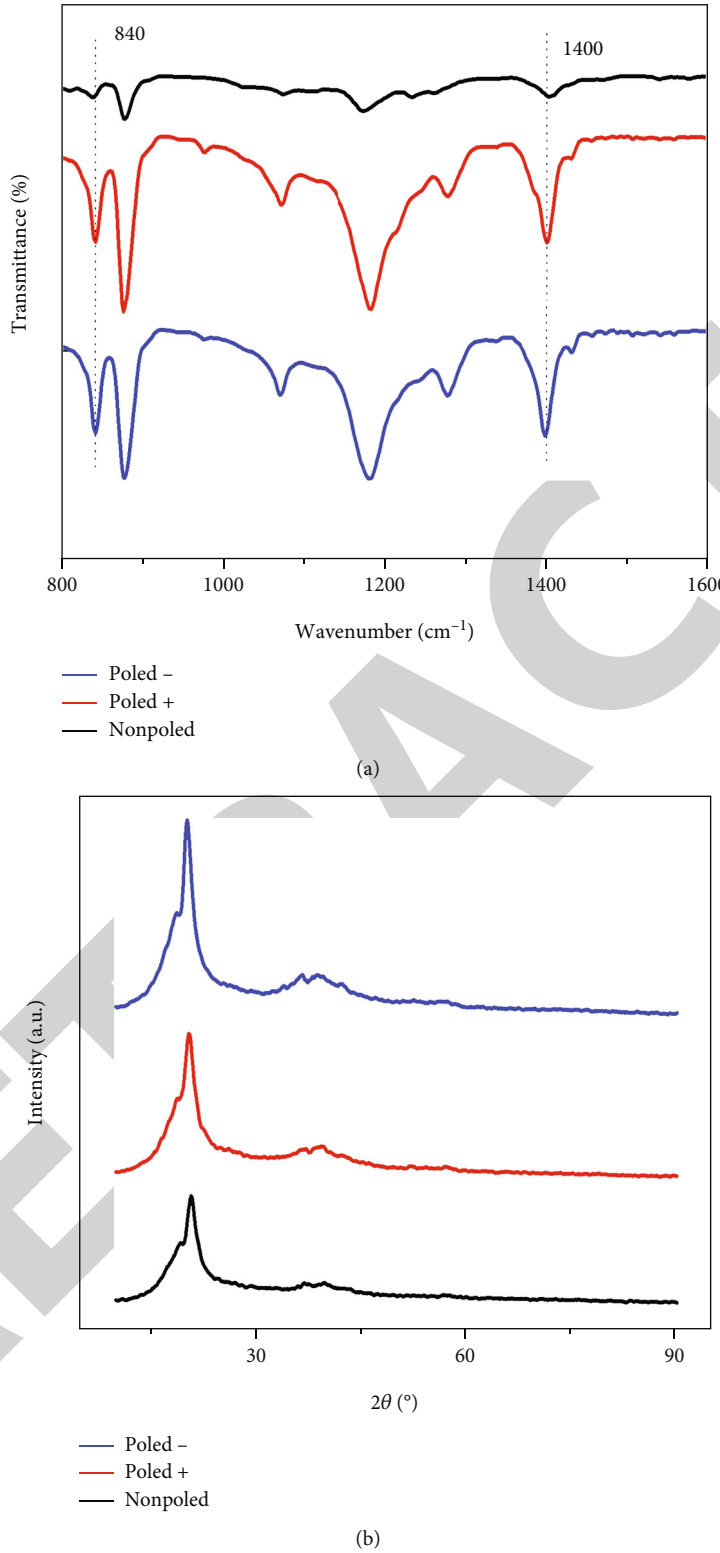

Figure 1: Piezoelectric characterization of P(VDF-TrFE) membranes. (a), (b) The FTIR spectra and XRD patterns for P(VDF-TrFE) membranes before and after polarization, showing the amount of electroactive β-phase.

proliferative abilities [27, 28]. However, based on our results, no significant differences in surface contact angle and topography of P(VDF-TrFE) films before and after polarization were observed. Therefore, the findings exclude the effects of the topography and wettability of biomaterials on cell behavior.

Biocompatibility is the ability of a biomaterial to elicit an adequate host response, crucial for its clinical applicability.

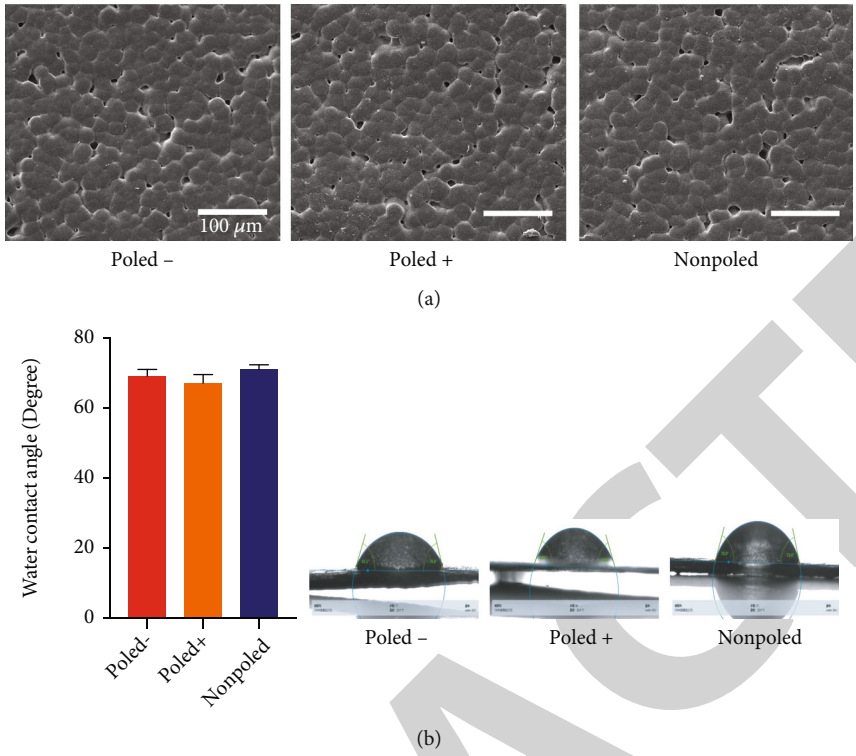

Figure 2: SEM images and Water contact angle of P(VDF-TrFE) membranes. (a), (b) SEM images and water contact angle for P(VDF-TrFE) membranes before and after polarization.

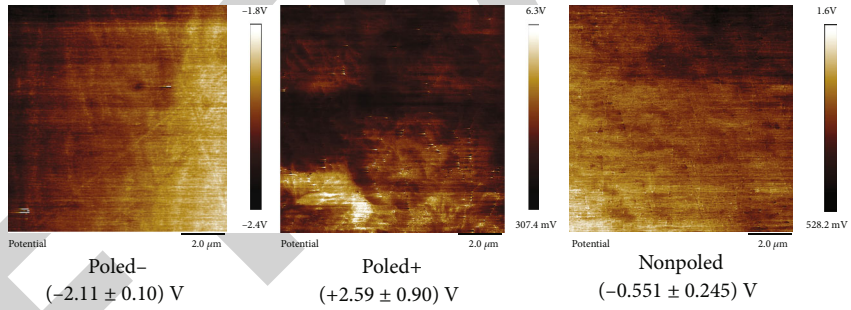

Figure 3: Physical characterization of differently poled P(VDF-TrFE) membrane. The KPFM images depict the distribution of relative surface potential for positively, negatively, and neutrally P(VDF-TrFE).

Electroactive biomaterials are promising bioactive materials; thus, they have gained increasing interest owing to their biological safety. Several studies suggest that biocompatible piezoelectric materials can serve as tissue stimulators and scaffolds to promote tissue regeneration [19, 29]. As a nonbiodegradable biomaterial, good biocompatibility is crucial to achieving long-term retention in the body for widespread utility. Therefore, the biosafety of electroactive P(VDF-TrFE) membranes must be carefully evaluated and considered. Moreover, the dynamic interaction between endothelial cells and material is complex, and the surface properties of biomaterials critically influence this dynamic interaction. The surface potential of biomaterials is an important regulatory factor for cellular responses and cell signaling in tissue therapy [20]. For a biomaterial with good piezoelectric and ferroelectric properties, the surface potential developed after polarization also affects the behavior of HUVECs. We analyzed the effects of electroactive P(VDF-TrFE) membranes on the cell viability of HUVECs by a dead-live assay. No significant cytotoxicity or effects on cell viability in HUVECs were observed for the P(VDF-TrFE) membranes. The good performance of P(VDF-TrFE) membranes as biomaterials was also preliminarily confirmed. This result is consistent with those reported previously by Hitscherich [16].

To better understand the effects of P(VDF-TrFE) membranes with different surface potentials on the proliferation of HUVECs, the CCK-8 assay was performed for quantification. All groups showed good biocompatibility. In particular, the negative groups significantly promoted the proliferation of HUVECs relative to the control group. Similar trends have been reported by Szewczyk for PVDF fibers with

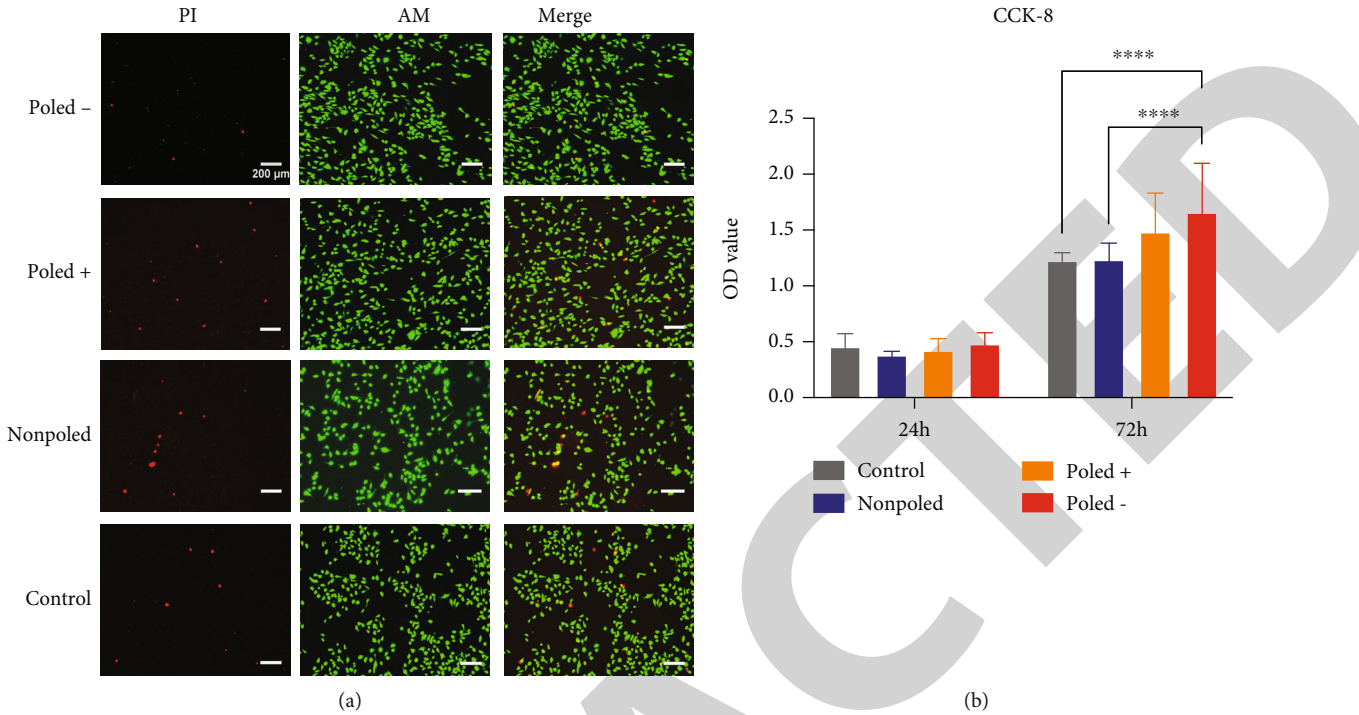

Figure 4: Effect of P(VDF-TrFE) membranes with differential surface potentials on cell morphology and proliferation. (a) The fluorescent representative images were observed after HUVECs in direct contact with the P(VDF-TrFE) membranes with differential surface potentials for 24 h, stained by AM/PI. The red fluorescence depicts apoptotic cells stained by PI, while the green fluorescence shows live cells with membrane integrity identified by AM (scale bar = 200 μm). (b) Quantitatively cell viability was measured by CCK-8 assay. A two-way ANOVA is used to analyze the data that come from three independent tests. **** $p < 0.0001$.

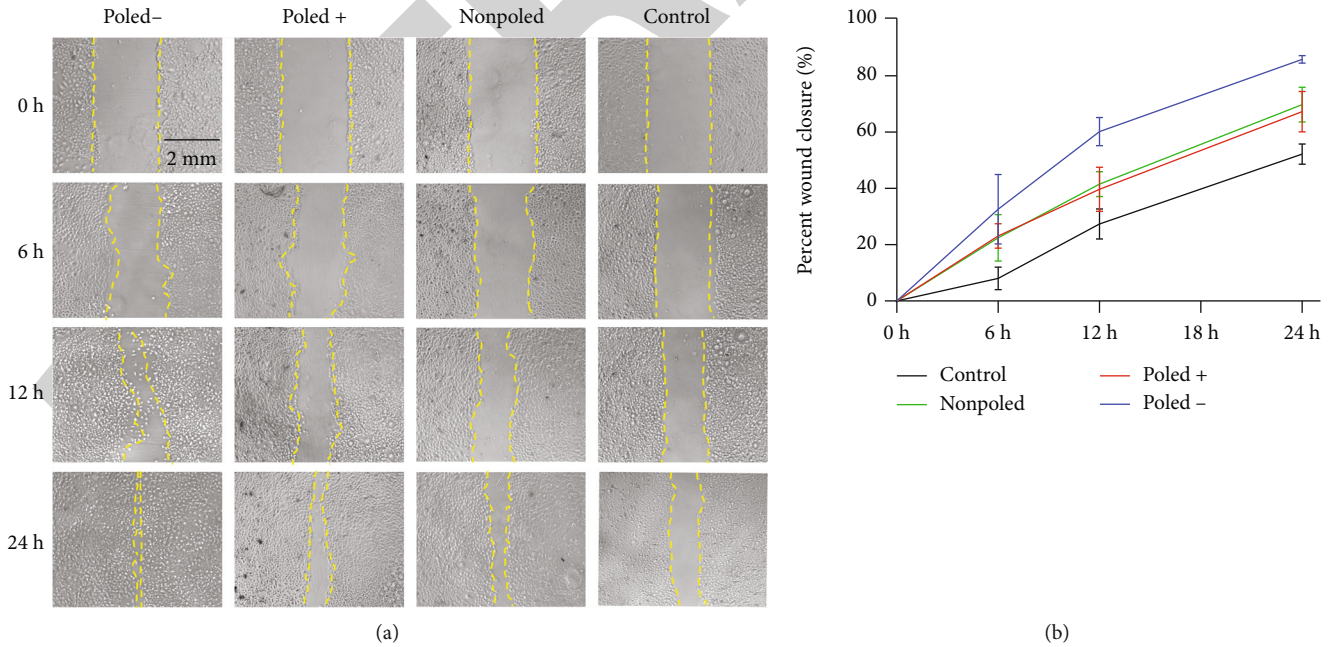

Figure 5: Effects of P(VDF-TrFE) membranes with differential surface potentials on cell migration by scratch wound assay. (a) The representative images observed at 0 h, 6 h, 12 h, and 24 h after the initial width of scratches of each group was about 2 mm. (b) The closure ratio analysis approach is used to calculate the healing rate: would closure (percent) = [(0 h scratch area − scratch area of different time point)/0 h scratch area] × 100. A two-way ANOVA is used to analyze the data that come from three independent tests (scale bar = 2 mm).

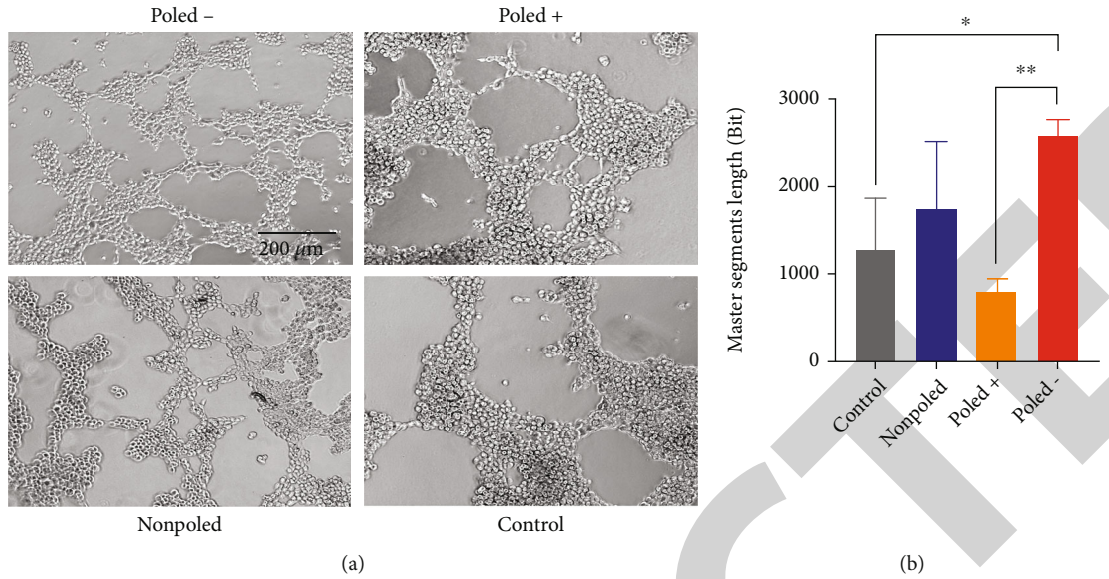

Figure 6: Effects of P(VDF-TrFE) membranes with differential surface potentials on tube formation. (a) The representative images showed the effect of P(VDF-TrFE) membranes with differential surface potentials on the angiogenic ability of HUVECs. (b) Relative tube formation and master segments length were quantified by ImageJ software. A one-way ANOVA is used to analyze the data that come from three independent tests (scale bar = 200 μm). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$.

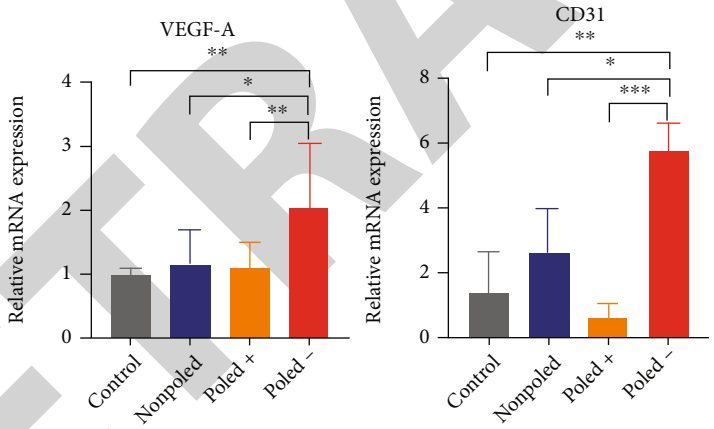

Figure 7: Effects of P(VDF-TrFE) membranes with differential surface potentials on gene expression. The results of VEGF-A and CD31 expression in HUVECs co-cultured with differential P(VDF-TrFE) membranes are summarized in this figure. The data from three independent tests were analyzed with a one-way ANOVA. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$.

different surface potentials. The scaffolds built using PVDF (-) fibers show greater potential for bone regeneration than PVDF (+) [30].

In addition to cell proliferation, endothelial cell migration is also important for angiogenesis [31]. Upon blood vessel injury, endothelial cells migrate to fill the resulting open space and restore the structural integrity of the vessels [32]. Thus, a cell proliferation assay provides the most direct and interpretable data. However, these only represent a part of events during angiogenesis and do not capture the entire process. The formation of new blood vessels can occur through rapid cell multiplication and is triggered by cell migration. Thus, cell migration was evaluated. The scratch–wound assay was performed to evaluate the effects of different surface potentials on cell migration. Notably, the negative group was the most effective in increasing cell migration relative to the other membranes. This general trend is in line with the results obtained for cell proliferation. Interestingly, previous studies suggest that electrical stimulation guides endothelial cell migration toward the anode (M. [11]; M. [33]). Similarly, electrical stimulation benefits the proliferation of HUVECs on a conductive scaffold [13]. The impact is related to the voltage output of the biomaterials.

During angiogenesis, VEGF-A plays an equally active role as a growth factor with important pro-angiogenic effects. It triggers the proliferation and migration of endothelial cells, induces tubulogenesis, promotes endothelial cell

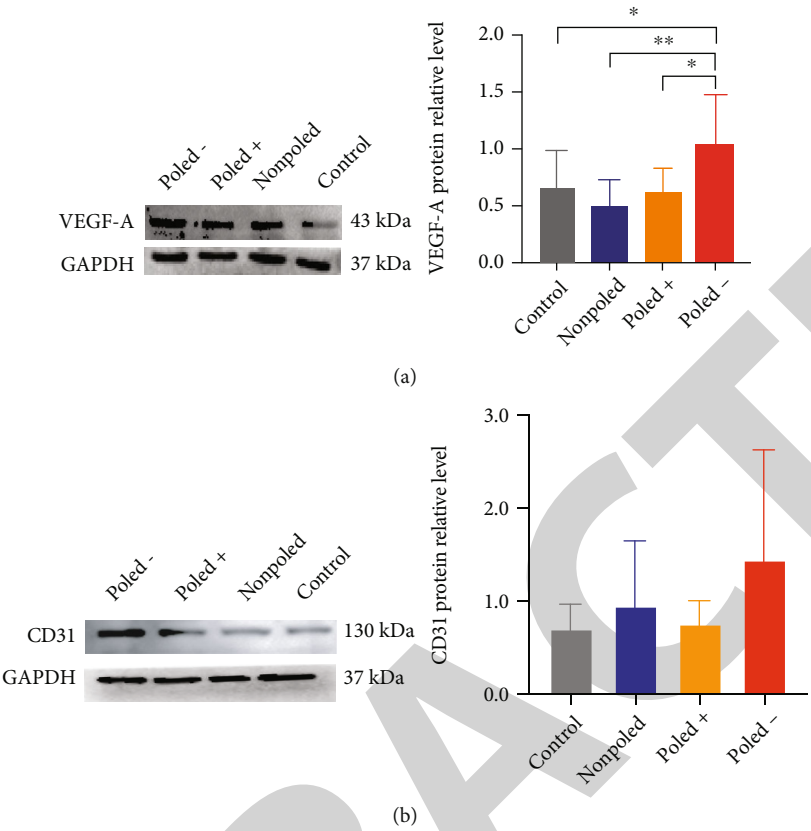

Figure 8: Effects of P(VDF-TrFE) membranes with differential surface potentials protein expression. As angiogenesis factors, VEGF-A (a) and CD31(b) protein expression levels were examined. The data from three independent tests were analyzed with a one-way ANOVA. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$.

survival, and inhibits apoptosis ([34]; X. [35, 36]). Previous studies report that endogenous electrical stimulation affects VEGF release from HUVECs *in vitro*, thereby increasing the mRNA expression of VEGF (H. [12]). In the present study, the level of VEGF-A expression was examined and was found to be significantly upregulated in the negative group, consistent with the results of previous experiments indicating that the negative group promoted cell proliferation, migration, and tube formation in HUVECs, possibly by regulating the expression of VEGF-A. Zhao et al. (Q. [37]) also prepared scaffolds with different surface potentials by the electrostatic spinning of emulsions using power supplies with different polarities. Scaffolds made with negative voltage emulsions better promoted endothelial cell functions, consistent with our results. In the present study, we analyzed the level of CD31 expression, an important angiogenic marker by qRT-PCR and western blotting. The gene expression of CD31 was significantly upregulated in the negative group relative to other groups. Protein expression of CD31 was also upregulated in the negatively poled group. This suggests that the P(VDF-TrFE) membranes with negative surface potential are likely to affect the level of CD31 expression, thus influencing the migration of HUVECs and the formation of tubular structures *in vitro*.

The surface of the poled P(VDF-TrFE) electroactive membrane generated differential surface potentials. According to the ion attraction in the electric double layer, when different groupings of samples are immersed in the medium simulating the *in vivo* environment, some ions are selectively adsorbed onto the sample surface owing to electrostatic reactions [38]. Specifically, on the surface of samples with negative surface potential, cations and positively poled ionic groups are actively adsorbed (W. [39]). The VEGF-A protein exhibits positive electrical properties, and thus, it adhered to the surface of the negative group owing to the electrostatic interaction. The deposition of calcium ions on negative surfaces further formed a cationic layer, consequently promoting the adhesion of proteins and cells [40]. The surface of the nonpoled group was electrically neutral and did not attract inorganic ions, amino acids, proteins, and other substances floating in the medium and, thus, did not affect the adhesion and function of cells or proteins relative to the polarized samples.

Previous studies suggest that the electrical properties of piezoelectric materials contribute to the formation of cellular actin bundles and maturation of adherent spots, which further positively regulates cellular maturation and cellular piezoelectric self-stimulation and induces intracellular calcium transients [41]. Increased calcium ion concentration has

long been recognized as a key pro-angiogenic mechanism underlying the intersection of multiple signaling cascades and is recruited by different mitogens to promote and regulate endothelial cell fate. Moreover, growth factors and chemokines induce an angiogenic switch by increasing the calcium ion concentration to stimulate endothelial cell proliferation, adhesion, migration, and tube formation [42]. This may partially explain why biomaterials with different surface potentials exert differential effects on the behavior of HUVECs. However, this is only a speculative hypothesis based on our results, and more experiments are needed to verify it. Future experiments to elucidate the mechanism of action are necessitated to better understand the principle of action underlying piezoelectric materials.

In this study, biomaterials with differential surface potentials were found to affect cell behavior and angiogenesis *in vitro*. Based on our analysis of the P(VDF-TrFE) membranes with differential surface potentials over months without any additional biochemical modifications, the P(VDF-TrFE) membranes with differential surface potentials were found to promote angiogenesis for tissue regeneration, a research hotspot in the field of bone regenerative medicine. However, the exact underlying mechanism remains unclear, and although an increasing trend of expression of some important markers was detected, further experiments are needed to investigate the mode of action to better understand this biomaterial for promoting its future application in the clinical settings.

5. Conclusion

In conclusion, differentially poled P(VDF-TrFE) membranes were prepared and characterized for the effects of electrical surface potentials of piezoelectric P(VDF-TrFE) on cellular behaviors and angiogenesis in HUVECs. Differentially poled P(VDF-TrFE) membranes triggered different cell behaviors in HUVECs. In summary, piezoelectric materials with differential surface potentials showed significant differences in regulating the functional secretion from HUVECs, which in turn affected subsequent angiogenesis processes. P(VDF-TrFE) membranes with negative surface potential showed better enhancement of angiogenesis. These findings have important implications for piezoelectric materials as a promising technique for guided bone regeneration with proangiogenic activity.

Data Availability

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

Conflicts of Interest

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

Authors' Contributions

YX and MC contributed equally as the first author. YX and MC designed the study. CL and MC prepared the experimental materials. PZ and YX performed the experiments. SY and YH analyzed the experimental data. YX and MC wrote the original draft. SX and CL reviewed and edited the original manuscript. All authors participated in the review of the draft and approved the manuscript.

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Retraction

Retracted: Solitaire™ Stent Thrombectomy System in the Treatment of Acute Lower-Limb Ischemia: Comparisons in Safety and Effectiveness with Conventional Catheter-Directed Thrombolysis Therapy

BioMed Research International

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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] H. Huang, J. Gu, H. Su et al., "Solitaire™ Stent Thrombectomy System in the Treatment of Acute Lower-Limb Ischemia: Comparisons in Safety and Effectiveness with Conventional Catheter-Directed Thrombolysis Therapy," *BioMed Research International*, vol. 2022, Article ID 6997221, 9 pages, 2022.

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Research Article

Solitaire™ Stent Thrombectomy System in the Treatment of Acute Lower-Limb Ischemia: Comparisons in Safety and Effectiveness with Conventional Catheter-Directed Thrombolysis Therapy

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Objective. The study aimed to investigate the safety and efficacy of the Solitaire™ AB Stent System (ev3 Inc., Plymouth, MN, USA) for the treatment of acute lower extremity ischemia (ALLI) compared with conventional catheter-directed thrombolytic therapy. *Methods*. Retrospective analysis of patients with ALLI treated in the Department of Interventional Radiology at the First Hospital of Nanjing from January 2017 to April 2020 divided into a conventional (CDT) group ($n = 106$) and a percutaneous mechanical thrombectomy (PMT) group ($n = 55$) according to the procedure. PMT was performed using the Solitaire™ AB stent system. The combined clinical outcomes of mortality, major amputation, recurrent ischemia, and major morbidity were compared between the two groups. *Results*. Of the 161 patients, 128 (79.5%) did not have a composite clinical outcome after 12 months of follow-up, namely, 78 CDT patients and 50 PMT patients, with significant differences in composite clinical outcome (26.4% vs. 9.1%, $P = 0.010$) and mortality (19.8% vs. 7.3%, $P = 0.037$) between them. Thrombolytic drug dose (19.34 ± 5.93 vs. 13.55 ± 6.54 mg, $P < 0.001$) and length of hospital stay (8.29 ± 3.91 vs. 5.49 ± 1.18 days, $P = 0.003$) were significantly lower in the PMT group. *Conclusion*. PMT with the Solitaire™ AB Stent System is safer and more effective in treating patients with Rutherford stage I-IIB ALLI, with the advantage of rapid opening of obstructed vessels, shorter thrombolysis time, reduced thrombolytic dose, and improved blood flow to the infrapopliteal vessels.

1. Introduction

Acute lower limb ischemia (ALLI) is a vascular surgical emergency caused by embolism, arterial thrombosis, arterial entrapment, or trauma, resulting in a sudden reduction or interruption of blood supply to the limb, resulting in a drastic reduction of blood supply to the relevant tissues, which can seriously threaten the survival of the limb and even endanger life [1, 2]. Early diagnosis, rapid restoration of lower limb perfusion, and reduction of perioperative mortality and amputation rates are the keys to the treatment of acute lower limb ischemia [3, 4]. The main etiologies of acute lower extremity ischemia include arterial embolism due to embolus dislodgement or arterial thrombosis based on atherosclerosis [5, 6]. With the increasing trend of aging population in China, the incidence of arterial thrombosis on the basis of atherosclerosis has also increased significantly and has gradually surpassed that of arterial embolism [7]. The most common source of embolism in acute arterial embolism is cardiogenic emboli, which account for about 75–80% of emboli, namely, atrial fibrillation, arrhythmia-induced appendage thrombosis after myocardial infarction, redundancy on valves, and intra-atrial mucinous tumors [8]. The typical clinical manifestations are the 6P signs, i.e., limb pain, waxy pallor, decreased skin temperature, pulselessness, abnormal sensation, and paresthesia.

The onset of acute limb ischemia can cause an abrupt interruption of blood supply to the skin, nerves, muscles, and other tissues, as there is not enough time for new blood

vessels to grow to compensate for the perfusion of blood to the lower limb [9], which can seriously threaten limb survival. The tolerance of different tissues to ischemic time is different; irreversible damage occurs after 4–6 hours of ischemia in nerves, 6–8 hours in muscle tissues, and 8–12 hours in skin, so we need to develop the appropriate treatment plan quickly according to the degree of ischemia [10].Rutherford's staging [11], one of the clinical staging of ALLI, was proposed in 1986 and updated in 1997. It is based mainly on the assessment of limb appearance, skin temperature, motor and sensory function, and arteriovenous Doppler flow signals to determine whether the limb is alive, threatened, or has developed irreversible damage [12] and classifies ALLI as grades I, IIa, IIb, and III. For patients with Rutherford grade I and IIa ischemia, the appropriate treatment can be selected by performing appropriate tests to determine the cause; for patients with Rutherford grade IIb, immediate hemodynamic reconstruction should be performed, depending on the degree of ischemia, the cause of ischemia, the duration of ischemia, postoperative complications, and the patient's physical condition. Patients with Rutherford grade III may require amputation to save their lives.

The common treatments for acute lower extremity ischemia include surgical and endoluminal treatments, mainly incisional thrombectomy, catheter-directed thrombolysis (CDT), bypass surgery, endarterectomy, percutaneous mechanical thrombectomy (PMT), and hybrid procedures combining two or more surgical modalities [13]. Despite timely thrombolytic therapy or arteriotomy for embolization, amputation occurs in 10% to 15% of patients during hospitalization, and approximately 15% to 20% of patients die within 1 year of onset [14]. There is growing evidence that surgery often fails to achieve satisfactory revascularization due to residual thrombus in the distal vessels and greater surgical trauma, and CDT is thought to be associated with a higher risk of bleeding and a greater incidence of distal embolism, often leading to a poor prognosis [15, 16]. In recent years, the Solitaire™ AB stent for thrombectomy (ev3 Inc., Plymouth, MN, USA) has been widely used in the field of acute ischemic stroke, with recanalization rates of 66%–88% in occluded vessels [17, 18]. A retrospective study showed that mechanical revascularization using the Solitaire™ AB device with manual thrombus aspiration is a fast, safe, and effective way to reduce the requirement for CDT [19]. However, to our knowledge, no studies have compared it with conventional endovascular therapy. Therefore, this study compared the safety and efficacy of Solitaire™ stent thrombectomy with conventional CDT therapy in the treatment of ALLI.

2. Materials and Methods

The retrospective clinical study was approved by the ethics committee of Nanjing First Hospital. The medical records of all patients treated at Nanjing First Hospital were archived in the hospital information system database, and patients were selected for enrollment by searching this database from January 2017 to April 2020 according to the inclusion/exclusion criteria of the study. As this was a retrospective study, patient consent was waived.

2.1. Inclusion Criteria. Inclusion criteria include (1) patients with a confirmed diagnosis of acute lower extremity ischemia based on clinical presentation, signs, bilateral lower extremity vascular ultrasound, and CTA; (2) onset ≤14 days; (3) no previous history of lower extremity arterial surgery; and (4) complete clinical and imaging data

2.2. Exclusion Criteria. Exclusion criteria include (1) contraindications to anticoagulation or thrombolysis, (2) non-acute lower extremity ischemia, (3) treated with vascular bypass surgery, (4) arterial embolism or arterial thrombosis caused by trauma, and (5) no surgical treatment or missing clinical data

Preoperative preparation: For patients suspected of acute lower limb ischemia based on the present medical history and physical examination, relevant investigations should be actively completed after admission, especially the lower limb artery CTA (model: SOMATOM Force) and the ultrasound of both lower limbs to clarify the level of vascular occlusion and the degree of blockage and to assess the ischemia of the lower limbs. If there is no contraindication to anticoagulation, the patient should be given low-molecular heparin anticoagulation therapy immediately. To prevent the development of thrombus from spreading, the patient can be treated with poppy bases to expand blood vessels and improve microcirculation to buy time for blood vessel reconstruction. Anticoagulation should be contraindicated for patients with recent traumatic brain injury, recovery from cerebral hemorrhage, and severe hepatic and renal insufficiency. If the patient has severe pain in the lower limbs, symptomatic treatment such as oxygen, sedation, pain relief, and appropriate rehydration should be given. If the patient is in urgent need of surgical treatment, the surgical mode should be decided according to the patient's ischemic classification, ischemic genesis, systemic condition and imaging data. The patient's surgical risk should be minimized, and the patient and family should be informed of the surgical risks and possible postoperative complications to improve the preoperative preparation.

All procedures were performed under local anesthesia via the ipsilateral femoral artery or contralateral femoral artery approach. After identifying the diseased blood vessels by lower-limb angiography on the lesion side, in the CDT group, a thrombolytic catheter (Medtronic, Inc. Minneapolis, MN, USA) was placed into the thrombotic segment and recombinant tissue plasminogen activator (rt-PA) (Actilyse®; Boehringer Ingelheim, Ingelheim am Rhein, Germany) was subsequently given, followed by infusion with a dose of 0.4–0.85 mg/h through the thrombolytic catheter. Next, lower-limb arteriography was performed every 24 ± 4 h for re-examination. In the PMT group, a Solitaire™ AB stent (6 × 30 mm or 4 × 20 mm) was applied to perform thrombus aspiration of the blood vessels of the diseased segment; then, CDT could be completed after the thrombus load of the diseased segment was relieved (Figure 1). A bolus injection of 5 mg of rt-PA was administered intraoperatively, if necessary.

During thrombolysis, daily detection of hematological indices was conducted, namely, blood cell counts, electrolyte levels, and renal and coagulation functions, and the fibrinogen content was measured at least once a day. The thrombolysis

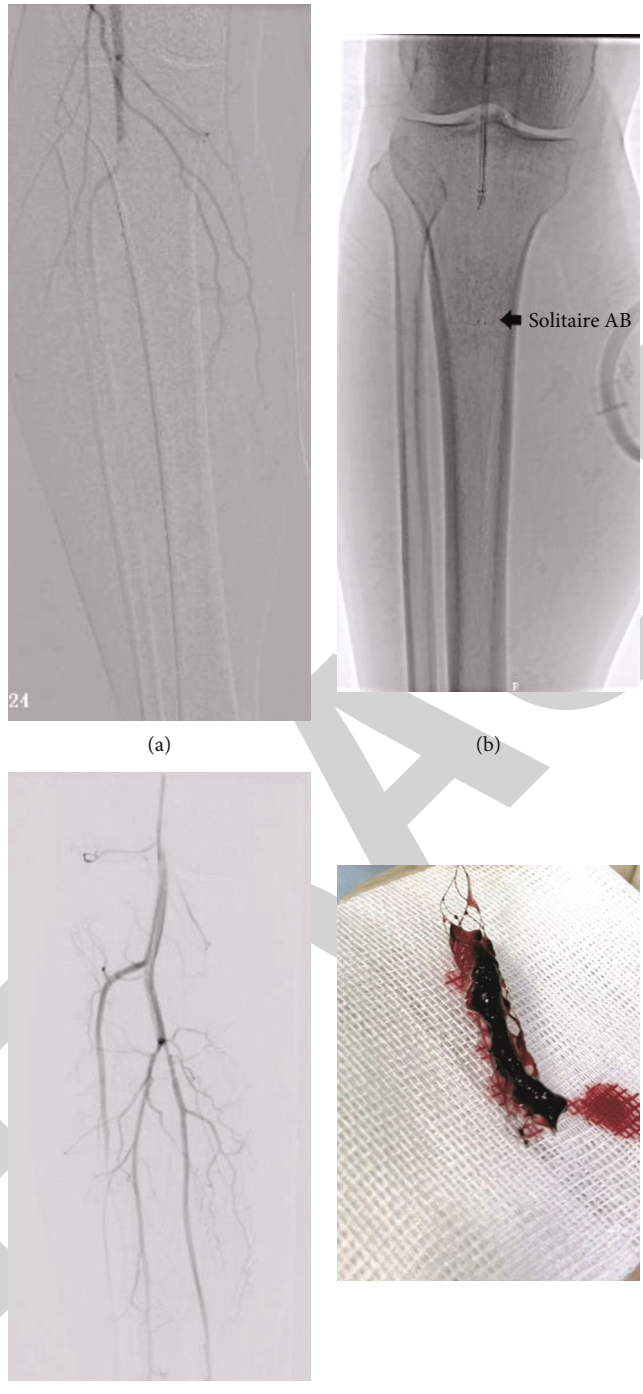

Figure 1: Bracket legend. Note: (a) Angiography shows acute below-the-knee artery occlusion, (b) Solitaire™ AB stent insertion through the below-the-knee arteries, (c) angiography after mechanical thrombo-aspiration revealed patency, and (d) macroscopic aspect of the aspirated thrombi.

rate was adjusted according to the fibrinogen test results, and the hematological indices were re-examined at the end of thrombolytic therapy. When necessary, endovascular treatment could be used as an auxiliary technique (stent implantation or percutaneous transluminal balloon angioplasty) to restore artificial blood vessels, implants, or blood vessels to be unobstructed and to realize the full perfusion of distal blood vessels. Subcutaneous injection of low-molecular-weight heparin was not performed routinely during thrombolytic therapy, but clopidogrel (75 mg/day) alone or combined with aspirin was given to patients with thromboembolism attributable to arteriosclerosis obliterans for ≥6 months. Warfarin or new anticoagulants were given orally in a continuous manner to patients with atrial fibrillation, cardiac thrombosis, thromboembolism, or unexplained hypercoagulability. In short, personalized decisions were made for different patients, and the aforementioned drugs were used in combination with each other in some patients.

2.3. Observation and Follow-Up. After treatment, the patients were followed up with at 1, 6, and 12 months. The primary outcome for analysis was the occurrence of any event of a composite clinical outcome (CCO) during the first year after treatment (1). The occurrence of any of these events was considered an adverse outcome, and the patient was classified as reaching a primary outcome of this study. The components of the CCO included (1) recurrent ischemia; (2) major amputation (above the ankle) or death; (3) life-threatening hemorrhage, either intracranial or blood loss, producing hypotension and requiring resuscitation; and (4) vascular complications, e.g., perforation, occlusion, pseudoaneurysm, or dissection requiring unplanned or emergent surgical repair. The secondary outcomes were the incidence of complications and the runoff score of thrombolytic therapy. The patients were considered to have diabetes mellitus if they were receiving treatment with oral hypoglycemic agents or insulin. Hypertension was defined as a systolic pressure of >140 mmHg or diastolic pressure of >90 mmHg in two or more blood pressure measurements and/or a previous diagnosis of hypertension or the administration of antihypertensive drugs. Hyperlipidemia was defined as any or all elevated blood lipid and/or lipoprotein levels based on hematological examination. Amputation was defined as amputation at or above the ankle. The runoff score (0–19) was determined according to the Society for Vascular Surgery guidelines, with higher scores indicating greater obstruction of the popliteal and inferior genital arteries [20].

2.4. Statistical Analysis. The SPSS statistical software package (version 18.0; IBM Corporation, Armonk, NY, USA) was adopted for statistical analysis. Normally distributed data are expressed as mean ± standard deviation values, while qualitative data are expressed as frequencies (percentages). Furthermore, the t test was used to compare the measured data between two groups, and Fisher's exact test or the chi-squared test was used to compare numerical data between the groups. Then, we visualized analysis results using the R software (version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria), and subgroup analysis was performed according to the Kaplan-Meier method.

3. Results

From January 2017 to April 2020, a total of 161 patients were enrolled in this study. Of these, 106 patients were treated with CDT (CDT group) and 55 patients with ALLI who underwent Solitaire™ stent thrombectomy (PMT group) were obtained to compare the treatment effectiveness with CDT. The mean age of the patients was 72.51 years (standard deviation, 8.76 years; range, 49–93 years), and the study included 84 men (52.2%) and 77 women (47.8%). The classification scheme of acute limb ischemia was as follows: 9 cases of Rutherford I, 89 cases of Rutherford IIa, and 63 cases of Rutherford IIb. There was no significant difference in baseline data between the 2 groups except in the number of patients with hyperlipidemia. The baseline data are presented in Table 1.

The treatments performed in the CDT and PMT groups are summarized in Table 2. At the 1-year follow-up, the event rate for the CCO in the CDT group was 26.4% compared to that of 9.1% in the PMT group ($P = 0.010$). In terms of the CCO, the groups showed significantly different rates of death (19.8% vs. 7.3%; $P = 0.037$) and life-threatening hemorrhage (15.1% vs. 3.6%; $P = 0.029$). Between the two groups, there was no significant difference in major amputation (3.8% vs. 1.8%; $P = 0.498$), ongoing/recurrent ischemia (1.9% vs. 1.8%; $P = 0.976$), or vascular complications (1.9% vs. 1.8%; $P = 0.976$). Two fasciotomies were performed following the completion of thrombolytic therapy in the CDT group. Moreover, five more patients in the CDT group and one patient in the PMT group developed an intracranial or gastrointestinal hemorrhage and died within days of their procedure. The percentage of patients who underwent stenting significantly differed between the CDT and PMT groups (45.3% vs. 27.3%, $P = 0.026$), and significant differences were found in thrombolytic duration (38.09 ± 14.20 vs. 24.56 ± 10.98 h, $P < 0.001$) and rt-PA thrombolytic dose (19.34 ± 5.93 vs. 13.55 ± 6.54 mg, $P < 0.001$) between the groups. Technical success was achieved for 91 patients in the CDT group and 54 patients in the PMT group (85.9% vs. 98.2%, $P = 0.013$).

Regarding fibrinogen levels, there was no significant difference between the CDT and PMT groups before treatment (2.99 ± 0.50 vs. 2.98 ± 0.57 g/L, $P = 0.221$), but an obvious difference was observed after treatment (1.54 ± 0.63 vs. 1.82 ± 0.53 g/L, $P = 0.041$). Considering hemoglobin content, we failed to find a significant difference between the CDT and PMT groups before (104.77 ± 11.19 vs. 108.05 ± 11.25 g/L, $P = 0.609$) or after (90.90 ± 13.46 vs. 95.85 ± 12.19 g/L, $P = 0.594$) treatment. The runoff score did not differ between the CDT and PMT groups before treatment (13.28 ± 2.32 vs. 13.44 ± 2.57 points, $P = 0.384$), whereas it was significantly higher in the CDT group after treatment (7.19 ± 3.25 vs. 5.53 ± 1.84 points, $P < 0.001$).

At 1-year follow-up, Kaplan-Meier estimates of the proportion of CCO were greater in the CDT group than in the PMT group ($P = 0.015$; Figure 2(a)). In the subgroup analysis, Kaplan-Meier estimates of the proportion of patients without AF disease or CCO did not differ significantly between treatment groups (89.5% in the CDT group and 93.3% in the PMT group; $P = 0.664$; Figure 2(b)). In contrast, in the atrial fibrillation subgroup, Kaplan-Meier estimates of the CCO-free rate at 12 months were higher in patients treated with CDT than in those treated with PMT (70.1% in the CDT group versus 90.0% in the PMT group; $P = 0.023$; Figure 2(c)). In patients with Rutherford classification I–IIa, there was no significant difference in CCO rates between the two groups (Figure 2(d)), but significantly more patients with Rutherford classification IIb had CCO in the CDT group compared with the PMT group (Figure 2(e)).

4. Discussion

Acute lower extremity ischemia is a common clinical vascular surgical emergency that can seriously affect the life of the patient and the survival of the affected limb if the patient is

Table 1: Patient baseline data.

Parameters	CDT group ($n = 106$)	PMT group ($n = 55$)	P value
Age (years)	72.99 ± 9.06	71.56 ± 8.09	0.328
Gender (%)	—	—	0.817
Male	56 (52.8%)	28 (50.9%)	—
Female	50 (47.2%)	27 (49.1%)	—
Affected limb (%)	—	—	0.664
Left	54 (50.9%)	30 (54.5%)	—
Right	52 (49.1%)	25 (45.5%)	—
BMI (kg/m^2)	22.19 ± 2.93	22.74 ± 2.54	0.238
Symptom duration (h)	45.38 ± 24.94	39.93 ± 28.47	0.212
Rutherford classification	—	—	0.289
I	8 (7.6%)	1 (1.8%)	—
IIa	56 (52.8%)	33 (60.0%)	—
IIb	42 (39.6%)	21 (38.2%)	—
History of smoking	42 (39.6%)	23(41.8%)	0.788
History of past illness	—	—	—
Atrial fibrillation	87 (82.1%)	40 (72.73%)	0.168
Rheumatic heart disease	1 (0.9%)	2 (3.6%)	0.269
Hypertension	74 (69.8%)	34 (61.8%)	0.306
Diabetes mellitus	33 (31.1%)	19 (34.6%)	0.660
Renal dysfunction	21 (19.8%)	12 (21.8%)	0.765
Cerebral infarction	19 (17.9%)	13 (23.6%)	0.389
Malignant tumor	17 (16.0%)	8 (14.6%)	0.804
Hyperlipidemia	81 (76.4%)	33 (66.0%)	0.030*
Proximal embolism site	—	—	0.365
Iliac artery segment	3 (2.8%)	4 (7.3%)	—
Femoral artery segment	26 (24.5%)	15 (27.3%)	—
Popliteal artery segment/popliteal–distal artery	77 (72.6%)	36 (65.5%)	—

Notes: CDT: catheter-directed thrombolysis; PMT: percutaneous mechanical thrombectomy; BMI: body mass index.

Table 2: Treatments, complications, and treatment outcomes of patients in the CDT and PMT groups.

	CDT group	PMT group	P value
Stenting	48 (45.3%)	15 (27.3%)	0.026*
Thrombolysis duration (hours)	38.09 ± 14.20	24.56 ± 10.98	<0.001*
rt-PA dosage (mg)	19.34 ± 5.93	13.55 ± 6.54	<0.001*
Technical success	91 (85.9%)	54 (98.2%)	0.013*
Length of hospital stay(days)	8.29 ± 3.91	5.49 ± 1.18	0.003*
Composite clinical outcome	28 (26.4%)	5 (9.1%)	0.010*
Death	21 (19.8%)	4 (7.3%)	0.037*
Major amputation	4 (3.8%)	1 (1.8%)	0.498
Recurrent ischemia	2 (1.9%)	1 (1.8%)	0.976
Life-threatening hemorrhage	16 (15.1%)	2 (3.6%)	0.029*
Vascular complication	2 (1.9%)	1 (1.8%)	0.976

Notes: CDT: catheter-directed thrombolysis; PMT: percutaneous mechanical thrombectomy; rt-PA: recombinant tissue plasminogen activator.

not treated with timely intervention. It is one of the most common causes of amputation, with approximately 1.5 amputations in 10,000 people per year [21]. Amputation rates in patients with acute lower extremity ischemia have been documented to range from 10% to 15% and 30-day mortality rates from 15% to 25% [22]. The outcome of the

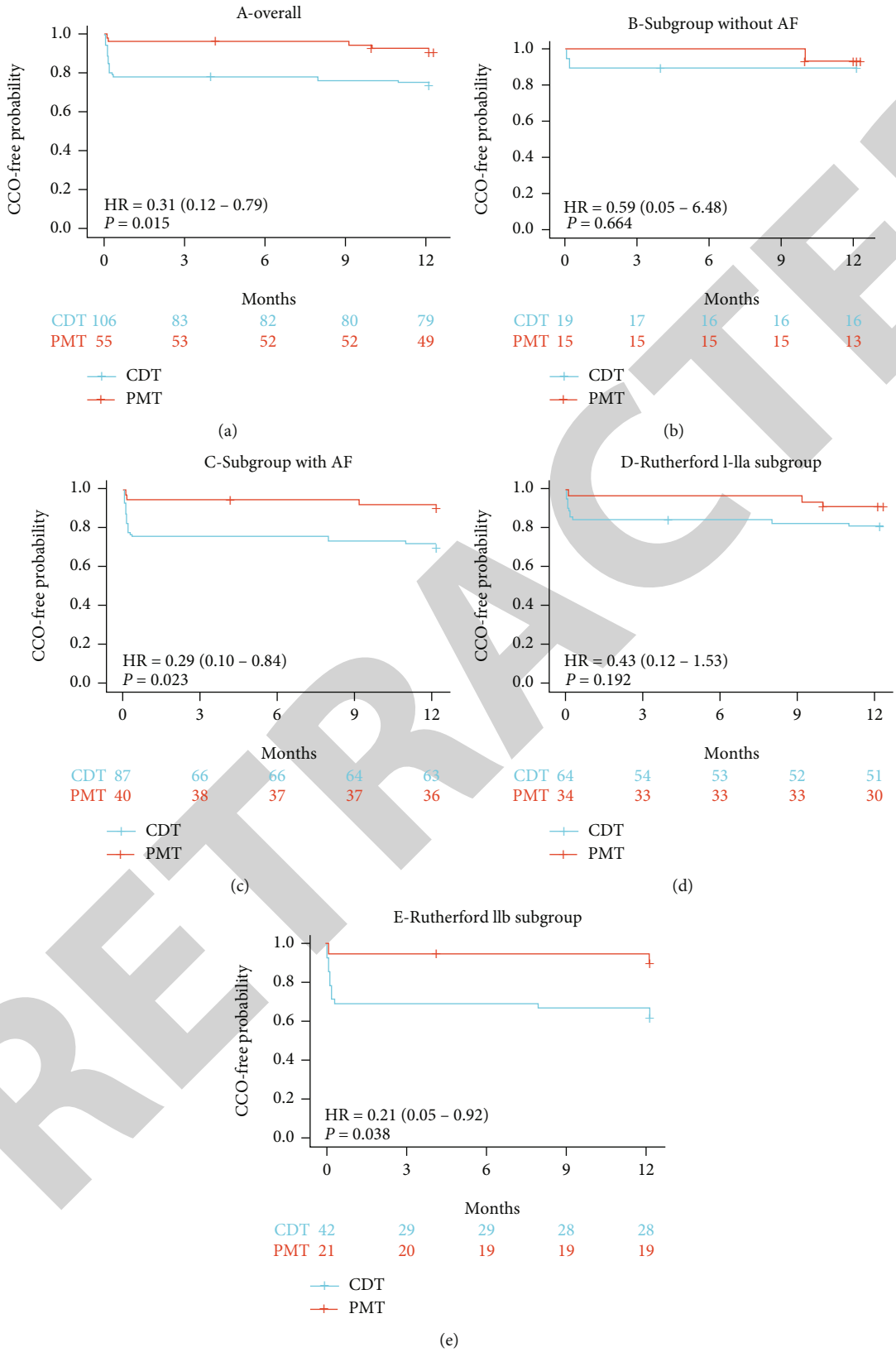

Figure 2: Kaplan-Meier cumulative event curves at 12 months of follow-up. Note: (a) overall cohort, (b) no atrial fibrillation subgroup, (c) atrial fibrillation disease subgroup, (d) Rutherford classification I–IIa subgroup, and (e) Rutherford classification IIb subgroup.

affected limb in patients with acute lower limb ischemia is related to the duration of lower limb ischemia, and the longer the duration of ischemia, the higher the risk of the affected limb facing necrosis. Therefore, timely hemodialysis is important for such patients. The duration of lower extremity ischemia in patients with lower extremity atherosclerosis and atherothrombosis varies from a few hours to several months. Since atherosclerosis is a progressive process, the affected extremity has developed a rich collateral circulation during the long-term ischemia and is able to tolerate a longer period of ischemia. The diversity of clinical presentations combined with the complexity of the arterial wall structure makes it difficult for clinicians to evaluate and treat these patients.

The current clinical treatment of acute lower extremity ischemia is divided into three main categories: (1) surgical thrombectomy (ST) with Fogarty catheter; (2) catheter-directed thrombolysis (CDT); (3) noninvasive and minimally invasive percutaneous mechanical thrombectomy (PMT). Percutaneous mechanical thrombectomy (PMT) and hybrid treatment (HT) combine intracavitary therapy with surgical thrombectomy and multiple methods of thrombectomy. Both incisional thrombectomy and catheter-contact thrombolysis are important treatment modalities for patients with acute lower limb ischemia. Incisional thrombectomy with balloon catheter-based thrombectomy maximizes the removal of femoropopliteal artery thrombus in patients with acute lower extremity ischemia but has little effect on the embolization of some small arteries below the knee. Repeated embolization is more likely to damage the intima of the artery and cause secondary thrombosis after surgery, which aggravates the ischemia of the affected limb. Catheter-contact thrombolysis technique has a high success rate, is well tolerated by patients, and is equally effective for some small branches of the infrapopliteal artery and thrombus in the microcirculation and is increasingly used in acute lower limb ischemic diseases [23]. Due to the high risk of recent bleeding and distal embolism with catheter contact thrombolysis, it is often used clinically in combination with other techniques to reduce the risk of bleeding.

The Solitaire™ AB stent is a widely used technology in the field of cerebral ischemic stroke and has been shown to be effective in patients who do not respond well to thrombolytic therapy. Interestingly, a large body of evidence suggests that the Solitaire™ AB stent can rapidly remove dislodged emboli, open the vessel, and improve the efficiency of thrombolysis and that the Solitaire™ AB stent is suitable for a wide range of vessel sizes with a minimum available vessel diameter of 1.5 mm, suggesting that it can be applied to emboli in distal branches of lower extremity arteries [24, 25]. Rapid opening of the vessel is important in patients with ALLI, but thrombolysis is often less effective in some patients (e.g., those with atrial fibrillation) due to the stiff texture of the emboli. The Solitaire™ AB stent allows for rapid removal of the emboli, thereby opening the outflow tract and improving the efficiency of thrombolysis. This may explain why the Solitaire™ AB stent works better in AF and in the Rutherford IIb subgroup.

This study found that Solitaire™ AB stenting can significantly improve the prognosis of ALLI patients while reducing the thrombolysis time and the runoff score. The device displays the advantages of quickly opening blocked vessels, restoring blood flow, and improving the efficiency of thrombolysis. This study's results illustrated that compared to the CDT group, the CCO rate, mortality, thrombolysis time, thrombolytic agent dose, and length of hospital stay were significantly reduced in the PMT group; meanwhile, PMT had obvious advantages concerning postoperative fibrinogen levels and the runoff score. It is well known that lower runoff scores indicate improved blood flow in below-the-knee vessels, and a large number of studies have also confirmed that increased blood flow in below-the-knee vessels improves the long-term effect of lower-extremity arterial therapy [26, 27].

This study has some drawbacks. (1) This study has certain limitations, being a single-center, retrospective study, not a randomized controlled study, and there may be information bias and selection bias in the collection of study subjects, which may have an impact on the study results. (2) In general, the cases collected in this study were of high age, with many comorbid diseases, and mainly patients with Rutherford ischemic classification of grade II, which may not accurately reflect the actual situation and overall prognosis of the disease, and a large sample and multicenter study is still needed to obtain relatively accurate results. (3) The operators in this study were not the same person, and since each person has different surgical methods and techniques, this may have an impact on surgical decision making, surgical outcomes, postoperative complications, and reintervention rates. It is hoped that homogeneity will be ensured in future studies to minimize errors.

5. Conclusion

Acute lower extremity ischemia is a common disease in vascular surgery and often threatens the life safety of the patients and the survival of the limb. It requires the receiving physician to make the correct diagnosis and choose the correct treatment in the shortest possible time. In summary, PMT with Solitaire™ AB stent is safe and effective in treating patients with Rutherford stage I-IIB ALLI. This strategy is characterized by rapid opening of blocked vessels, shortened thrombolysis time, reduced thrombolytic dose, and improved blood flow to the infrapopliteal vessels.

Data Availability

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Nanjing First Hospital, Nanjing Medical University (protocol code 2021092203, date of approval: 22nd, Sep, 2021).

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

H.H. and H.S. contributed to the conceptualization of the study; Z.L and Y.S. devised the methodology; J.K. helped carry out the software; J.K. and L.C. performed the validation; H.H. and J.K. developed the formal analysis; J.G. directed the investigation; J.G. gathered the resources; H.H. and Y.Y. contributed to the data curation; H.H. and Y.S. wrote and prepared the original draft of the manuscript; H.H., L.C., X.H. and J.G. wrote, reviewed, and edited the manuscript; H.H. helped supervise the visualization of the study; J.G. contributed to the supervision of the study; H.S. took the lead in administering the project; J.K. helped in the acquisition of funding. All authors have read and agreed to the published version of the manuscript.

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Research Article

Laser Speckle Flowmetry for the Prognostic Estimation Study of Permanent Focal Ischemia in Mice

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The distal middle cerebral artery occlusion (dMCAO) model that mainly targets the cortex and causes low mortality is developed for the study of permanent focal ischemia, and it is highly appropriate for the study in the aged population. The two most common methods used to establish dMCAO models are dMCAO alone and dMCAO plus ipsilateral common carotid artery occlusion (CCAO). Up to now, studies on the prognosis of the two types of dMCAO models and the accuracy of cerebral blood flow (CBF) in predicting prognosis have not yet been reported. In the present study, we established permanent focal ischemia models in two groups of aged mice by dMCAO alone or by dMCAO plus ipsilateral common carotid artery occlusion (CCAO). CBF was evaluated by laser speckle flowmetry (LSF) before and after surgery. Cerebral infarction was assessed by TTC staining at day 2 after surgery and MAP2 staining at day 21 after surgery. In addition, behavioral outcomes were evaluated using the modified Garcia scoring system, adhesive removal test, and foot-fault test. Our results showed that compared with those in the dMCAO alone group, the mice in the dMCAO plus CCAO group had a larger cerebral infarct size and more severe neurological deficits. According to the results of the correlation analysis, the area of the ischemic core region on CBF imaging in the dMCAO group was helpful in predicting the infarct volume. In addition, the total CBF of the ischemic area in the dMCAO plus CCAO group showed a significant correlation with Garcia scores 3 days after surgery, but there was no significant correlation of CBF imaging with the foot-fault test 7 days after surgery. These results suggest that the total CBF of the ischemic area might be helpful to predict the severity of neurological damage at the acute stage.

1. Introduction

Stroke is the second leading cause of both disability and death worldwide and poses a staggering burden at both societal and individual levels [1, 2]. Of all strokes, approximately 87% are ischemic strokes, and the global incidence of ischemic stroke is approximately 101.3 per 100,000 population [2]. A variety of animal models, particularly in rodents, have been developed to investigate the underlying pathophysiological mechanisms and explore therapeutics for ischemic stroke [3, 4]. Different murine models of ischemic stroke lead to different degrees of cerebral injury and neurological deficits [5, 6]. The distal middle cerebral artery occlusion (dMCAO) model is a rodent stroke model that mainly targets the cortex and exhibits low mortality, so it is highly appropriate for the studies in the aged population [7]. Permanent distal MCA occlusion alone or plus ipsilateral common carotid artery occlusion (CCAO) are two common methods for permanent focal ischemia model preparation. Nevertheless, no studies have examined the distinctions of

the two types between operations on cerebral infarct size and neurological deficits.

Laser speckle flowmetry (LSF) provides a rapid and wide-field characterization of light scattering particle motion through camera exposure, and it has become widely used as a blood flow imaging tool for measuring blood flow in the brain, skin, retina, mesenterium, and kidney [8–10]. Cerebral blood flow (CBF), measured by LSF, is widely used in studies of experimental stroke models [11, 12]. In a cerebral ischemia model, cerebral artery occlusion significantly decreases local cerebral blood flow, leading to neuronal death and neurological impairments [13–15]. Therefore, CBF detection is commonly applied to assess the blockage of the middle cerebral artery during the cerebral ischemia model-making process [14, 16]. In addition, low CBF was considered to be correlated with poor behavioral or cognitive functions after stroke [17]. However, studies on the correlations between the CBF of dMCAO mice and prognosis have not yet been reported. Thus, whether the LSF imaging of CBF is useful for the prognostic estimation of the dMCAO model remains to be investigated.

In this study, we compared and contrasted the CBF and cerebral injury of the two dMCAO models. The results indicate that CBF, cerebral infarct, and neurological functions vary widely between the dMCAO alone group and the dMCAO plus CCAO (dMCAO+CCAO) group. In addition, the CBF-related parameters from LSF imaging did not have a strong correlation with the severity of cerebral infarction and functional impairments in the dMCAO models.

2. Materials and Methods

2.1. Animals and Experimental Design. Adult male C57BL/6J (9 months old) mice were used to model permanent focal ischemia. All experimental procedures were performed according to the Guide for the Care and Use of Laboratory of Shandong First Medical University. With ad libitum access to food and water, all animals were housed in a 12-hour light/dark cycle with controlled temperature and humidity. In all experiments, investigators were blind to the assignment of the experimental groups.

2.2. Murine Model of Distal Focal Ischemia. According to previous researches, distal permanent focal cerebral ischemia was produced by permanent distal MCA occlusion (dMCAO) alone and dMCAO plus ipsilateral common carotid artery (CCA) occlusion [18, 19]. In brief, with a rodent ventilator (RWD, China), mice were anesthetized with 3% isoflurane and maintained anesthesia with 1.5% isoflurane in a mixture of 30% O_2/70% N_2O. First, an incision was made in the midline neck skin, and then, the left CCA was isolated and occluded by ligation. Then, the temporal muscle was coagulated with electrical current through an incision between the left eye and the ear. A burr hole was opened, and a craniotomy was performed to expose the distal part of the MCA. The distal MCA was occluded by microbipolar coagulation after cutting open the dura mater. Finally, the skin was sutured. Throughout the surgery, the mice's rectal temperature was monitored and kept at 37 ± 0.5°C. A sham operation involved the same anesthesia and procedure but did not involve CCAO or dMCAO. The mice in the dMCAO alone group received the same anesthesia and dMCAO procedures but without CCAO.

2.3. Laser Speckle Contrast Imaging of Cerebral Blood Flow (CBF). The CBF of all mice was measured both before and after surgery. Real-time two-dimensional CBF was measured using laser speckle flowmetry (RFLSI III, RWD, CN), as previously reported [18]. The mouse was anesthetized and placed in the prone position. Then, the skull was exposed by an incision of the skin along the midline of the scalp. The LSF was elevated to an appropriate height above the skull surface. A whole-brain scan was performed by using LSF. To evaluate CBF changes, regions of interest (ROIs) were selected manually, and data were analyzed using LSCI_V 1.0.0 software (RWD, CN).

Figure 1(a) presents the optical configuration of the laser speckle flowmetry used in this study. Briefly, high-resolution blood flow speckle images were recorded by a CMSO camera while the skull is illuminated by a laser at a wavelength of 785 nm. As shown in Figure 1(b), three different types of images were acquired with the laser speckle imaging system: real pictures, speckle pictures, and pcolor pictures. The regions where the CBF exhibits less than 30% of baseline CBF were defined as ischemic core areas. Meanwhile, the regions where the CBF exhibits 30–50% of baseline CBF were defined as penumbra [19]. LSCI_V 1.0.0 software (RWD, CN) was used to determine the regions and calculate the areas.

2.4. Measurements of Infarct Volume or Tissue Loss. 2,3,5-Triphenyltetrazolium chloride (TTC) staining was used to assess the infarct volume 2 days after surgery, and microtubule-associated protein 2 (MAP2) immunofluorescence staining was used to evaluate the tissue loss 21 days after surgery. According to our previous literature [20], for TTC staining, the mouse forebrains were removed at 48 hours after surgery and sliced into 1-mm-thick brain slices, followed by immersion in 2% TTC/saline solution at 37°C for 10 minutes. The normal brain area was stained red, while the infarct area was not stained. As a neuron-specific marker, MAP2 was used to label surviving neurons. In brief, the forebrains of mice were removed at 21 days after surgery, and a routine procedure was performed for frozen tissue sections (25-μm-thick). Brain slices from 8 classical layers were extracted to perform routine immunofluorescence staining with anti-MAP2 antibody (Santa Cruz Biotechnology). To be specific, selected brain sections were incubated with MAP2 primary antibody (1 : 200, Abcam, USA) overnight at 4°C and then with suitable secondary antibodies (488-conjugated donkey antirabbit IgG, 1:800, Jackson Immunoresearch, USA). A confocal microscope (Nikon, Japan) was used to capture the pictures. Infarct volume or tissue loss was quantified from the stained sections by using ImageJ software. The infarct volume was calculated by subtracting the noninfarcted volume of the ipsilateral hemisphere from the volume of the contralateral hemisphere.

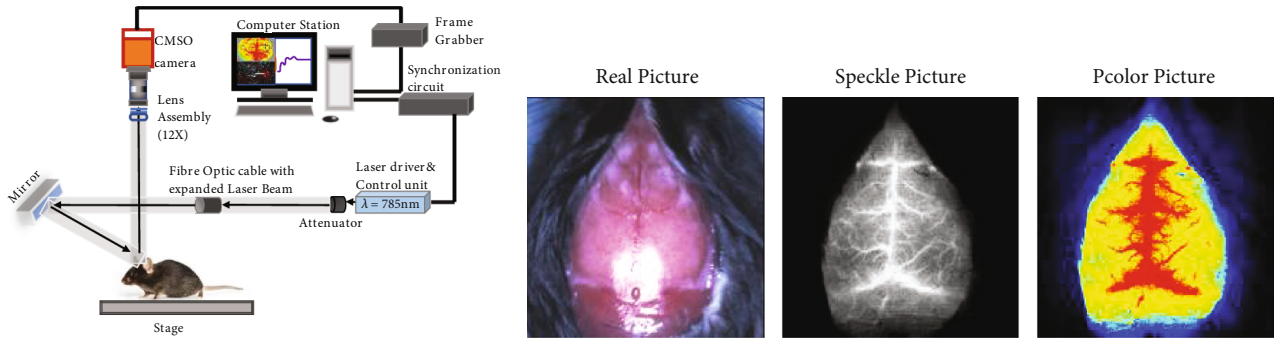

FIGURE 1: Schematic diagram of the laser speckle imaging system. (a) Schematic diagram of the RFLSI III laser speckle perfusion imager. Speckle images are acquired by the laser at 785 nm. Scattered laser light from the brain is captured by a CMSO camera, followed by digitization by a computer-based frame grabber. (b) Representative images of cerebral blood flow. Left image: real picture of the mouse brain. Middle image: laser speckle contrast imaging of cerebral blood flow. Right image: pseudocolor image of the middle image. Each image covers an area of $1.2 \times 1.2\,cm^2$, corresponding to 2048×2048 pixels.

2.5. Behavioral Tests. A blinded behavioral test was performed on mice to evaluate their sensorimotor functions. In this study, we assessed comprehensive neurological function following dMCAO using the Garcia scoring system [18]. The modified Garcia scoring system consists of five kinds of items (3 points/item, maximal score = 15), including body proprioception, forelimb walking, limb symmetry, lateral turning, and climbing.

In the adhesive removal test [21], adhesive tapes of the same size ($0.3 \times 0.4\,cm^2$) are applied with equal pressure to the animal paws. The seconds to contact and remove each adhesive tape will be recorded, with a maximum of 60 s. Mice will be trained once daily before surgery for 3 days and regularly tested (3 trials per day per mouse with 15-minute interval between different mice) after surgery at the indicated time points. The mean latency of three trials to remove the tapes will be calculated.

The foot-fault test [16, 22] focuses on deficits in motor control. Mice will be placed on an elevated steel grid with an opening of $2.25\,cm^2$ ($1.5 \times 1.5\,cm^2$) and videotaped for 1 minute. Mice will be pretrained for 3 days before surgery and regularly tested after surgery at the indicated time points. The number of total steps and foot faults of the right limbs will be counted by a blinded investigator. Errors versus total steps taken by the contralateral limbs were used to calculate foot-fault percentages.

2.6. Statistical Analysis. All data are presented as means ± SEM. The differences among means of groups were analyzed using two-way ANOVA or Student's two-tailed t test with the normally distributed data, and the correlation analyses were performed using Pearson *correlation* in GraphPad Prism software 7.0. A p value < 0.05 was considered statistically significant.

3. Results

3.1. Cerebral Blood Flow Shows a Significant Difference between the dMCAO Alone Group and the dMCAO+CCAO Group. CBF changes could be monitored by using LSF. First, we wished to explore the CBF differences between the dMCAO alone group and the dMCAO+CCAO group. As shown in Figure 2(a), distal focal cerebral ischemia was produced by permanent distal MCA occlusion (dMCAO) alone and dMCAO plus ipsilateral CCA occlusion (dMCAO+CCAO). CBF was detected before and 5 minutes after surgery [23]. The whole brain showed a high blood flow perfusion pattern before surgery, whereas the CBF on the left side decreased dramatically after surgery in both groups (Figures 2(b) and 2(c)). There were no visible differences in the baseline CBF of the left-side brain between the dMCAO group and the dMCAO+CCAO group. However, the blood flow perfusion in the left MCA territories decreased sharply after surgery, and the CBF in the left-side brain of the mice in dMCAO+CCAO group mice was significantly lower than that in dMCAO alone group (Figure 2(d), 103.99 ± 14.58 PU in dMCAO group and 84.6 ± 13.67 PU in the dMCAO+CCAO group, $p < 0.01$). These results confirmed that the CBF in the left side of the brain was significantly different between the dMCAO+CCAO mice and the dMCAO mice.

3.2. The dMCAO+CCAO Operation Results in Enlarged Brain Infarcts Compared to the dMCAO Operation. To explore the effects of different surgical approaches on brain infarcts, we used TTC staining 2 days after surgery for infarct volume calculation and MAP2 immunofluorescence staining 21 days after surgery for tissue loss assessment. No infarct area was observed in the sham group while noticeable infarct areas were observed in both model groups, as evidenced by TTC negatively stained areas (Figure 3(a)). In addition, compared to dMCAO mice, dMCAO+CCAO mice exhibited significantly larger infarct volumes (Figure 3(b). dMCAO mice $7.74 \pm 2.59\,mm^3$ vs. dMCAO+CCAO mice $27 \pm 3.82\,mm^3$, $p < 0.001$). Similarly, brain tissue loss was observed in MAP2-stained sections of the two model groups (Figure 3(c)), which was significantly larger in the dMCAO+CCAO group than in the dMCAO group (Figure 3(d). MCAO mice $18.02 \pm 3.73\,mm^3$ vs. dMCAO+CCAO mice $39.08 \pm 3.8\,mm^3$, $p < 0.001$). Taken together, these data

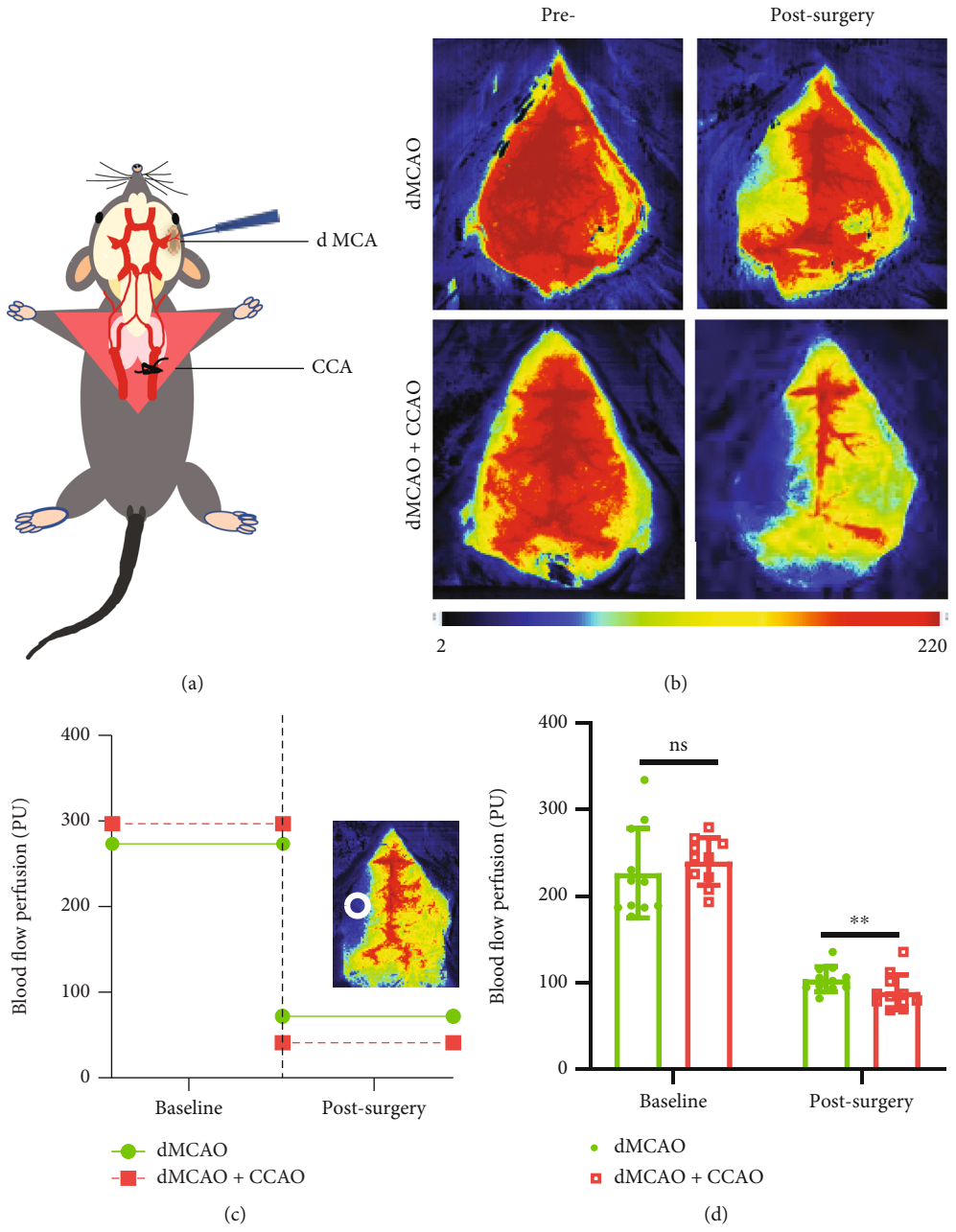

Figure 2: Laser speckle contrast imaging of different operations for distal MCAO. Cerebral blood flow (CBF)-related data were collected by laser speckle flowmetry 5 minutes after the operation. (a) Schematic diagram of the surgery. (b) Representative laser speckle images of cerebral blood flow (CBF) recorded from dMCAO and dMCAO+CCAO mice brain. (c) Representative line graph of CBF in the infarct core area before and after surgery. (d) Quantification of CBF in the infarct core area before and after surgery. $n = 10 - 11$. Data are expressed as the mean ± SEM. The differences between groups were analyzed using the Student's two-tailed t test with the normally distributed data. ns: no significance, $**p \leq 0.01$, $***p \leq 0.001$.

indicate that the dMCAO+CCAO operation results in enlarged brain infarcts compared to the dMCAO operation.

3.3. Tissue Loss May Be Correlated with the Area of Ischemic Core Regions on the CBF Imaging in the dMCAO Group. To investigate whether laser speckle imaging of CBF could help predict the severity of ischemic injury, we evaluated the correlation between the ischemia-related area on CBF imaging and the volume of tissue loss 21 days after surgery. The laser speckle imaging of CBF indicated that compared with dMCAO alone ones, dMCAO+CCAO mice had a significantly larger area of the ischemic core region (Figure 4(a), $2.04 \pm 0.49\,mm^2$ in dMCAO alone group and $6.6 \pm 2.24\,mm^2$ in dMCAO+CCAO group, $p < 0.0001$) but a smaller area of ischemic penumbra (Figure 4(c), $6.04 \pm 1.12\,mm^2$ in dMCAO alone group and $4.69 \pm 1.17\,mm^2$ in dMCAO+CCAO group, $p < 0.05$). There were no significant differences in the CBF of the ischemic core area

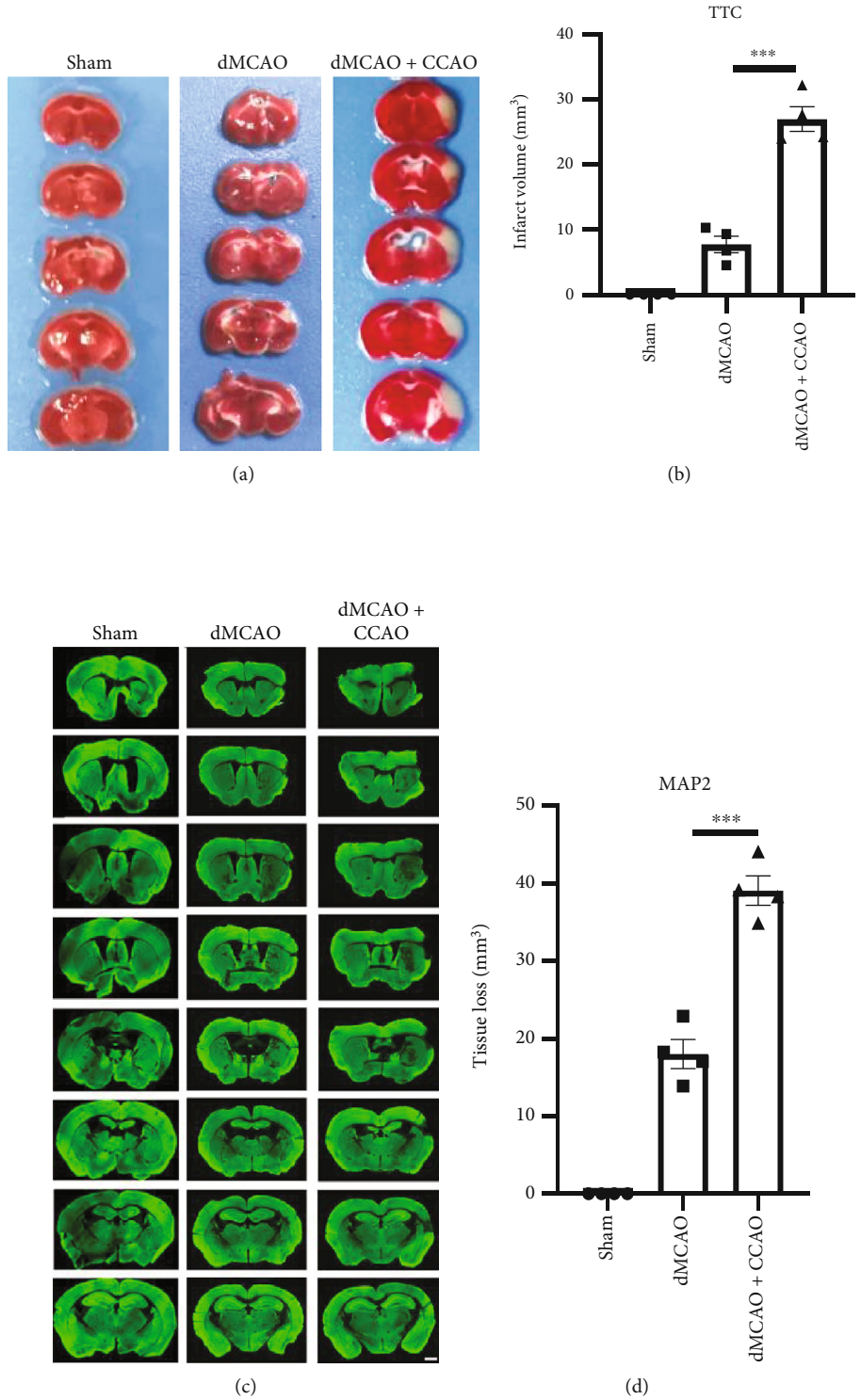

Figure 3: Infarct volume and tissue loss caused by two kinds of operations in the distal MCAO model. (a) Representative images of 2,3,5-triphenyltetrazolium chloride (TTC) staining for infarct measurement 2 days after surgery. (b) Quantification of infarct volume by TTC staining. $n = 4$. (c) Brain sections were immunostained by MAP2 21 days after surgery. Representative brain slices with MAP2 showed reduced cerebral tissue atrophy at 21 d after ischemia. (d) Quantification of tissue loss by MAP2 immunostaining. $n = 4$. Data are expressed as the mean ± SEM. The differences between groups were analyzed using the Student's two-tailed t test with the normally distributed data. $***\ p \leq 0.001$.

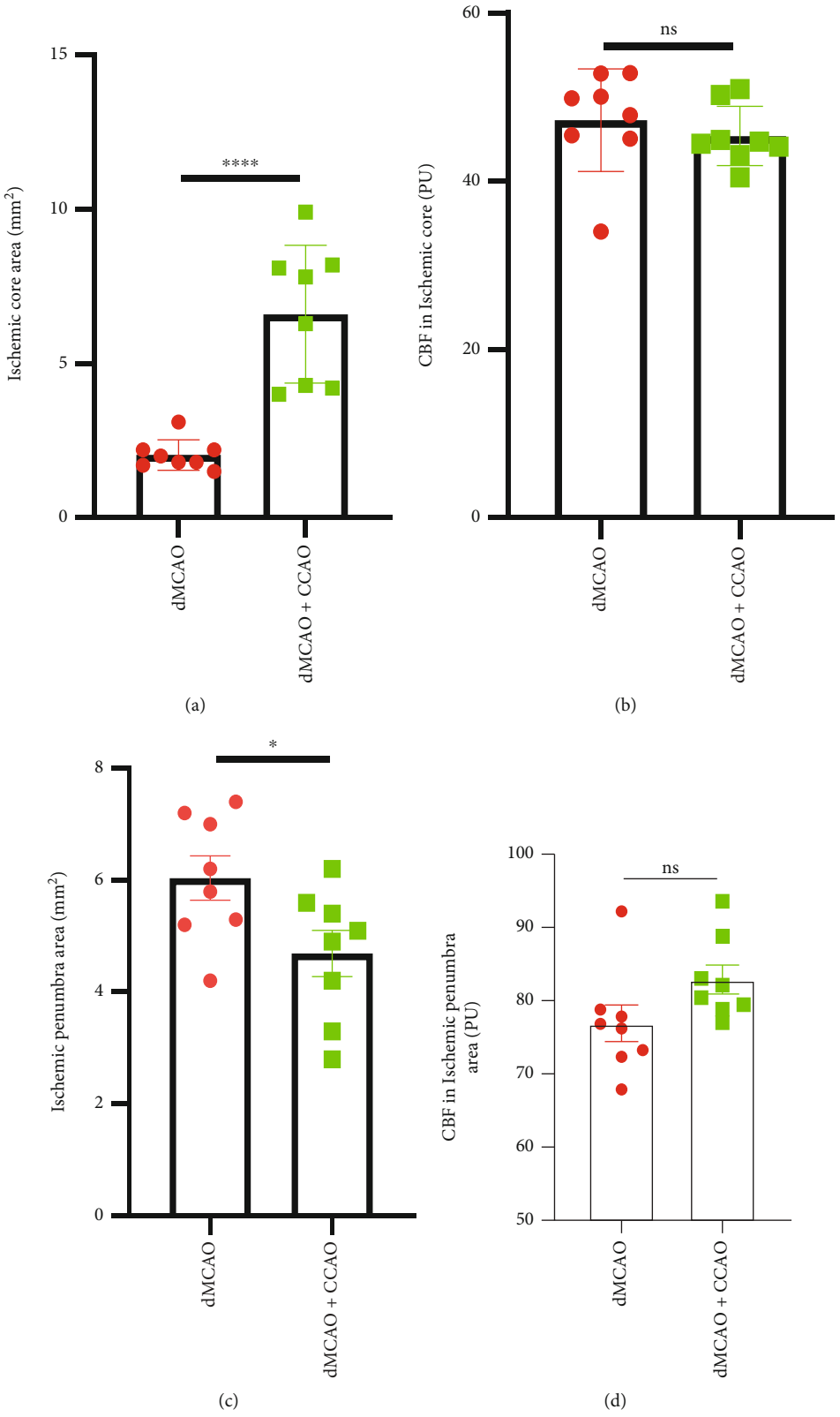

Figure 4: Continued.

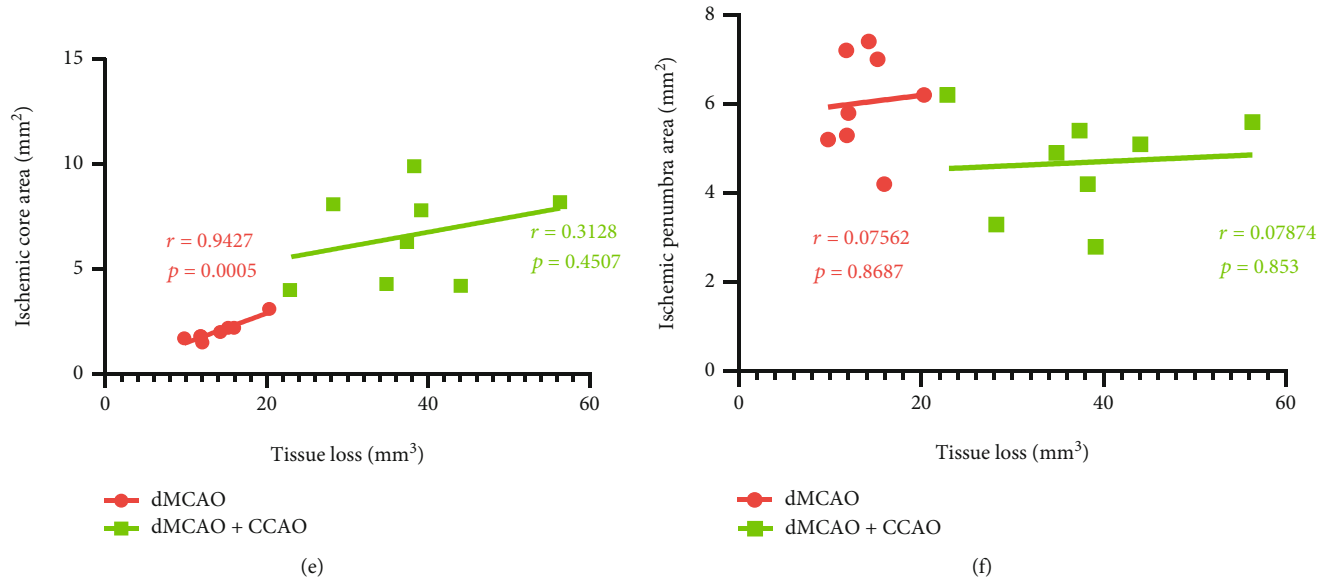

Figure 4: The correlation between tissue loss and CBF in the ischemic core or penumbra area. Tissue loss was measured by MAP2 immunostaining 21 days after surgery. CBF-related data were collected by laser speckle images 5 minutes after the operation. Quantification of areas of ischemic core region (a) and penumbra region (c) by laser speckle images. Comparison of the overall mean CBF in the ischemic core area (b) and penumbra area (d) between the dMCAO and dMCAO+CCAO groups. The correlation between the volume of tissue loss and the area of ischemic core regions (e) or penumbra regions (f). $n = 8$. Data are expressed as the mean ± SEM. The differences between groups were analyzed using the Student's two-tailed t test with the normally distributed data. The correlation analyses were performed using *Pearson correlation*. ns: no significance, $*p \le 0.05$, $***p \le 0.001$.

and penumbra area between the dMCAO group and the dMCAO+CCAO group (Figures 4(b) and 4(d)). The volume of tissue loss 21 days after surgery exhibited a positive correlation with the ischemic core area of CBF imaging in dMCAO mice (Figure 4(e), $r = 0.9427$, $p = 0.0005$). Nevertheless, this correlation was not remarkable in dMCAO+CCAO mice. The correlation between tissue loss and the ischemic penumbra area was also not remarkable in either group (Figure 4(f)). These data suggest that the area of ischemic core region on CBF imaging is helpful in predicting the infarct volume after dMCAO surgery.

3.4. dMCAO+CCAO Mice Exhibit Greater Deterioration in Sensorimotor Functions than dMCAO Mice. To assess the neurofunctional differences between the dMCAO alone group and the dMCAO+CCAO group, we employed the Garcia scoring system, the adhesive removal test, and the foot-fault test to examine the neurobehavioral capacity before and up to 14 days after surgery. Compared with dMCAO mice, dMCAO+CCAO mice showed lower scores in comprehensive neurological impairment at day 3 after surgery (Figure 5(a), $p < 0.05$). In the adhesive removal test, dMCAO+CCAO mice exhibited prolonged sensorimotor deficits lasting for 14 days after surgery (Figure 5(b), $p < 0.05$). Similarly, the dMCAO+CCAO mice exhibited a higher foot-fault rate than the dMCAO mice, which lasted for at least 14 days after surgery (Figure 5(c), $p < 0.05$). These results demonstrate that the dMCAO+CCAO operation results in more severe neurological deficits in mice than the dMCAO operation.

3.5. Decreased CBF in the Sensorimotor Cortex May Be Correlated with Neurological Impairments in the dMCAO+CCAO Group. Next, we assessed whether the neurological impairments after dMCAO+CCAO surgery were linked to CBF-related indicators by laser speckle imaging. CBF imaging was captured 5 minutes after surgery, and the most representative time points were selected for neurological function tests (day 3 for the Garcia scoring and the adhesive removal test, day 7 for the foot-fault test). Pearson correlation was used for the correlation detection. As shown in Figures 6(a) and 6(d), the Garcia scores exhibited a positive correlation with the total CBF in the ischemic core area ($r = 0.7619$, $p = 0.0104$) and an inverse correlation with the total CBF in the ischemic penumbra area ($r = 0.7102$, $p = 0.0214$). There were no significant correlations between total CBF in the ischemic core (or penumbra) area and adhesive removal time in the adhesive removal test (Figures 6(b) and 6(d)) or foot-fault rate in the foot-fault test (Figures 6(c) and 6(f)). In addition, the areas of ischemic core (or penumbra) regions also exhibited no significant correlation with the neurological functions (data was not shown). These results suggest that the total CBF of the ischemic region may be to some extent correlated with neurological impairments in the acute phase of ischemic injury, but CBF imaging cannot accurately indicate the severity of long-term neurological damage.

4. Discussion

The goals of the present study were to compare the outcomes of two types of operations for permanent focal cerebral

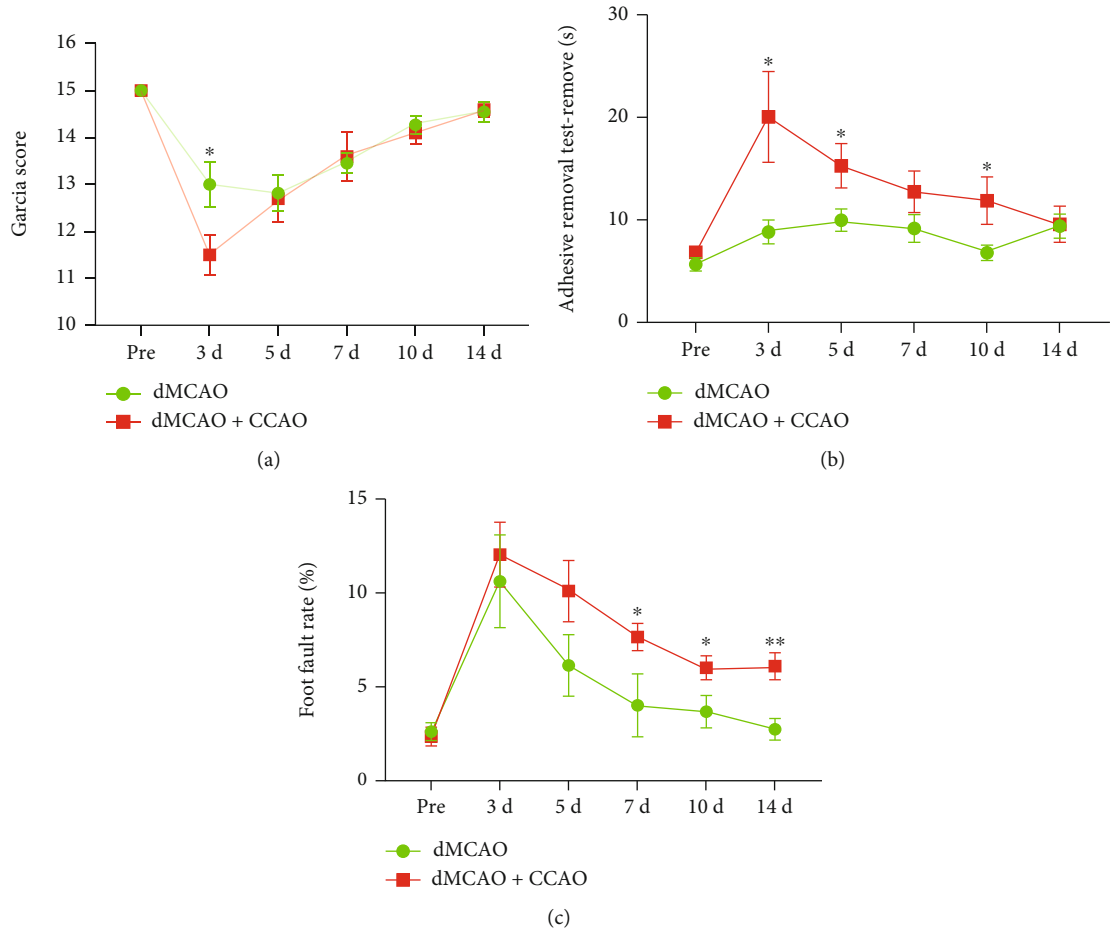

Figure 5: Neurobehavioral functions were different between the dMCAO and dMCAO+CCAO groups. Three neurobehavioral tests were performed to assess poststroke neurological deficits up to 14 d after dMCAO or dMCAO+CCAO surgery. (a) Neurological deficiencies were evaluated based on the criteria of Garcia assessments. The dMCAO+CCAO group mice performed differently on the Garcia score than the dMCAO group mice on postoperative day 3. (b) The adhesive removal test and foot-fault test (c) were performed to assess sensorimotor impairment after surgery. $n = 10 - 11$. Data are expressed as the mean ± SEM. The differences among groups were analyzed using the two-way ANOVA test with the normally distributed data. $*p \leq 0.05$, $**p \leq 0.01$.

ischemia in mice and to evaluate the possibility of prognostic estimation through laser speckle flowmetry imaging for cerebral ischemia. In this study, we established a permanent focal cerebral ischemia model by two methods: dMCAO alone and dMCAO plus CCAO. Compared with mice in the dMCAO alone group, mice in the dMCAO+CCAO group had a larger cerebral infarct size and more severe neurological deficits. According to the results of the correlation analysis, the area of the ischemic core region on CBF imaging in the dMCAO group had a significant correlation with the infarct volume. Thus, the severity of ischemia injury after dMCAO surgery could be largely predicated through CBF imaging by the operator. In addition, the total CBF of the ischemic region in the dMCAO+CCAO group showed a significant correlation with Garcia scores 3 days after surgery, and there was no significant correlation of CBF imaging with the results of foot-fault test 7 days after surgery. To sum up, the CBF imaging cannot accurately indicate the infarct volume and the severity of long-term neurological damage after dMCAO+CCAO surgery in mice. The total CBF of the ischemic area could help the operator to predict the severity of acute neurological damage.

In this study, we chose the dMCAO mouse model for experimental permanent focal ischemia. Compared with other cerebral ischemia models such as the routine intraluminal thread MCAO model, distal MCAO has high survivability and reproducibility of infarct lesions [24]. This method is suitable for the observation of ischemic injury involving neuronal death and neurological functional impairments. In addition, the distal MCAO model can be performed without regard to the diameter of the middle cerebral artery, which could influence the stability of the model [24]. The distal MCAO model could be established by distal MCA occlusion alone or dMCAO plus CCA occlusion. Previous studies reported that the infarct regions of dMCAO without CCAO mice were restricted to the cortex [25]. The small range of the infarct area may limit the application of the dMCAO alone model. The present study is the first to evaluate the differences between the two types of operations for the distal MCAO model. From the results of TTC staining 2 days after

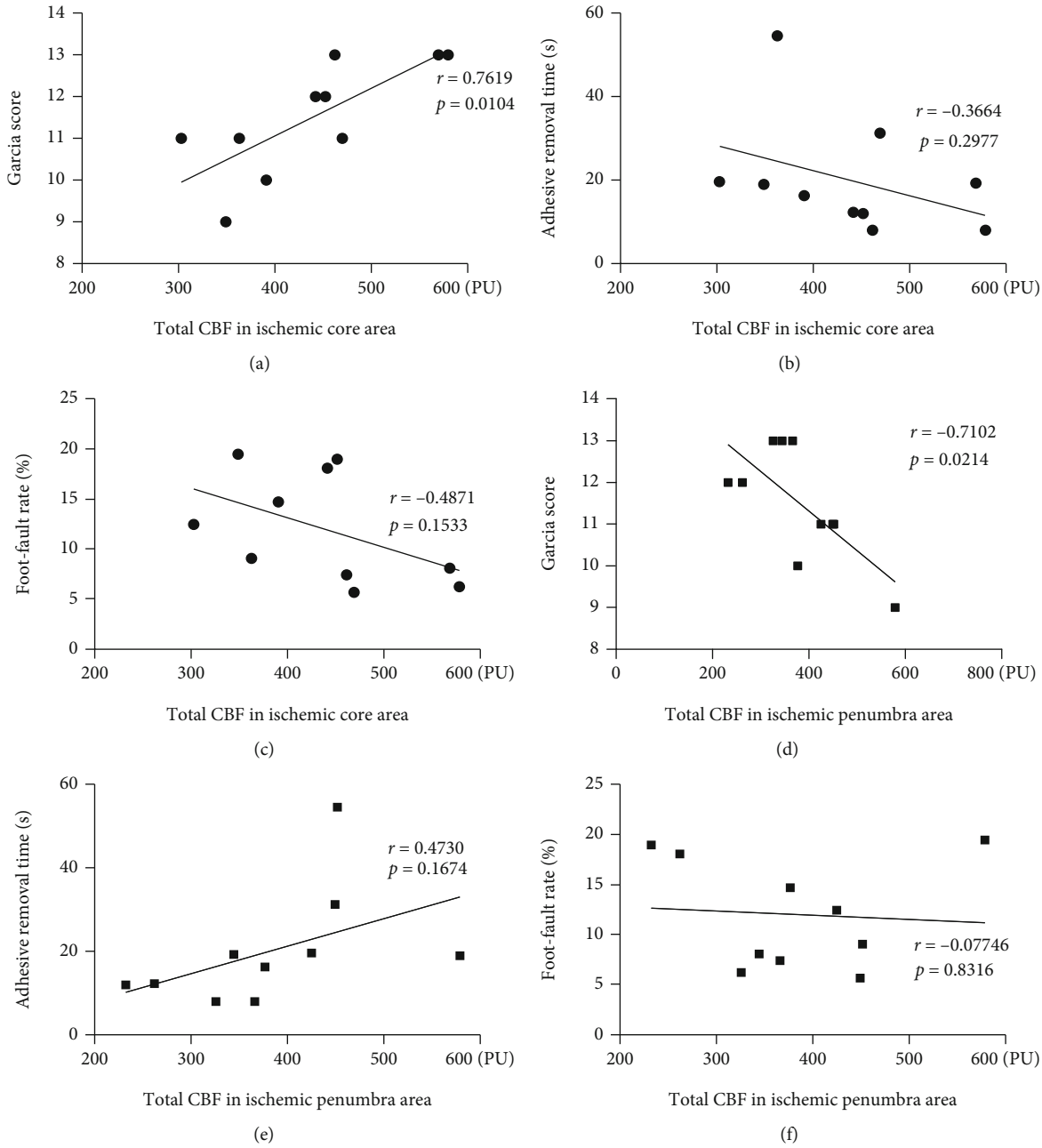

Figure 6: The correlation between neurobehavioral functions and total CBF in the ischemic core or penumbra area in the dMCAO+CCAO group. Functional neurological evaluation was performed 3 days after dMCAO+CCAO surgery. The correlation between the total CBF in the ischemic core area and Garcia score (a), adhesive removal time (b), or foot-fault rate (c). The correlation between the total CBF in the ischemic penumbra area and Garcia score (d), adhesive removal time (e), or foot-fault rate (f). The correlation analyses were performed using *Pearson correlation*.

surgery and MAP2 staining 21 days after surgery, noticeable infarct areas and tissue loss were observed in both model groups, and the dMCAO+CCAO mice presented a larger infarct volume than dMCAO alone mice. The larger infarct area in dMCAO+CCAO mice might be related to the impairment of the collateral circulation by ipsilateral CCA occlusion [24, 25].

The Garcia score, adhesive removal tests [21], and foot-fault tests [23] were used to assess the neurobehavioral capacity before and up to 14 days after surgery. These behavior tests are classical methods for sensorimotor deficit assessment. Consistent with the infarct volume results, mice in the dMCAO+CCAO group presented more severe neurological deficits throughout 14 days after surgery than those in the dMCAO alone group. Therefore, we can conclude that the two types of operations of the dMCAO model result in varying degrees of cerebral injuries and neurobehavioral deficits, which could meet the researchers' different demands for the permanent focal ischemia model.

With the advantage of full-view field imaging of surface blood flow, LSF has been widely used to identify ischemic tissue and to predict infarct volume in rodent cerebral

ischemia models [26, 27]. This study is the first to use LSF to monitor CBF changes in two types of operations for a distal MCAO model of peri-ischemia. The ischemic core and penumbra regions are defined as the regions where CBF decreases to less than 30% and 30–50% of baseline, respectively [28]. Several important novel findings were made according to the CBF data. First, compared to the dMCAO alone group, the ischemic core area was significantly larger, while the CBF in the whole left hemisphere was lower in the dMCAO+CCAO group after surgery. This might be due to the lower arterial blood pressure by additional occlusion of the CCA during ischemia [29]. Second, tissue loss might be correlated with the size of the ischemic core area on the CBF imaging in the dMCAO alone group, but such association was not evident in the dMCAO+CCAO group. Third, decreased CBF in the sensorimotor cortex may be correlated with neurological impairments in the dMCAO+CCAO group. The infarction of the sensorimotor cortex leads to neurological impairments, and MCA is the main artery that supplies blood to the sensorimotor cortex [30]. In this study, we used Garcia scoring scale to evaluate comprehensive neurological functions following ischemic injury, and the Garcia score exhibited a positive correlation with the total CBF in the ischemic core area and an inverse correlation with the total CBF in the ischemic penumbra area. These results suggest that the total CBF in the ischemic area may help predict the early lesion of the sensorimotor cortex.

In conclusion, the dMCAO+CCAO mice exhibited marked differences in CBF-related parameters compared to those in the dMCAO alone mice, and a strong correlation was also found between CBF and the cerebral infarction and the functional outcomes. In addition, the CBF imaging can help to predict the infarct volume in the dMCAO alone mice and the severity of neurological damage at the acute stage in the dMCAO+CCAO mice. These findings may help the operators to predict the prognosis of the permanent focal ischemia to a certain degree.

Data Availability

The original datasets generated for this study are available on request to the corresponding author.

Ethical Approval

All animal experiments were approved by the Institutional Animal Care and Use Committee of Shandong First Medical University and conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

Conflicts of Interest

The authors declared no potential conflicts of interest for the research, authorship, and publication of this article.

Authors' Contributions

Y.W. designed the study and wrote the manuscript. C.L. and GQ.Z. performed the experiments and processed the data. Q.T. and M.Y. helped perform the experiments. Cong Li and Guoqing Zhou contributed equally to this work.

Acknowledgments

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Retraction

Retracted: Clinical Indications for Extubation in Coma Patients with Severe Neurological Craniocerebral Injury with Meta-Analysis

BioMed Research International

Received 20 June 2023; Accepted 20 June 2023; Published 21 June 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. Ma, Z. Han, W. He, and G. Liu, "Clinical Indications for Extubation in Coma Patients with Severe Neurological Craniocerebral Injury with Meta-Analysis," *BioMed Research International*, vol. 2022, Article ID 8012018, 9 pages, 2022.

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Research Article

Clinical Indications for Extubation in Coma Patients with Severe Neurological Craniocerebral Injury with Meta-Analysis

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Computer searches of the PubMed, Cochrane Library, and Embase databases for randomized controlled studies on the effects of intensive nutrition on clinical outcomes in patients with severe craniocerebral injury were conducted from the time of database creation to June 11, 2022, along with manual searches of the relevant literature. Two investigators independently screened the literature, extracted data, and evaluated the risk of bias of the included studies before the effect sizes were combined using RevMan 5.3 statistical software provided by the Cochrane Collaboration Network, and publication bias was detected using Stata 12.0 software. Meta-analysis showed that total protein levels were higher in the intensive nutrition group than in the regular nutrition group (WMD = 4.96 g/L (1.57-8.34), $P < 0.001$); IgA levels were significantly higher in the intensive nutrition group than in the regular nutrition group (SMD = 0.79 (0.51-1.07), $P < 0.001$; SMD = 0.98 (0.58-1.38), $P < 0.001$); IgG levels were significantly higher in the fortified group than in the regular group (SMD = 0.98 (0.58-1.38), $P < 0.001$); CD4/CD8 was significantly higher in the fortified patients than in the regular patients with a combined effect size of WMD = 0.33 (0.18-0.48) ($P <$ RR = 0.45 (0.27-0.75), $P = 0.002$). The results show that effective support of early enteral nutrition can reduce the occurrence of gastrointestinal complications in patients, give them a better adaptation process to the gastrointestinal tract, and ensure the degree of tolerance of their gastric mucosa, thus absorbing more nutrition. Fortification significantly reduced the incidence of gastric retention in patients with craniocerebral injury (RR = 0.19 (0.07-0.49), $P < 0.001$). In the subgroup analysis of the three groups, it was shown that, depending on the starting time, the total protein level and IgG level were better in the early nutrition at 24 h than in the late nutrition above 24h and that, depending on the starting dose, the total protein level, IgA, IgG, and CD4/CD8 were better in the intervention at doses above 30 mL/h, using the starting dose of 30 mL/h as the cut-off point. In the subgroup analysis based on different nutrition methods (enteral and parenteral nutrition), IgA levels and the incidence of bloating and diarrhea were better than those of parenteral nutrition in the indicators of enteral nutrition.

1. Introduction

Severe traumatic brain injury (STBI) is a common neurosurgical condition that is caused by direct or indirect violence to the head [1], and the Glasgow Coma Scale (GCS) stipulates that a person who is in a coma for more than 6 h or in a coma again after an injury is considered to be in severe traumatic brain injury (STBI). Severe traumatic brain injury (STBI) is a common acute and critical condition in neurosurgery [2, 3]. Severe traumatic brain injury accounts for 13%-21% of craniocerebral injuries and is characterized by critical and dangerous conditions, complexity, high mortality rate, and poor prognosis [4–6]. Patients with severe craniocerebral injury all have different degrees of coma, cannot eat on their own, and have a significant metabolic response to systemic stress, resulting in impaired nutritional intake, metabolic disorders, and depletion of the body's original nutritional reserves, leading to varying degrees of malnutrition soon after admission to the hospital [7]. Enteral nutrition (EN) are usually used in clinical practice, while PN is the intravenous supply of nutrients required by the patient, and EN is the gastrointestinal supply of metabolically necessary nutrients and various other nutrients [8]. The PN is the intravenous supply of nutrients needed by the

patient, while the EN is the gastrointestinal supply of metabolically required nutrients and other nutrients [8, 9]. Active and rational nutritional support can improve the overall treatment of the disease and improve the prognosis. With the recognition of PN complications and gastrointestinal stress dysfunction, EN, especially early enteral nutrition, is gaining attention and has even become the first choice for surgical nutritional support [10].

Therefore, while early/late enteral nutrition is strictly limited, the dosage limit should be controlled accordingly. In 2012, the European and American guidelines on surgical nutrition were interpreted [11], and it was suggested that because the gastrointestinal tract of critically ill patients has a gradual process of adaptation and tolerance to enteral nutrition, so when enteral nutrition is implemented in the early stage, it is necessary to start with a small dose and gradually increase the corresponding dose to meet the patient's daily energy requirement. The guidelines recommend that small doses should start from 20 to 50 mL/h and large doses from 100 to 120 mL/h to meet the daily energy requirement. Although enteral nutrition support is currently the most commonly used adjuvant therapy in the clinical treatment of severe craniocerebral injury, the patient's gastrointestinal tract is hypoperfused, which reduces the function of the gastrointestinal tract and prevents the patient from absorbing nutrients properly. Fortified nutrition can effectively improve the gastrointestinal flora, thus providing protection to the gastrointestinal mucosal barrier and improving the immunity of the body [12]. Fortified nutrition means the addition of additional nutrients to the original general nutritional support, called fortified nutrition, which is fortified with nutrients such as glutamine, alanylglutamine, probiotics, and arginine. The purpose of fortification is to enable people to obtain a higher level of comprehensive and reasonable nutritional satisfaction and maintain a higher level of health needs under the normal demands of physiological life and labor. Its important significance and role is to make up for the deficiencies of natural food ingredients, supplement the loss of food nutrients, apply to the needs of special groups and special occupations, and also standardize the reduction of nutritional deficiency diseases or complications caused by nutritional deficiencies, which can effectively save considerable medical costs for the country.

Although the importance of nutritional support is unquestionable, the clinical effect of enteral nutrition can be reduced by different feeding methods of enteral nutrition. The study was selected in terms of language, and only Chinese and English literature was searched, which will have incomplete literature inclusion. The total number of literature included in this study was 39 articles with 3165 study subjects, which still makes it difficult to achieve a large sample for observational analysis. Due to the insufficient sample size of the included studies and the heterogeneity of the literature included in this study in terms of sample and methodology, there is a large variation in the intensity of the intervention programs that can be studied as well as the duration of the intervention, and the range of interventions for the experimental and control groups is also large, which has an impact on the combined results. The reliability of the combined results is affected to some extent. In the subgroup analysis of the three groups, it was shown that, depending on the starting time, the total protein level and IgG level were better in the early nutrition at 24 h than in the late nutrition above 24 h and that, depending on the starting dose, the total protein level, IgA, IgG, and CD4/CD8 were better in the intervention at doses above 30 mL/h, using the starting dose of 30 mL/h as the cut-off point. In the subgroup analysis based on different nutrition methods (enteral and parenteral nutrition), IgA levels and the incidence of bloating and diarrhea were better than those of parenteral nutrition in the indicators of enteral nutrition.

2. Related Work

Severe traumatic brain injury (STBI) mainly refers to brainstem injury, extensive brain contusion, and extensive skull fracture due to multiple causes, and patients with STBI are often unable to eat on their own due to varying degrees of impaired consciousness. Patients with severe injuries rapidly enter a hypermetabolic state, followed by a high catabolic state in which the daily nutritional requirements exceed the normal basal caloric and protein consumption, resulting in a negative nitrogen balance [12]. If energy supplementation is not timely, the chance of being in a high metabolic and low nutritional state increases the susceptibility to infection due to poor immune function and slow wound healing, thus affecting the repair and functional compensation of the central nervous system and increasing the morbidity and mortality of patients [13]. For patients with STBI, tracheotomy and enteral nutrition support within 12~24 hours of admission is more beneficial to the recovery of patients [14]. The quality of the literature was evaluated according to the Cochrane Risk of Bias Assessment Tool.

The purpose of this review is to analyze the current controversial issues such as different starting times, starting doses, and different feeding methods of enteral nutrition, so as to provide a reference basis for the development of clinical nutritional support protocols, improve patient outcomes, and shorten patients' hospital stays [15]. The secretion of metabolic hormones such as adrenocorticotropic hormone, catecholamine and glucagon increases in patients with severe craniocerebral injury, accompanied by an increase in energy demand. Parenteral nutrition cannot meet the energy demand of the body after craniocerebral trauma, coupled with the limitation of fluid input in acute cerebral edema and the occurrence of gastrointestinal dysfunction [16]. The intestine is the central organ of high metabolism after trauma, and the barrier function of the intestinal mucosa becomes impaired under the stress state, and the intestinal bacteria can be displaced through the mucosal barrier and infections can occur.

Without timely nutritional support in the early stage of injury, malnutrition will soon result, which will affect the recovery of disease and neuronal repair, and even increase the rate of disability and death. Enteral nutrition in patients with severe craniocerebral injury can be administered through nasogastric tube, nasoduodenal tube, transnasal jejunal tube, and transgastric/jejunostomy feeding. Among

them, the simplest and most commonly used enteral nutrition route that is not sensitive to the osmotic pressure of the nutrition solution is transgastric enteral nutrition, but it is not suitable for patients with poor gastrointestinal motility or impaired emptying [17]. For long-term nutritional support (more than 4 weeks), gastro-/jejunostomy feeding is the preferred method, preferably with continuous infusion by infusion pump for 12-24 hours and uniform feeding rate. In addition, enteral nutrition infusion pump is also suitable for patients with heavy cranial injury with artificial airway to reduce gastric retention, avoid gastrointestinal irritation, and reduce the occurrence of adverse reactions such as abdominal distension [18]. The percutaneous endoscopic gastrostomy/jejunostomy can be left in place for a long time, effectively reducing the rate of detachment and avoiding restriction of movement and pressure on the skin and mucosa of patients [19].

3. Materials and Methods

3.1. Inclusion and Exclusion Criteria. Subjects involved in the literature met the following criteria: clinically definite diagnosis of heavy craniocerebral injury by cranial CT or MRI, Glasgow coma score of 3 to 8, expected treatment time ≥ 7 d, and any gender. Those in pregnancy and patients with cancer and gastrointestinal injuries, combined with severe multiple injuries and cardiopulmonary insufficiency, were excluded, as shown in Figure 1.

The intervention group was given intensive nutrition, i.e., additional nutrients including glutamine, alanine glutamine, probiotics, ω-3 fatty acids, arginine, and dietary fiber on top of the normal nutritional support in the control group. The following are the indicators: nutritional indicators: total serum protein; immunological indicators: IgA, IgG, and CD4/CD8; outcome indicators: morbidity and mortality rate; and adverse reaction indicators: total infection rate, bloating and diarrhea, and gastric retention.

Two investigators independently screened the literature according to inclusion and exclusion criteria and used a predesigned data extraction form to extract relevant information, including (i) basic characteristics of the study: first author's name, year of publication, country, and sample size; (ii) basic characteristics of the study population: mean age, male proportion, and mean GCS score; (iii) information related to the intervention: type of fortification, nutrition mode, nutrition initiation time, nutrition initiation dose, feeding route, feeding method, and nutrition duration; and (iv) outcome indicators: total protein level, IgA, IgG, CD4/CD8, morbidity and mortality rate, total infection rate, incidence of bloating and diarrhea, and incidence of gastric retention. The investigators cross-checked the extracted information one by one and resolved any disagreement through discussion or consultation with a third party; if the information material of the study was incomplete, the authors were contacted to obtain relevant information; if no relevant data were obtained, the literature was excluded.

For each of the included studies, each entry was assessed according to the above 7 criteria and evaluated according to "low risk," "unclear," and "high risk" criteria. "Low risk" indicates low bias, representing a low risk of bias; "unclear" is moderate bias, indicating a lack of information to determine the level of risk or unclear bias; "high bias " is a high level of bias, indicating a high risk of a bias. This work was evaluated independently by two investigators, two of whom were the investigator himself and one doctoral student, both of whom were trained in statistics and related professions and both of whom had the ability to complete quality evaluation independently and to discuss or consult a third party to resolve any disputes about the evaluation findings when they existed.

Effect sizes were combined using RevMan 5.3 statistical software provided by the Cochrane Collaboration Network. Categorical variables were analyzed using relative risk (RR), and continuous data were analyzed using mean difference (MD) or standardized mean difference (SMD), and 95% confidence intervals (CI) were calculated for each effect size. The random-effects model was used to combine the effect sizes. In addition, subgroup analyses of study outcome indicators were performed according to the time of initiation (early nutrition (within 24 h) and late nutrition (more than 24 h)), starting dose (small dose (<30 mL/h) and large dose (≥30 mL/h)), and feeding method (pump-in and drip). Stata 12.0 software was used to detect publication bias, and P values for both Begg's test and Egger's test > 0.05 suggested no publication bias; $P \leq 0.05$ suggested publication bias.

3.2. Literature Search Results. Based on the search strategy, a total of 960 relevant papers were searched, including 450 in PubMed, 317 in Embase, 49 in Cochrane Library, 75 in Wanfang database, and 69 in CNKI database, and 699 papers were screened for reading abstracts after deleting 261 duplicate papers. The remaining 73 papers were read in full text, and finally, 39 papers were included in this study, as shown in Figure 2.

The basic characteristics of the included study subjects and the interventions are shown in Figure 3. All 39 included papers used a randomized group design, 10 papers used random assignment concealment, 7 papers were blinded to study subjects or investigators, 4 papers were blinded to the outcome analysis process, all 39 papers reported complete results, 33 papers had no selective reporting bias, and 33 papers had no other bias.

3.3. Meta-Analysis Results. Random-effects model was used to combine the results, which showed that the total protein levels in the patients with intensive nutrition intervention were higher than those in the regular nutrition group, and the difference was statistically significant (WMD = 4.96 g/L (1.57-8.34), $P < 0.001$), as shown in Figure 4. The cut-off point was 24 h. Nutritional support given within 24 h was defined as early nutrition and beyond 24 h as late nutrition, depending on the onset of nutritional support. Based on the time of initiation, subgroup analyses were performed for the outcome indicators of total protein, IgA, IgG, CD4/CD8, morbidity and mortality, total infection rate, incidence of bloating and diarrhea, and incidence of gastric retention.

Fifteen papers evaluated the effect of fortification interventions on IgA levels. 15 papers evaluated the effect of

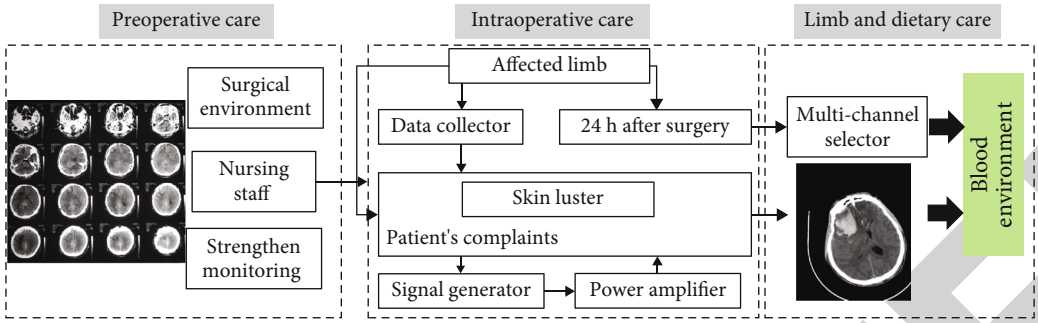

Figure 1: Inclusion and exclusion criteria.

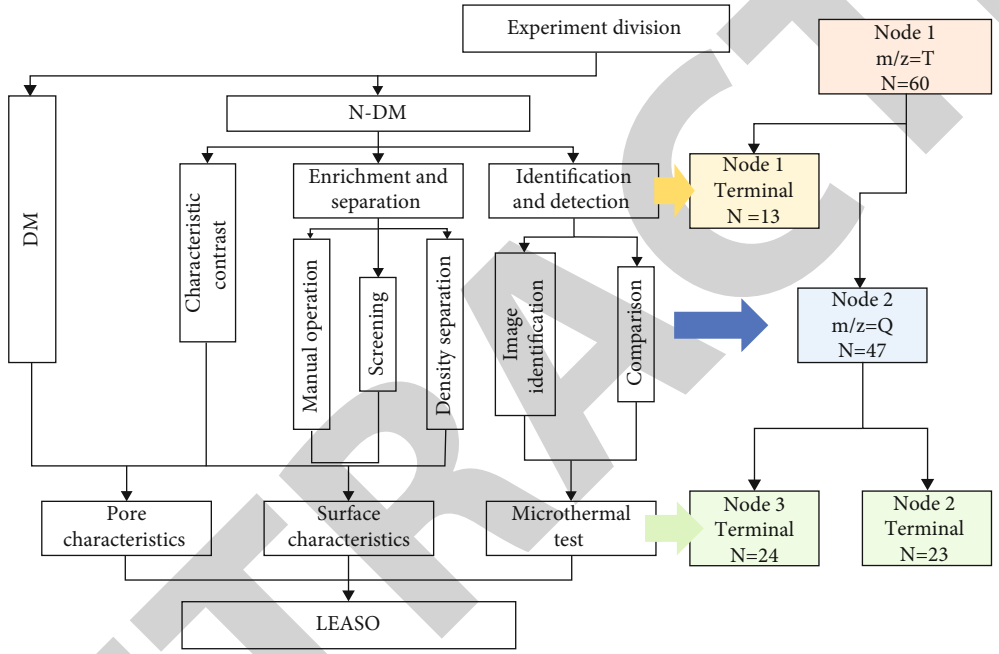

Figure 2: Flow chart of literature screening.

fortification on IgG levels, and due to the inclusion of different units of IgA in the literature, the combined effect sizes were standardized mean difference (SMD). The heterogeneity test result $I^2 = 79\%$; $P < 0.001$, suggesting a significant heterogeneity. The difference was statistically significant ($P < 0.001$), as shown in Figure 5.

The results of the subgroup analysis showed that early nutrition was better than late nutrition in terms of total protein levels (WMD: 7.34 g/L vs. 3.46 g/L) and IgG levels (SMD: 0.95 vs. 0.89), and the incidence of bloating and diarrhea was lower (RR: 0.42 vs. 0.45) for patients with craniocerebral injury treated with intensive nutrition. Conversely, late nutritional support IgA levels (SMD: 0.89 vs. 0.56) were higher than early nutritional support and had a lower incidence of morbidity and mortality (RR: 0.38 vs. 0.75), total infection rate (RR: 0.40 vs. 0.49), and gastric retention (RR: 0.19 vs. 0.27), as shown in Figure 6. In contrast, small doses of enteral nutrition can reduce the gastrointestinal motility burden and improve gastrointestinal tolerance in critically ill patients due to its small dose; its nourishing effect will maintain the structure and integrity of intestinal mucosa, reduce bacterial translocation and related infections, and thus promote the recovery of gastrointestinal and other organ functions.

However, it was more effective than the starting low-dose intervention in terms of total protein levels. However, the effect of the initial low-dose intervention was better than the initial high-dose intervention in terms of total infection rate (RR: 0.39 vs. 0.59), bloating and diarrhea (RR: 0.40 vs. 0.43), and gastric retention (RR: 0.43 vs. 0.04). The results of the subgroup analysis, based on the different nutrition methods (enteral and parenteral nutrition), suggested that IgA levels were higher with enteral fortification than with parenteral nutrition (SMD: 0.85 vs. 0.57), and the incidence of bloating and diarrhea (RR: 0.43 vs. 0.63) was lower than with parenteral nutrition, while total protein levels (WMD: 9.27 vs. 4.27), IgG (SMD: 1.36 vs. 0.87), and CD4/CD8 (SMD: 1.03 vs. 0.54) were higher than enteral nutrition, and the morbidity and mortality rate (RR: 0.31 vs. 0.51) and total infection rate (RR: 0.31 vs. 0.50) were lower than enteral nutrition.

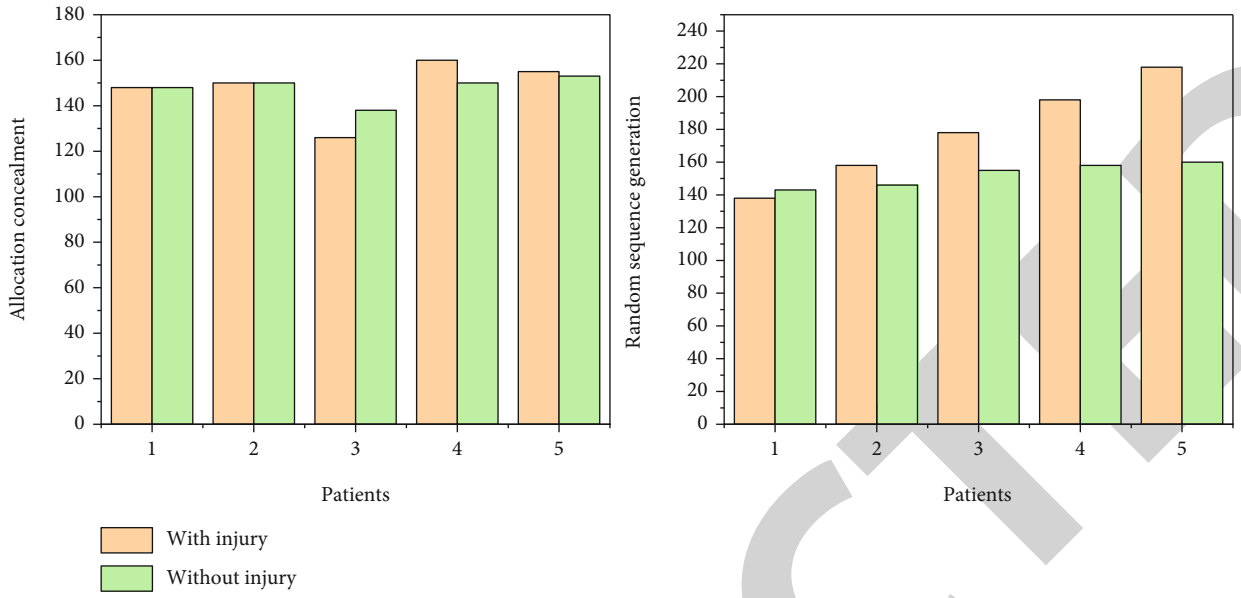

Figure 3: Risk of bias chart.

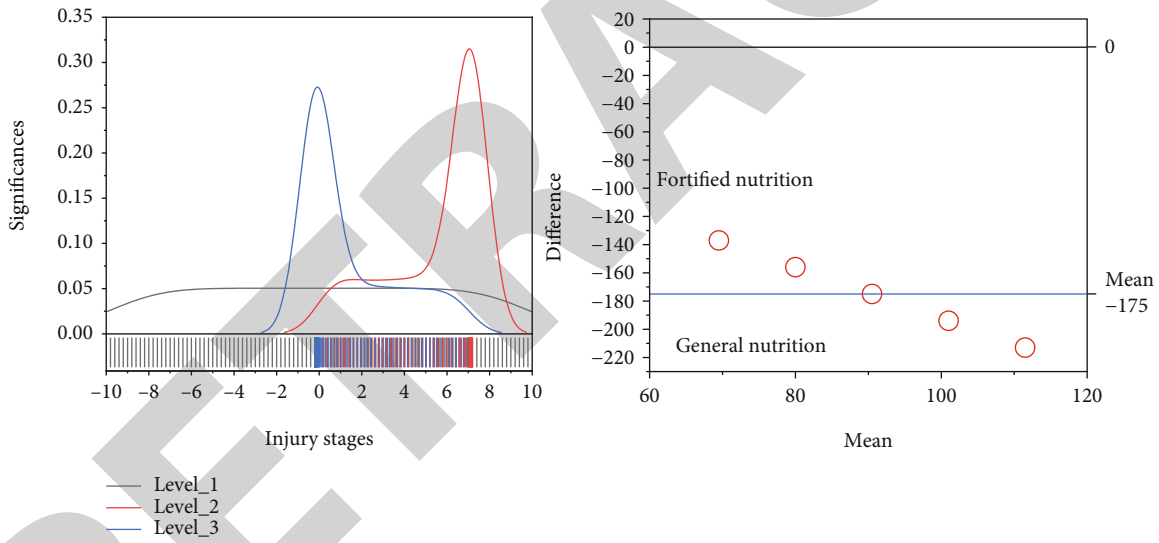

Figure 4: Forest plot of the effect of intensive versus general nutrition on total protein levels in patients with craniocerebral injury.

4. Discussion

However, heavy craniocerebral injury can cause serious impairment of consciousness, which leads to difficulties in eating and causes gastrointestinal digestive disorders, resulting in insufficient nutritional intake of the body, which hinders the recovery of the body state. Studies have shown that early enteral nutrition support for patients with severe craniocerebral injury can improve immunity and promote recovery of trauma and neurological function. It has also been shown that fortified nutrition can be a better way to provide adequate nutrition for patients with heavy craniocerebral injury. The use of fortified nutrition combined with early enteral nutrition support for patients with heavy craniocerebral injury can effectively improve the postoperative nutritional status of the body, enhance nutritional support, and have significant effects on the recovery of patients. Depending on the starting dose, the starting small-dose group (starting dose < 30 mL/h) and the starting high-dose group (starting dose ≥ 30 mL/h) were divided. Subgroup analysis showed that the starting high-dose intensive nutritional support was more effective than the starting low-dose intervention in terms of total protein levels (WMD: 2.67 vs. 1.29), IgA (SMD: 0.59 vs. 0.39), IgG (SMD: 0.99 vs. 0.69), and CD4/CD8 (SMD: 0.45 vs. 0.43).

Therefore, in the evaluation of postoperative recovery of patients with severe craniocerebral injury who have implemented intensive nutrition, the assessment of immune indicators is an essential part, which can visually present the postoperative recovery of patients, and we also found that

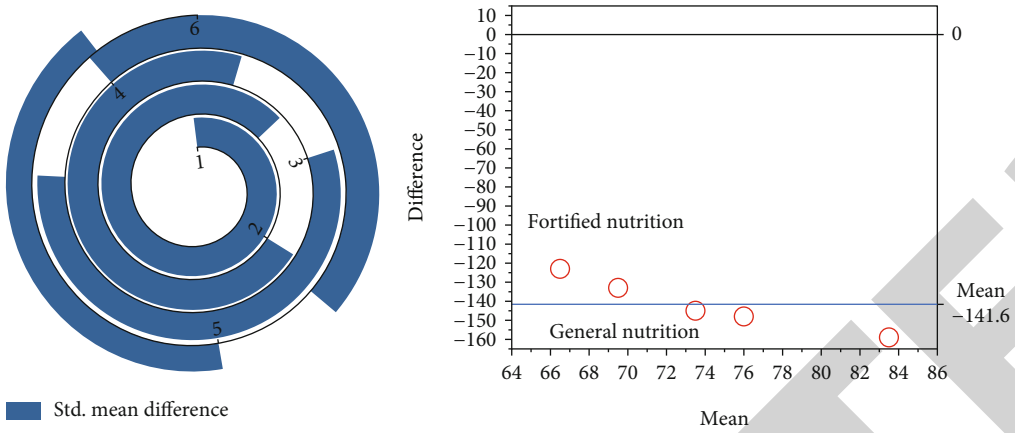

Figure 5: Forest plot of the effect of intensive versus general nutrition on IgA levels in patients with craniocerebral injury.

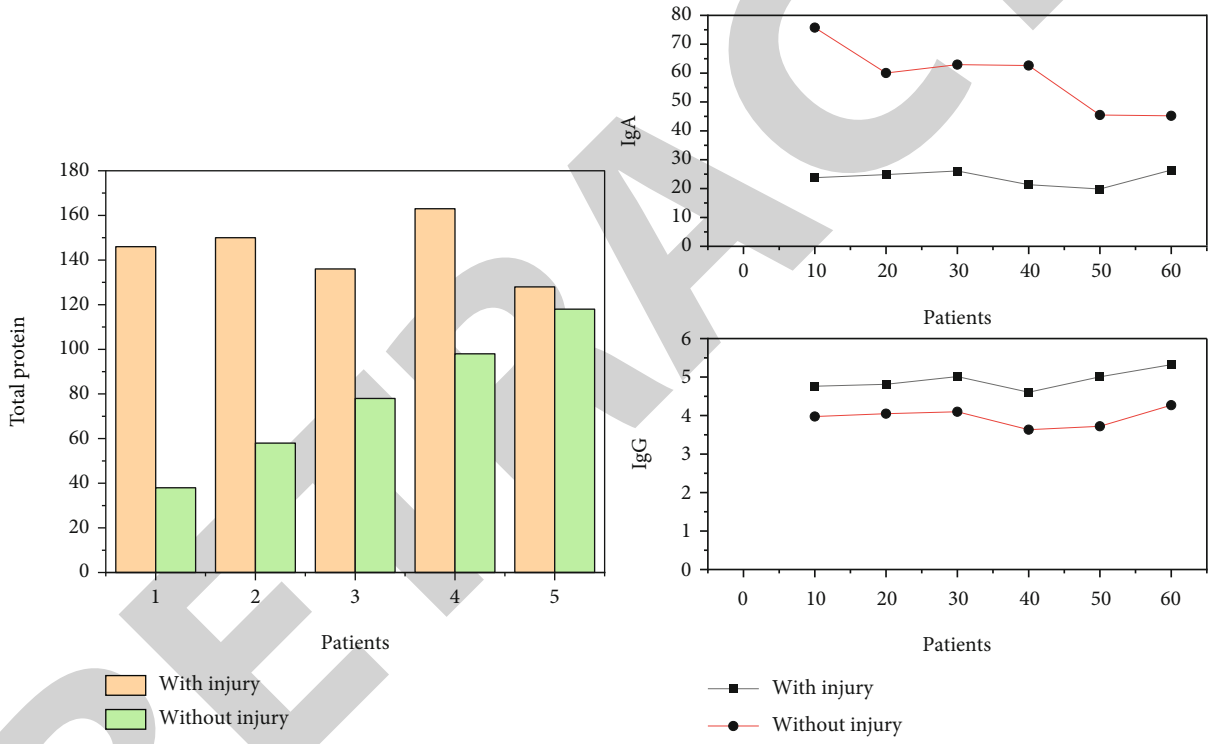

Figure 6: Subgroup analysis of the effect of fortified versus regular nutrition at different starting times on the outcome of patients with craniocerebral injury.

early enteral nutrition implemented with intensive nutrition did recover faster than patients who did not implement intensive nutrition. Therefore, it can be shown that fortification has advantages in improving the nutritional status and promoting the recovery of immune function in patients with severe craniocerebral injury. It also indicates that enteral nutrition with fortification can be an important adjunct to the treatment of patients with severe craniocerebral injury. The results of the analysis showed that the morbidity and mortality rate and infection rate of the intensive nutrition group were significantly lower than those of the general nutrition group, with the morbidity and mortality rate $P = 0.002$ and the infection rate $P < 0.001$, both of which were statistically significant, as shown in Figure 7. Heavy craniocerebral injury is caused by violence or indirect violence leading to extensive skull fracture and brainstem injury in patients, and the treatment of heavy craniocerebral injury is also one of the difficult problems in neurosurgery, with high morbidity and mortality and disability rates. Intensive enteral nutrition can effectively improve the immune function of patients with heavy craniocerebral injury, thus reducing the morbidity and mortality rate and infection rate and promoting the recovery of patients.

The number of patients with gastric retention in the fortified nutrition group was also significantly less than that in the ordinary feeding group, $P < 0.001$, as shown in Figure 8.

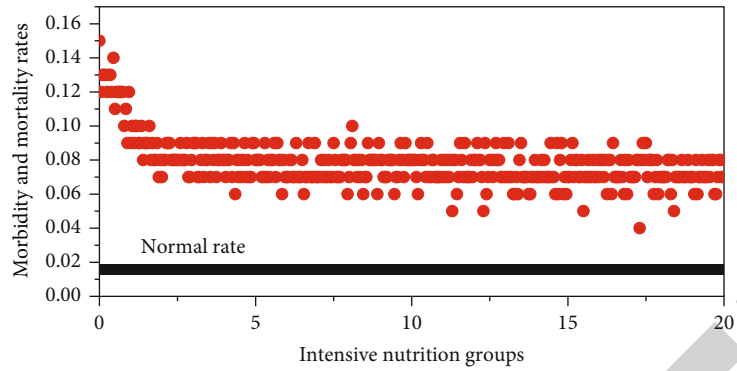

Figure 7: Morbidity and mortality rates and infection rates in the intensified nutrition group.

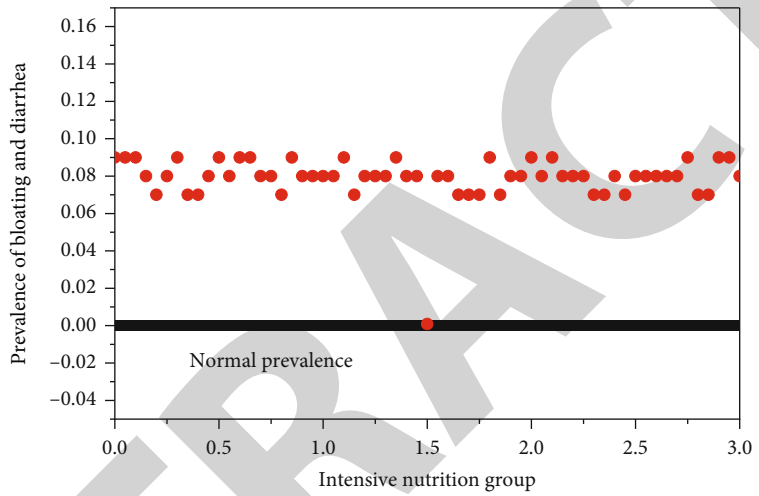

Figure 8: Prevalence of bloating and diarrhea in the intensive nutrition group.

Patients with severe craniocerebral injury can directly affect patients' feeding and nutrient digestion and absorption due to their heavy injuries, long-term bed rest can trigger malnutrition in patients, perfect and reasonable nutrition measures are crucial in the treatment process, which can better improve patients' prognosis and reduce the occurrence of postoperative complications in patients, and the implementation of intensive nutrition can effectively improve the quality of enteral nutrition care for patients with heavy craniocerebral injury. The temporal subgroup analysis provides an intuitive understanding of the temporal partitioning that allows clinical staff to more effectively use temporal cutoffs when choosing to implement fortification. In recent years, with the accumulation of clinical experience and the continuous development and improvement of neurosurgical emergency medicine, early nutritional support in heavy craniocerebral injury is more and more widely used, and it also shows significant advantages in clinical application; early nutritional support is not only beneficial to the recovery of patients' diseases but also can make heavy craniocerebral injury patients'. Because of the systemic metabolic disorder, increased energy consumption, and accelerated protein decomposition after heavy craniocerebral injury, patients have severe hypoproteinemia, which in turn accelerates the process of brain injury and increases the morbidity and mortality rate; therefore, timely and effective nutritional support is especially important.

In the subgroup analysis of starting low dose and starting high dose, the small-dose group was significantly better than the high-dose group in terms of total infection rate and intervention effect of gastrointestinal complications, while the clinical effect of immune level showed that the clinical effect of the high-dose group was better than that of the small-dose group. Patients with severe craniocerebral injury are often associated with functional impairment of the intestinal mucosa by mechanisms such as ischemia-reperfusion injury, oxidative stress, and inflammatory response mediated by inflammatory transmitters, as shown in Figure 9. Studies have concluded that different doses of intensive nutrition, both small and large doses, can favor the reduction of plasma diamine oxidase while increasing serum glutamine levels to varying degrees, thus effectively promoting intestinal mucosal repair. The 2006 European Nutrition Guidelines, 2008 Australian Nutrition Guidelines, and 2009 US Nutrition Guidelines all recommend full-dose early nutrition, but their evidence levels are all weak at the 2012 AGI guidelines (acute gastrointestinal injury), and the 2013 Canadian guidelines for nutrition in critically ill patients

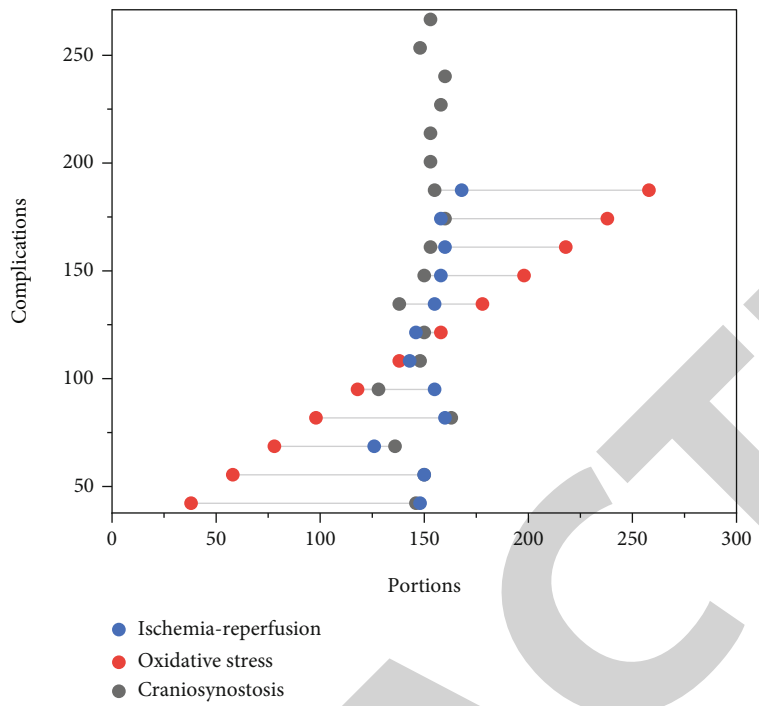

Figure 9: Analysis of complications in patients with severe craniosynostosis.

do not give clear recommendations on dose. Although there is still a large controversy regarding the dosage application for the implementation of fortification, the issue of dosage is carried far on the basis of whether to implement fortification early, but it is pointed out through multiple investigations that the advantages of small-dose fortification are greater than large-dose starting fortification. The outcome indicators of IgA, morbidity and mortality, total infection rate, and gastric retention were better in late nutrition combined with fortification than in early nutrition.

5. Conclusion

It provides a favorable evidence-based basis for clinical practice in this field. The IgA level in the intensive nutrition group was significantly higher than that in the general nutrition group (SMD = 0.79 (0.51-1.07), $P < 0.001$); the IgG level in the intensive nutrition group was higher than that in the general nutrition group (SMD = 0.98 (0.58-1.38), $P < 0.001$); the CD4/CD8 in the intensive nutrition patients was significantly higher than that in the general nutrition group. The combined effect size of patients was WMD = 0.33 (0.18-0.48) ($P < 0.001$); fortified nutrition significantly reduced the morbidity and mortality rate of patients with craniocerebral injury (RR = 0.45 (0.27-0.75), $P = 0.002$); the infection rate in the fortified nutrition group was significantly lower than that in the general nutrition group (RR = 0.48 (0.39-0.61), $P < 0.001$); fortification reduced the incidence of bloating and diarrhea by 55% compared to the general nutrition group (RR = 0.45 (0.35-0.58), $P < 0.001$); fortification significantly reduced the incidence of gastric retention in patients with craniocerebral injury (RR = 0.19 (0.07-0.49), $P < 0.001$). In the subgroup analysis of the three groups, it was shown that, depending on the starting time, the total protein level and IgG level were better in the early nutrition at 24 h than in the late nutrition at more than 24 h and that, depending on the starting dose, the total protein level, IgA, IgG, and CD4/CD8 were better in the intervention at more than 30 mL/h.

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 known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Retraction

Retracted: The Understanding of Vital Pulp Therapy in Permanent Teeth: A New Perspective

BioMed Research International

Received 3 October 2023; Accepted 3 October 2023; Published 4 October 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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Review Article

The Understanding of Vital Pulp Therapy in Permanent Teeth: A New Perspective

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The indications of vital pulp therapy (VPT) are expanding, which cases are suitable for VPT, and how to improve the success rate of VPT is a problem that often bothers us. The main purpose of VPT is to eliminate pulpitis by promoting the formation of reparative dentin or calcium bridge, so that it can continue to perform various physiological functions, and finally achieve the purpose of preserving pulp vitality and long-term preservation of affected teeth. Pulp capping and pulpotomy are the most common methods for VPT. The research field of VPT has attracted the attention of many scholars, who have studied it from many aspects (such as indications, material selection, operation requirements, and long-term prognosis). This article reviews the recent advances in the techniques of VPT in permanent teeth.

1. Introduction

Caries, pulpitis, periapical disease, periodontitis, and dental trauma are common diseases in stomatology. A common feature of these diseases is that they may involve pulp tissues, causing inflammation and subsequently necrosis of pulp tissues. Root canal therapy (RCT) is the most common and successful method to solve this kind of problems. Studies have shown that most teeth with sufficient root fillings and appropriate restorations are able to maintain function and health for more than 20 years [1]. However, the traditional RCT is related to several drawbacks. Some studies have shown that all RCT systems will lead to the accumulation of stress along the tooth structure. Excessive tooth tissue cutting in RCT may lead to insufficient tooth resistance, resulting in the occurrence of tooth fracture [2]. Thus, RCT is always related with a certain risk of failure.

With the development of oral materials and equipment and the deepening of basic oral research, Gutmann [3] has successively put forward the concept of minimally invasive endodontics (MIE). It is advocated to preserve healthy dentin as much as possible from the diagnosis of the teeth to the preparation of pulp holes and the enlargement and formation of root canals. At the same time, histological and microbiological studies have found that the inflammation and microbial infection of irreversible pulpitis may only exist in the local pulp tissue near the lesions and do not involve the entire pulp [4]. A few millimeters away from the infected, necrotic pulp, the pulp tissue is usually free of inflammation and bacteria [5]. The traditional concept is that once bacteria infect the pulp, the pulp tissue cannot repair itself, and the treatment requires complete removal of the pulp [6]. However, current research has found that dental pulp tissue can prevent the penetration of bacteria in dentin by producing reactive or reparative dentin [7]. Pulpitis-derived stem cells showed similar proliferative capacity and multidirectional differentiation potential as healthy dental pulp-derived stem cells [8], suggesting that pulp in irreversible pulpitis can be properly retained and should not be completely removed.

Recently, according to the concept of the MIE, some scholars suggested that the mature permanent teeth with

pulp exposure and irreversible pulpitis should be treated with less invasive VPT, a feasible advantage alternative to traditional pulp therapy [9]. The concept of vital pulp preservation is beneficial to simplify clinical operation and long-term retention of the teeth, which will become the trend of pulp treatment in the future. Especially due to the fact that vitality is a crucial predictor for tooth preservation, therapeutic procedures keeping the teeth vital appear contemporary. Many recent studies including some controlled studies have showed that young or mature permanent teeth clinically diagnosed with reversible or irreversible pulpitis could be successfully treated with VPT (Tables 1 and 2).

In clinical practice, VPT can generally be divided into indirect pulp capping, direct pulp capping, and pulpotomy, among which pulpotomy can be further divided into partial pulpotomy and total pulpotomy, which are applied differently in different age stages. This narrative review article will summarize the current evidence on these therapeutic procedures and derives practical consequences based on the available literature.

2. VPT of Young Permanent Teeth

Young permanent teeth refer to permanent teeth that have erupted but have not yet established occlusal relationship and have not been fully formed and mature in morphology and structure. Their characteristics include short clinical crown, wide pulp cavity, thin tooth hard tissue, short root, and trumpet-shaped apical foramen. Generally, within first 3-5 years after the eruption of permanent teeth, the root can be gradually developed and completed [10, 11]. During this period, various factors, such as caries, developmental deformity, and trauma, may cause pulp lesions or even pulp necrosis and spread to surrounding tissues. After pulp necrosis, the root development cannot continue in physiological manner [12]. Because the apical orifice is open, the conventional RCT cannot tightly seal the lumen, so it is not suitable for the control of the infection. In addition, due to the thin root canal wall and poor resistance, the tooth became easier to fracture [13]. Therefore, the research on endodontics of young permanent teeth has attached more importance in recent years.

Compared with developed permanent teeth, the pulp tissue of young permanent teeth has the characteristics of rich blood supply and high cell composition, which makes its regeneration and repair ability stronger. Therefore, the remaining pulp after VPT can promote the physiological development of apical foramen of young permanent teeth [14].

VPT for young permanent teeth include indirect pulp capping, direct pulp capping, partial pulpotomy, and total pulpotomy. Among them, indirect pulp capping and direct pulp capping preserve the complete pulp and have a more positive effect on tooth development, while partial pulpotomy and total pulpotomy belong to partial pulp preservation.

2.1. Indirect Pulp Capping of Young Permanent Teeth. Indirect pulp capping is a routine treatment for deep dentin caries in young permanent teeth. The traditional indirect pulp capping of young permanent teeth using calcium hydroxide preparation, Dycal, showed a high success rate ranging between 77.78% and 93% [15–17]. For deep caries of young permanent teeth, the effect of two-step indirect pulp capping is superior against one step [18]. In recent years, with the emergence of new technologies, the one-step method has also been widely used, and bioceramic materials have also been affirmed in many studies on indirect pulp capping of young permanent teeth [19]. Radiographic and clinical results of TheraCal and Biodentine also suggest that they can be used as alternative materials for IPT in young permanent teeth [17], with a success rate of approximately 95.83%. Recently, Sharma et al. have found that the use of Biodentine combined with laser has an additional effect on the formation of tertiary dentin. The antibacterial laser can penetrate dentinal tubules and accelerate the formation of dentin bridges in deep caries lesions [20].

2.2. Direct Pulp Capping of Young Permanent Teeth. For direct pulp capping of young permanent teeth, it is currently believed that the effect of bioceramic material as pulp capping material is excellent, and its performance is better than that of traditional pulp capping material calcium hydroxide (CH). The success rate of calcium hydroxide ranged from 70% to 100% [21], while the success rate of bioceramic materials was significantly higher than that of CH, with a success rate ranging between 92.6% and 100% [22–24]. This suggests that both mineral trioxide aggregate (MTA) and Biodentine are viable substitutes for CH, and the use of bioceramic materials can significantly improve the success rate of treatment. Among them, Biodentine has the advantage of not causing tooth discoloration and has better development prospects [25]. Due to the use of bioceramic materials, the indications for the diameter of pulp exposure for direct pulp capping of young permanent teeth can also be relaxed appropriately. This result is not only related to the selection of materials, but the selection of cases also has an impact on the results of the study; some studies have shown that the success rate of cases with mechanical pulp exposure is higher than that of caries-derived pulp exposure [26]. A good crown closure also helps to improve the success rate [27].

2.3. Pulpotomy of Young Permanent Teeth. The cellular component of the coronal pulp tissue of young permanent teeth is richer than that of the root pulp tissue, while the fibrous tissue is on the contrary; moreover, the coronal pulp tissue is less than the root pulp tissue [28]. Therefore, in terms of histology, partial pulpotomy has the least impact on the development of young permanent teeth, and the prognosis is better. Relevant clinical studies have also confirmed this [29–32]. Related research on bioceramic materials is also available, whereby most studies show the excellent prospects of new bioceramic materials in pulpotomy treatment [33–37]. Some studies have used Biodentine, MTA, and CH to perform partial pulpotomy in terms of caries treatment of immature permanent molars. All three showed a high success rate [31, 38]. There are also some studies showing that pulp preservation of young permanent teeth may

Table 1: Success rate of different therapeutic strategies in young permanent teeth. CE: carious exposure; TE: trauma exposure.

	Etiology	CH		MTA		Biodentine	
		Follow-up	Success rate (%)	Follow-up	Success rate (%)	Follow-up	Success rate (%)
Indirect pulp therapy	CE	16 months [15]	91.66%			16 months [15]	95.83%
		24 months [17]	77.78%			24 months [17]	94.44%
Direct pulp capping	CE	12 months [24]	86.36%	12 months [24]	86.36%	12 months [24]	100%
		7 years [103]	76.4%	12 months [104]	100%	12 months [104]	100%
				18.9 ± 12.9 months [102]	92.6%	18.9 ± 12.9 months [102]	96.4%
Pulpotomy	CE	24 months [30]	95%	24 Months [30]	94.4%		
		12 months [38]	96%	28.2 ± 2.7 months [37]	84.5%	1 years [46]	95%
		12 months [38]	97%	1 years [42]	91%		
	TE	1-2 years [105]	92.4%	35.1 months [106]	85.1%	18 months [107]	80%
						15 months [36]	91%
		2 years [108]	82.9%	18 months [109]	100%	18 months [107]	80%

Table 2: Success rate of different therapeutic strategies in mature permanent teeth. CE: carious exposure; TE: trauma exposure.

		CH		MTA		Biodentine	
Therapy	Etiology	Follow-up or study	Success rate (%)	Follow-up or study	Success rate (%)	Follow-up or study	Success rate (%)
Indirect pulp therapy	CE	1 years [60]	96.8%	2 years [61]	96.01%		
		2 years [61]	91.7%				
Direct pulp capping	CE	1.5 years [90]	83.3%	12-27 months [90]	56.2%	1.5 years [90]	92.3%
		5 and 10 years [90]	37% at 5 years 13 at 10 years	3.6 years [90]	91.3%	1-1.5 years [90]	82.6%
		13 years [90]	31.9%	1.5 years [90]	84.6%	6 months [67]	96%
		3 years [68]	52%	3 years [68]	85%	1 years	86%
		6 months [67]	74%	6 months [67]	91%	2-3 years	86%
		1 years	65%	1 years	86%		
		2-3 years	59%	2-3 years	84% 81%	3 years [25]	91.7%
		4-5 years	56%	4-5 years			
				3 years [25]	96%		
	TE	Matoug-Elwerfelli, M	79.4%-100% [110]	Matoug-Elwerfelli, M	80%-100% [110]	Matoug-Elwerfelli, M	80%-91% [110]
Pulpotomy	CE	5 years [90]	65%	24-42 months [90]	100%		100% clinical
		1-4 years [90]	91.6%	25 ± 14 months [90]	90%	1 years [90]	
		14-72 months [90]	92.3%	3 years [90]	92.7%		98.4% radio
		14-88 months [90]	65%	1.5 years [90]	84.6%		
	TE	1-2 years [105]	94.1%				

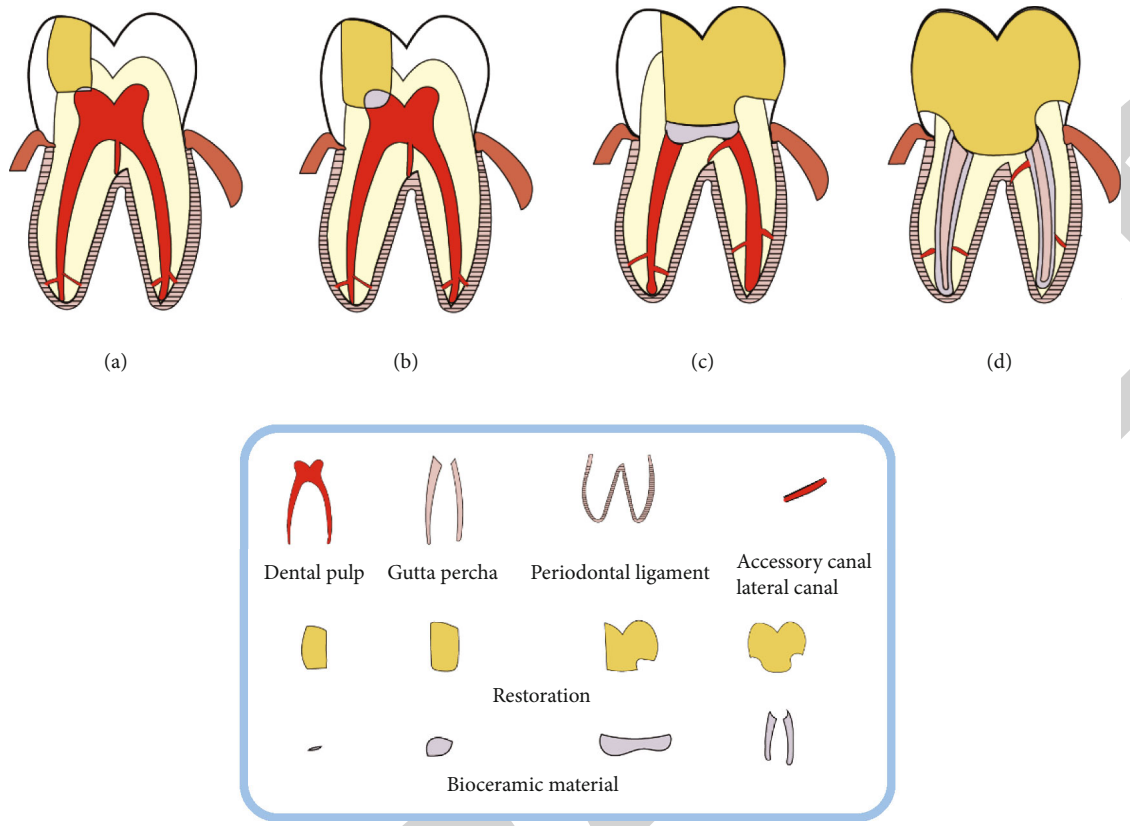

Figure 1: Schematic diagram of application of VPT. (a) Direct pulp capping, (b) partial pulpotomy, (c) total pulpotomy, and (d) root canal therapy.

have broader indications. For the indication of pulpotomy, the size of the pulp exposure, the time, and the location of pulp exposure, whether it is irreversible pulp inflammation and even periapical periodontitis, are not necessarily related [39–46]. It is suggested that the status and repairing ability of the pulp have more important significance in the prognosis of pulpotomy [47].

2.4. Pulp Regeneration of Young Permanent Teeth. In recent years, research on dental pulp regeneration has attracted the attention of many scholars. There are three methods used in clinical cases of young permanent teeth, namely, dental pulp revascularization, dental pulp stem cell (DPSC) transplantation, and deciduous tooth pulp autotransplantation.

As a relatively new and popular treatment method, pulp revascularization is mainly used to treat pulp necrosis of young permanent teeth with open apices. In 2017, a meta-analysis [48] compared the effects of regenerative pulp treatment based on pulp revascularization technology with MTA apical sealing. The results showed that the success rate of regenerative pulp treatment group was 91.3% ("success" is defined as clinically asymptomatic, radiographic complete healing of apical lesions) and that of MTA apical sealing group was 94.6%. There was no significant difference in tooth survival and success rate between the two groups, but 79% of the cases in the regenerative pulp treatment group continued to develop, indicating that pulp revascularization may be a more advantageous treatment scheme. Some scholars used Biodentine and MTA to compare the clinical and imaging effects of pulp revascularization of young permanent teeth and found that there was no significant difference between them [49]. Peng et al. [50] compared 60 young permanent teeth with pulp necrosis with MTA and glass ionomer cement (GIC). The results showed that MTA was better than GIC. MTA, as a common crown sealing material for pulp revascularization [51], has obvious therapeutic effect but can lead to crown discoloration [52]. With the emergence of new materials such as iRoot BP, Biodentine, and other bioceramic materials, it has been reported that using Biodentine as crown sealing material does not cause obvious crown discoloration [53], which provides more material options for avoiding complications after pulp revascularization.

There is one clinical study on the use of DPSC transplantation in the treatment of pulp regeneration in young permanent teeth. In 2018, Xuan et al. [54] recruited 40 young patients with posttraumatic dental pulp necrosis. After autologous DPSC implantation, the three-dimensional dental pulp tissue with blood vessels and sensory nerves was regenerated. No adverse events were observed after 24 months of follow-up. At present, there are few relevant studies on stem cell transplantation, and the number of cases is small, so more in-depth research is needed.

Cehreli et al. [55] recruited 4 patients aged 8-11.5 years, and five previously traumatized maxillary incisors were treated with a regenerative endodontic treatment protocol

that used 2.5% NaOCl irrigation and placement of calcium hydroxide dressing in the first visit. After 4 weeks, the intracanal medication was removed, and the whole pulp tissue harvested from the neighboring maxillary deciduous canine was transplanted into the disinfected root canal without induced apical bleeding. Following placement of a MTA coronal barrier, the access cavities were restored with acid-etch resin composite. Three patients were followed-up for 24 months and 1 patient for 12 months. All teeth demonstrated radiographic evidence of complete periapical healing, slight increase in dentinal wall thickness, and continued apical closure in the absence of clinical symptoms. A positive response to cold test was obtained in 1 incisor at 12 months and 2 at 24 months. At present, there is few research on the treatment of pulp necrosis of young permanent teeth by autologous pulp transplantation, and more in-depth studies are needed.

3. VPT of Mature Permanent Teeth

For the vital pulp preservation of mature permanent teeth, the previous concept believed that the dental pulp tissue is located in the hard tissue of the tooth, which is only connected with the outside world through the narrow apical foramen, lacks collateral circulation, and has a weak ability to resist infection. Therefore, the indications for the VPT of mature permanent teeth are limited to a very small range, which will be carefully selected in clinical practice, and RCT will be selected in majority of cases [56]. However, the research on pulp preservation of irreversible pulpitis in mature permanent teeth has also received continuous attention of many scholars. In the early days, it was reported that the irreversible pulpitis of mature permanent teeth can save parts of the pulp through pulpotomy with an appropriate clinical effect [57]. Afterwards, related research results have confirmed that for irreversible pulpitis of mature permanent teeth, as long as the diseased tissue is completely removed and appropriate pulp capping materials are selected, the remaining pulp tissue is likely to have a good prognosis [58, 59]. This points out on the direction for the further study of irreversible pulpitis in mature permanent teeth.

3.1. Indirect Pulp Capping of Mature Permanent Teeth. In the indirect pulp capping of mature permanent teeth, the overall success rate is relatively high. In the research on the indirect pulp capping of mature permanent teeth, whether partial caries removal or complete caries removal, the 12-month follow-up found that the indirect pulp capping can achieve a high success rate of 96%, which has no obvious relationship with the pulp capping agent used [60, 61]. Therefore, for the affected teeth without symptoms and signs of pulpitis before operation, the exposure of dental pulp tissue should be avoided as much as possible during operation [62].

3.2. Direct Pulp Capping of Mature Permanent Teeth. Traditional direct pulp capping can only be used for the small area of noncaries exposed pulp, and CH is used as the gold standard. With the application of bioceramic materials and the improvement of treatment level, the indications of direct pulp capping of mature permanent teeth have expanded, and the diameter of the perforating hole has gradually expanded to more than 1 mm. A number of studies performed direct pulp capping on the teeth with pulp exposure >1 mm, all of which showed the formation of dentin bridges, and the bioceramic material group was significantly better than the CH group [63–66]. More results show that CH as a pulp capping agent will lead to uncertain treatment results and reduce the long-term success rate [67, 68]. The research shows that the success rate of CH in 2-3 years is 52%-59%, while the success rate of bioceramic materials in 2-3 years is 85%-93.8% [25, 67]. To analyze the reasons, on the one hand, different biomaterials have different effects; on the other hand, the health status of exposed pulp is different, and the success rate of direct pulp capping of affected teeth in different age groups is significantly different. A study of 148,312 affected teeth showed a higher success rate in the "<18" age group compared to an overall success rate of 71.6% [69]. Another study also showed that participants under the age of 40 years were 1.23 times more likely to be successfully treated than those 40 years or older [70]. As a promising new capping agent, compared to MTA, Biodentine has the advantages of better sealing, faster coagulation, and no staining [71]. Recently, a new type of injectable-treated dentin matrix hydrogel (TDMH) has emerged, providing clinicians with a wider range of choices. Experiments demonstrate that TDMH has a greater potential to induce dentin bridge formation than Biodentine and MTA under standardized conditions [72, 73]. In addition to this, photoactivated disinfection exhibits a synergistic effect when used in combination with these materials [74, 75].

3.3. Pulpotomy of Mature Permanent Teeth. In the traditional treatment, pulpotomy is generally used for deciduous teeth. In recent years, this topic gained clinical interest, as an early case report of pulpotomy for deep caries exposed mature permanent teeth [57]. Later, more scholars began to study related content [76, 77]. For teeth with deep caries exposed pulp rather than irreversible pulpitis, partial pulpotomy is effective [38], while for teeth with irreversible pulpitis, total pulpotomy has a higher success rate [59, 78–80]. In 2021, a review analyzed the treatment results of total pulpotomy and partial pulpotomy in recent years. It was concluded that the clinical and radiographic success rates of total pulpotomy for mature permanent teeth were between 92.2% and 99.4%, while the success rates of partial pulpotomy were between 78.2% and 80.6% [81]. This suggests that the complete removal of infected tissue may be an important factor affecting pulpotomy of mature permanent teeth. A meta-analysis published by the Air Force Medical University in 2019 [82], the review published by Taha et al. in 2020 [71]and a number of clinical studies [83–86]also confirmed from different aspects that pulpotomy is a recommended treatment for deep caries exposed pulp of mature permanent teeth or even irreversible pulpitis, which can be used as an alternative to RCT [87–90]. In addition, some studies have combined total pulpotomy and nonsurgical endodontic (NSET) for mature mandibular permanent molars

diagnosed as irreversible pulpitis and apical periodontitis and achieved good results. This suggests that the combination of NSET and total pulpotomy is a feasible minimally invasive treatment for multiple mandibular teeth with irreversible pulpitis and apical periodontitis [91].

3.4. Pulpectomy of Mature Permanent Teeth. If the root pulp of the affected tooth is also infected, the clinical treatment plan should consider pulpectomy. However, due to the limitations of current technology and the complexity of the root canal system [92, 93], some bacteria in the lateral and accessory root canals cannot be eliminated completely, resulting in the failure of short-term root canal treatment [94, 95]. Therefore, how to deal with the pulp tissue in the lateral and accessory root canals has become a problem that clinicians need to consider. A study by Ricucci found that even in dead pulp teeth, living pulp tissue often exists in the lateral canals and apical ramifications. Forcing the packing material into the lateral root canal will cause unnecessary damage to the tissue and thus cause inflammation. The protection of the remaining living pulp tissue is conducive to the success of the treatment [96], suggesting that the content of VPT should not only consider the preservation of crown pulp and root pulp, but also the preservation of living pulp in the lateral canals and apical ramifications during pulpectomy. The tissues in the lateral canals and apical ramifications are as important as the dental pulp in the main root canal.

3.5. Pulp Regeneration of Mature Permanent Teeth. A few scientific research teams reported the follow-up records of pulp revascularization technology for mature permanent teeth [97–99], which showed good treatment effect, manifested in the disappearance or improvement of clinical symptoms and imaging lesions, but the overall treatment effect was worse than that of young permanent teeth. Due to the small number of cases and short research time, robust conclusion requires further research in the field.

Currently, there are two clinical case studies on pulp regeneration of mature permanent teeth. In 2017, Nakashima et al. [100] recruited 5 patients with irreversible pulpitis, expanded the mobilized DPSC mobilized by granulocyte colony-stimulating factor (G-CSF) in vitro, and then transplanted it into the root canal of pulpectomy together with G-CSF to form functional dentin. The report showed no adverse events or toxic reactions. To some extent, it proves the safety of autologous stem cell transplantation. However, in general, the number of cases in this study is small, the observation and follow-up time is short, and the long-term reliability needs further follow-up. In 2021, Feitosa et al. [101] reported a new method of autologous pulp transplantation that can be used for pulp regeneration in affected teeth. Three patients who need single premolar root canal treatment were selected for routine root canal preparation, and the root canal was rinsed with tri-antibiotic solution (ciprofloxacin, minocycline, and metronidazole). The dental pulp tissue of the third molar was carefully removed and put into the new root canal a few minutes before the transplantation operation, followed by coronal sealing. After 12 months of follow-up, Doppler imaging showed that all teeth were revascularized, tooth vitality was restored, and there were no signs of endodontic/periodontal radiolucency or complications. This method may be a potential new way of pulp regeneration treatment.

4. Summary and Conclusions

Nowadays, with the increasing awareness of minimally invasive therapy, the treatment of pulpitis must be newly evaluated with regard to long-term prognosis and tooth preservation. Not only the minimally invasive treatment of hard tissue, but also the preservation of pulp tissue is of great significance to the long-term retention of teeth. The preservation treatment of pulp tissue runs through all stages of endodontic treatment. In any case, the choice of treatment methods and materials must consider the need to promote the restoration of the remaining tissue.

With the emergence of bioceramic materials, the treatment level of pulpitis has been improved, and the indications of direct pulp capping have been gradually expanded. The requirements of direct pulp capping are no longer limited to 0.5 mm. Especially in young permanent teeth, direct pulp capping has been performed on affected teeth with pulp exposure up to 2.5 mm, showing good results [102]. Bleeding control within 10 minutes is an effective criterion for choosing direct pulp capping or pulpotomy for deeply carious exposed teeth [63, 68]. Less invasive, cost-effective, simple, and less time-consuming for patients and dentists, pulpotomy offers a new treatment modality for irreversible pulpitis.

In this paper, the available literature was reviewed, and it was found that some studies showed that the success rate of indirect pulp capping of young permanent teeth was lower than that of direct pulp capping. The possible reasons are as follows: (1) there are few studies related to indirect pulp capping of young permanent teeth, so the data is less representative; (2) it may be related to the selection of cases; different research centers have different inclusion criteria for cases; (3) It also suggests that the judgment of the pulp status of young permanent teeth is complicated and difficult. The pulp tissue of young permanent teeth is loose, the apical foramen is large, the blood supply is abundant, and the infection is easy to spread. Therefore, the relatively conservative indirect pulp capping in some cases is not effective.

Based on the findings of this narrative review, the following recommendations can be made for clinical practice: In the treatment of pulpitis, whether young permanent teeth or mature permanent teeth, VPT should be attempted as the first choice whenever possible. The requirements for VPT include (1) removal of infected tissue; (2) the hard tissue of the wound is complete without detritus; (3) the color and texture of the remaining pulp tissue were normal, and the bleeding could be controlled within 10 minutes. In the case of pulpectomy, the preservation of pulp tissue in the lateral root canal and accessory canal should also be one of the core problems in the process of root canal treatment. Bioceramic materials can improve the success rate of VPT, and it is recommended to use bioceramic materials as much

as possible in the treatment of endodontic diseases (Figure 1).

At present, there are still many problems to be solved in the research of clinical pulp preservation. Firstly, the classification method of simply dividing pulpitis into reversible pulpitis and irreversible pulpitis is no longer suitable for the actual situation of clinical treatment. The description of pulpitis according to the patient's age and infection range may be more in line with the actual needs of treatment; secondly, more effective methods are needed to judge the pulp state in the process of treatment, and more research results are needed for the selection of operation methods; thirdly, bioceramic materials are expected to have richer functions, so as to expand the indications and improve the success rate; finally, it is necessary to conduct large-scaled prospective randomized clinical trials to verify and define appropriate clinical guidelines.

Abbreviations

RCT: Root canal therapy
MIE: Minimally invasive endodontics
VPT: Vital pulp therapy
CH: Calcium hydroxide
MTA: Mineral trioxide aggregate
GIC: Glass ionomer cement
DPSC: Dental pulp stem cell
TDMH: Treated dentin matrix hydrogel
NSET: Nonsurgical endodontic
G-CSF: Granulocyte colony-stimulating factor.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

All listed authors meet the ICMJE criteria and all who meet the four criteria are identified as authors. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE. Wei Shang (171847002@masu.edu.cn) contributed as the first and co-corresponding author. Wei Shang conducted the systematic review, analyzed and interpreted the results, and wrote the manuscript, as well as supervised and administered the research project. Zeliang Zhang, Xicong Zhao, Qingquan Dong, Gerhard Schmalz, and Shaonan Hu edited and reviewed the manuscript. Gerhard Schmalz (Gerhard.Schmalz@medizin.uni-leipzig.de) contributed as the senior author. Wei Shang and Shaonan Hu (shaonan.hu@xs.ustb.edu.cn) contributed equally as the corresponding author. Wei Shang, Gerhard Schmalz, and Shaonan Hu supervised and administered the research project. All authors read and approved the final manuscript.

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Retraction

Retracted: Zonisamide's Efficacy and Safety on Parkinson's Disease and Dementia with Lewy Bodies: A Meta-Analysis and Systematic Review

BioMed Research International

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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) Manipulated or compromised peer review

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. Kong, J. Xi, Z. Jiang, X. Yu, H. Liu, and Z. Wang, "Zonisamide's Efficacy and Safety on Parkinson's Disease and Dementia with Lewy Bodies: A Meta-Analysis and Systematic Review," *BioMed Research International*, vol. 2022, Article ID 4817488, 17 pages, 2022.

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Review Article

Zonisamide's Efficacy and Safety on Parkinson's Disease and Dementia with Lewy Bodies: A Meta-Analysis and Systematic Review

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Objective. Clinical data has recently shown an association between Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and zonisamide. The purpose of this study was to thoroughly evaluate the efficacy and safety of zonisamide in PD and DLB. *Methods*.Pubmed, the Cochrane Library, Web of Science, and Embase databases were searched for all randomized clinical trials (RCTS) on the role of zonisamide in PD and DLB that were completed by April 18, 2022. UPDRS II (off) total score, UPDRS III total score, Daily "off" time, and UPDRS Part IV, Nos. 32, 33, and 34 were used as clinical efficacy endpoints. Adverse events reported in the RCTs will be considered in the final safety analysis. To better understand the effect of zonisamide on the efficacy and safety of PD and DLB, the UPDRS III total score and the six overlapping adverse events were examined in subgroups. Either a fixed effects model analysis (OR) or a random effects model analysis (MD) is used to figure out the mean difference (MD) and the relative risk. *Results*. Seven articles involving 1749 patients (916 PD and 833 DLB) were included in this study. Compared to the control group, zonisamide could significantly reduce the UPDRS III total score in patients with PD and DLB (WMD-2.27 [95% CI: -3.06, -1.48], $p < 0.0001$). For patients with PD, compared to the control group, zonisamide could significantly reduce the UPDRS II (off) total score (WMD-0.81 [95% CI: -1.36, -0.26], $p = 0.004$), daily "off" time (WMD-0.67 [95% CI: -1.10, 0.24], $p = 0.002$), and UPDRS part IV, No. 32 worsen (OR-3.48 [95% CI: 1.20, 10.10], $p = 0.02$). In terms of safety, compared with the control group, for patients with DLB, zonisamide could significantly increase the incidence of contusion (OR-0.60 [95% CI: 0.38, 0.96], $p = 0.03$) and may increase the probability of reduced appetite (OR-3.13 [95% CI: 1.61, 6.08], $p = 0.0008$). And for patients with PD, zonisamide may increase the probability of somnolence (OR-2.17 [95% CI: 1.25, 3.76], $p = 0.006$). *Conclusions*. For the analysis of the current study results, our results show that zonisamide could improve the motor function in patients with PD and DLB and improve the activities of daily living (off) and wearing off and decrease the duration of dyskinesia in patients with PD. In terms of safety, the use of zonisamide significantly increases the probability of contusion in patients with DLB and may increase the probability of reduced appetite in patients with DLB and somnolence in patients with PD. Zonisamide appears to be a new treatment option for patients with PD and DLB. However, the effectiveness and safety of zonisamide in the treatment of PD and DLB need to be further investigated.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with a prevalence of 0.3-1.0% in the general population and about 1-3% in people aged > 60 years [1–3]. The core feature of clinical PD is motor syndrome, defined as bradykinesia, in combination with either rest tremor, rigidity, or both [4]. Due to the growing population's aging, both the prevalence and incidence of PD are expected to rise by at least 30% by 2030, which will place

additional strain on society and the global economy [5]. Dementia with Lewy bodies (DLB) is the second most common form of dementia after Alzheimer's disease, accounting for 10–20% of all dementia cases [6, 7]. The central feature of DLB is progressive cognitive decline, with core clinical features including fluctuating cognition, recurrent visual hallucinations, rapid eye movement, sleep behavior disorder, and parkinsonism. DLB and PD belong to the same spectrum of diseases and have similar pathology, mainly in the form of a large number of alpha-synuclein-based Lewy bodies in the brain and autonomic nervous system [8, 9]. In the clinical management of PD and DLB, levodopa has been mentioned repeatedly and is particularly critical.

For PD patients, dopamine replacement therapy is currently the primary method of improving motor symptoms in Parkinson's disease, and while it helps to improve motor performance temporarily, it does not help to slow down the neurodegenerative process. In addition, the prolonged use of levodopa can lead to motor complications, including hypokinesia and dyskinesia [10], which can have severe effects on activities of daily living and quality of life [11–13]. Therefore, the improvement of wearing off without the worsening of dyskinesia is a therapeutic goal in patients with PD who experience wearing off [14], whereas for DLB patients, they usually respond less to dopaminergic treatment than PD patients. Even though some DLB patients may benefit from levodopa preparations to improve their own dyskinesia, the doses used are severely limited and do not achieve the best improvement due to concerns about worsening neuropsychiatric symptoms, including delirium and BPSD [15, 16]. Therefore, the improvement of levodopa in both PD and DLB patients is relatively limited and does not last consistently for a long period of time.

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) was discovered in Japan in 1974 as a sulphonamide with anticonvulsant properties and is widely used clinically for the treatment of partial-onset epilepsy and mixed epilepsy [17]. Zonisamide's pharmacological profile is complicated, and it has a lot of binding targets. The pharmacological mechanisms that have been confirmed so far are mainly inhibitory activities on voltage-gated sodium channels, T-type calcium channels, and MAO-B [18]. In addition, it has also been shown to have neuromodulatory effects on a variety of neurotransmitter systems, including cholinergic, serotonergic, glutamatergic, and monoaminergic systems in clinical trials [19]. The potential beneficial effects of zonisamide in relation to the nervous system have been progressively demonstrated in a variety of neurological disorders, including migraine, PD, neuropathic pain, and mood disorders [20, 21].

Initially, zonisamide showed an unexpected improvement in dyskinesia in the clinical treatment of epilepsy patients in combination with PD. Numerous clinical trials, case series, observational studies, and case reports have been published since then to support the efficacy of zonisamide in PD and DLB. Therefore, zonisamide could be a promising drug candidate for the treatment of PD and DLB. There is no comprehensive analysis of RCTs of zonisamide in PD and DLB; so, we conducted this study to investigate the efficacy and safety of zonisamide in PD and DLB.

2. Methods

2.1. Data Sources and Search Strategy. The design of this study was based on the results of a systematic review and meta-analysis (PRISMA) [22]. The protocol for this study was registered with PROSPERO [23]. We used the following databases to conduct an electronic search: Pubmed, Cochrane library, Web of science, and Embase are all available online. The following were the subject terms: "PD," "DLB," and "zonisamide." There are no restrictions on language, and the most recent search was conducted on April 18,2022.

2.2. Selection and Eligibility Criteria. Two reviewers independently screened the search results for titles, abstracts, and full text reviews, and disagreements were settled through consensus or discussion with a third independent author. RCTs on the efficacy of zonisamide in the treatment of PD and DLB are among the inclusion criteria. There were only original articles included. The following were the exclusion criteria: non-RCTs, nonhuman studies, duplicates, conference papers, meta-analyses, or systematic reviews.

2.3. Data Extraction and Outcomes. The reviewers extracted relevant data from each study independently into predesigned Excel spreadsheets, which included the following: country of origin; year of publication; and the first author; study duration; study population; intervention; number, sex, and age of participants; comorbidities; duration of PD or DLB; baseline patient data; and treatment outcomes. Among the outcomes were the UP-DRS II (activities of daily life) total score, the UPDRS III (motor function) total score, and the daily "off" time. UPDRS Part IV, No. 32 (duration of dyskinesia) includes the following: worsened, improved, no new onset, unchanged with scores ≥ 1, and new onset. UPDRS Part IV, No. 33 (disability caused by dyskinesia) includes the following: worsened, improved, no new onset, and unchanged with scores ≥ 1. UP-DRS Part IV, No. 34 (pain caused by dyskinesia) includes the following: worsened, improved, no new onset, and unchanged with scores ≥ 1. In addition, 39 adverse events were included as indicators of treatment safety outcomes. We calculated the means and standard deviations for continuous dating (MD). The data were transformed using existing formulae in the absence of a mean and standard deviation. A third reviewer resolved disagreements independently.

2.4. Statistical Analysis and Quality Assessment. Statistical analysis was performed using Review Manager 5.4. We analyzed continuous variables using standardized mean differences (SMD) and 95% confidence intervals (CI). The I^2 statistic was used to evaluate heterogeneity. I^2 values of 25%, 50%, and 75% were considered low, medium, and high heterogeneity, respectively. To summarize the data from all studies, random-effects models were used. Statistical significance was defined as P values less than 0.05. The funnel plot will be used to assess the risk of publication bias in studies.

The Cochrane Risk of Bias Assessment Tool was used to evaluate the RCT's quality, which included six criteria: randomized sequence generation, allocation concealment, patient blindness, trial participants, outcome evaluator blindness, incomplete outcome data, selective reporting, and other biases.

3. Results

3.1. Search Results. 673 studies were identified through the literature search, 112 of which were from PubMed, 60 from the Cochrane Library, 134 from the Web of Science, and 367 from Embase. After excluding 229 duplicates and reviewing 444 titles and abstracts, 435 outcomes were excluded, and the remaining 9 outcomes were reviewed in detail. A total of 7 RCTs were included in the meta-analysis, of which three RCTs were conducted on patients with DLB, and the other four RCTs were conducted on patients with PD [24–30]. The study selection process is summarized in the PRISMA flow chart in Figure 1.

3.2. Study Characteristics and Quality Assessment. Seven studies were conducted between 2007 and 2021, with a total of 1749 additional participants (in the experimental group, 1181 participants used zonisamide, while in the control group, 569 participants used a placebo). All patients were diagnosed with PD or DLB (all patients were asked to use concomitant levodopa preparations (including DCI combination drugs), and patients can continue to use other anti-Parkinson drugs such as dopamine agonists (DA), monoamine oxidase type B (MAO-B) inhibitors, amantadine or droxodopa, and anticholinergics during the study period. For patients with DLB, they were also allowed to continue using antidementia drugs during the study (specific drug type not mentioned). These concomitant doses and dosing regimens should remain stable for at least 4 weeks prior to the start of the formal study until the end of the study, and patients who are unable to follow these principles are considered to have dropped out of the final analysis. All of the studies were conducted in Japan, and the interventions lasted anywhere from 14 to 52 weeks, with the exception of the first RCTs (the earliest study), and the exclusion criteria were set for the remaining six RCTs to ensure that there was no overlap of patients in the study. According to the Cochrane Risk of Bias tool, seven RCTs were parallel-group studies and articles of generally moderate and high quality. The results of the seven RCTs' quality evaluations are summarized in Figures 2(a) and 2(b).

3.3. The Effect of Zonisamide on UPDRS III Total Score. A total of 7 RCTs reported the UPDRS III total score in 1636 patients (1094 zonisamide users and 542 nonusers). Four RCT studies included PD patients, and the other three included DLB patients. Our analysis demonstrated that zonisamide obviously reduces the UPDRS III total score among all patients compared with controls, which had statistical differences (WMD-2.27 [95% CI: -3.06,-1.48], $p < 0.00001$). There was low heterogeneity between studies ($p = 0.04$, $I^2 = 45\%$) (Figure 3(a)). In addition, our subgroup analysis showed that zonisamide significantly reduced the UPDRS III total score for both PD patients and DLB patients. And the results were all statistically significant (PD: (WMD-1.83 [95% CI: -2.53, -1.13], $p < 0.00001$) DLB: (WMD-2.09 [95% CI: -2.64, -1.53], $p < 0.00001$) (Figure 3(b)). By comparing subgroup differences, the effect of zonisamide in reducing the UPDRS III total score appears to be more pronounced in patients with DLB.

3.4. The Effect of Zonisamide on UPDRS II "Off" Total Score. A total of 3 RCTs reported the UPDRS II "off" total score in 538 PD patients (348 zonisamide users and 190 nonusers). The meta-analysis concluded that zonisamide reduced the UPDRS II "off" total score in PD patients compared to controls. There was a significant statistical difference (WMD-0.81 [95% CI: -1.36,-0.26], $p = 0.004$). There was low heterogeneity between studies ($p = 0.33$, $I^2 = 13\%$) (Figure 3(c)).

3.5. The Effect of Zonisamide on Daily "Off" Time. A total of 2 RCTs reported the daily "off" time of 614 patients (424 zonisamide users and 190 nonusers). Our study found that zonisamide significantly reduces daily "off" time in PD patients when compared to controls with statistically significant differences (WMD-0.67 [95% CI: -1.10, 0.24], $p = 0.002$). There was moderate heterogeneity between studies ($p = 0.05$, $I^2 = 57\%$), and through intragroup subgroup analysis, we observed that medium heterogeneity may be due to dose difference. (Figures 3(d) and 3(e)).

3.6. The Effect of Zonisamide on UPDRS IV, No. 32

3.6.1. Worsened. A total of 2 RCTs reported the UPDRS IV, No. 32 worsened in 285 patients (194 zonisamine users and 91 nonusers). Our study found that zonisamide significantly reduces the UPDRS IV No. 32 worsened in PD patients when compared to controls, with statistically significant differences (OR-3.48 [95% CI: 1.20, 10.10], $p = 0.02$). There was no evidence of heterogeneity between studies ($p = 0.88$, $I^2 = 0\%$) (Figure 4(a)).

3.6.2. Improved. A total of 2 RCTs reported the UPDRS IV, No. 32 improved in 285 patients (194 zonisamide users and 91 nonusers). When compared to controls, zonisamide was likely to increase the UPDRS IV, No. 32 improved in patients with PD. However, statistical diversity was limited (OR-0.92 [95% CI: 0.34, 2.55], $p = 0.88$). There was low heterogeneity between studies ($p = 0.28$, $I^2 = 22\%$) (Figure 4(b)).

3.6.3. No New Onset. A total of 1 RCTs reported UPDRS IV, No. 32 no new onset in 185 patients (122 zonisamide users and 63 nonusers). When compared to controls, zonisamide was likely to reduce the UPDRS IV, No. 32 no new onset in patients with PD. However, statistical diversity was limited (OR-0.92 [95% CI: 0.49, 1.72], $p = 0.79$). There was low heterogeneity between studies ($p = 0.29$, $I^2 = 10\%$) (Figure 4(c)).

3.6.4. Unchanged with Scores ≥ 1. A total of one RCTs reported UPDRS, IV No. 32 unchanged with scores ≥ 1 in

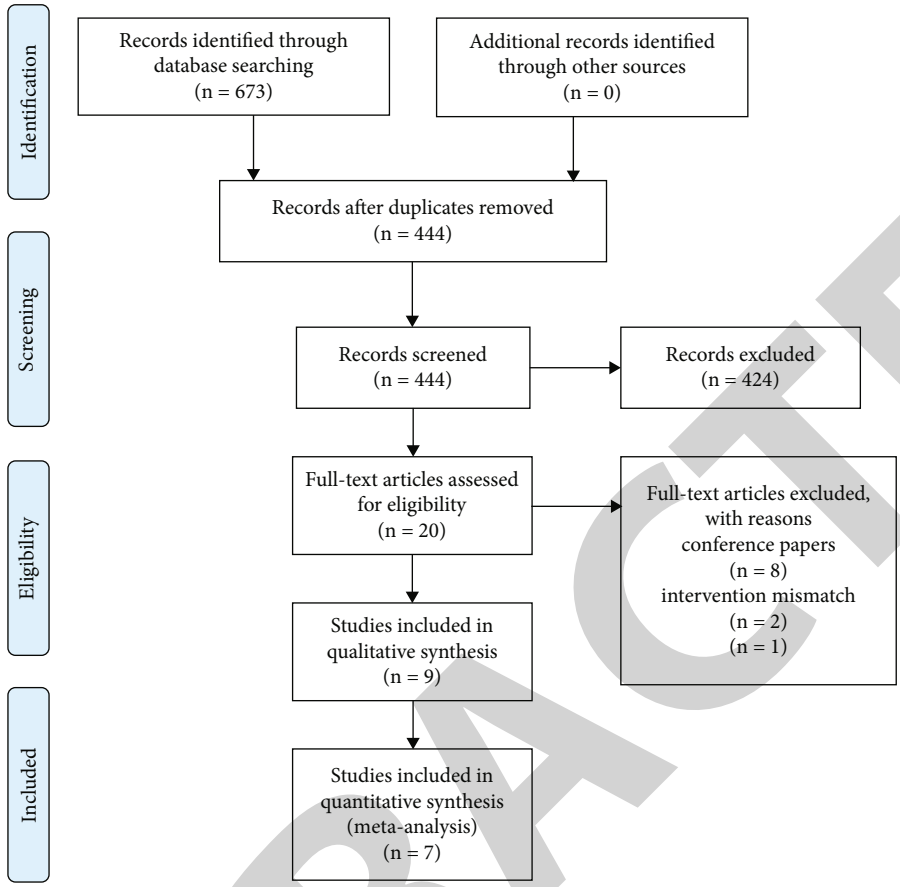


Figure 1: PRISMA flow chart.

185 patients (122 zonisamine users and 63 nonusers). When compared to controls, zonisamide was likely to increase the UPDRS, IV No. 32 unchanged with scores ≥ 1 in patients with PD. However, statistical diversity was limited (OR-0.98 [95% CI: 0.51, 1.90], $p = 0.96$). There was no evidence of heterogeneity between studies ($p = 0.61$, $I^2 = 0\%$) (Figure 4(d)).

3.6.5. New Onset. A total of 1 RCTs reported UPDRS IV, No. 32 new onset in 185 patients (122 zonisamide users and 63 nonusers). When compared to controls, zonisamide was likely to increase the UPDRS IV, No. 32 new onset in patients with PD. However, statistical diversity was limited (OR-4.16 [95% CI: 0.45, 38.14], $p = 0.21$). There was no evidence of heterogeneity between studies ($p = 0.82$, $I^2 = 0\%$) (Figure 4(e)).

3.7. The Effect of Zonisamide on UPDRS IV, No. 33

3.7.1. Worsened. A total of 2 RCTs reported the UPDRS IV, No. 33 worsened in 424 patients (278 zonisamine users and 146 nonusers). The effect of zonisamine on UPDRS IV, No. 33 worsened was not statistically significant when compared to the control group (OR-0.50 [95% CI: 0.21, 1.20], $p = 0.12$). There was no evidence of heterogeneity between studies ($p = 0.43$, $I^2 = 0\%$) (Figure 5(a)).

3.7.2. Improved. A total of 2 RCTs reported the UPDRS IV, No. 33 improved in 424 patients (278 zonisamine users and 146 nonusers). The effect of zonisamine on UPDRS IV, No. 33 improved was not statistically significant when compared to the control group (OR-1.60 [95% CI: 0.78, 3.28], $p = 0.2$). There was no evidence of heterogeneity between studies (Figure 5(b)).

3.7.3. Unchanged with Scores ≥ 1. A total of one RCTs reported the UPDRS IV, No. 33 unchanged with scores ≥ 1 in 375 patients (246 zonisamide users and 129 nonusers). The effect of zonisamine on UPDRS IV, No. 33 unchanged with scores ≥ 1 was not statistically significant when compared to the control group (OR-0.75 [95% CI: 0.38, 1.46], $p = 0.4$). There was no evidence of heterogeneity between studies ($p = 0.66$, $I^2 = 0\%$) (Figure 5(c)).

3.7.4. Zero (No New Onset). A total of 1 RCTs reported the UPDRS IV, No. 33 zero in 375 patients (246 zonisamine users and 129 nonusers). The effect of zonisamine on UPDRS IV, No. 33 zero was not statistically significant when compared to the control group (OR-1.14 [95% CI: 0.70,

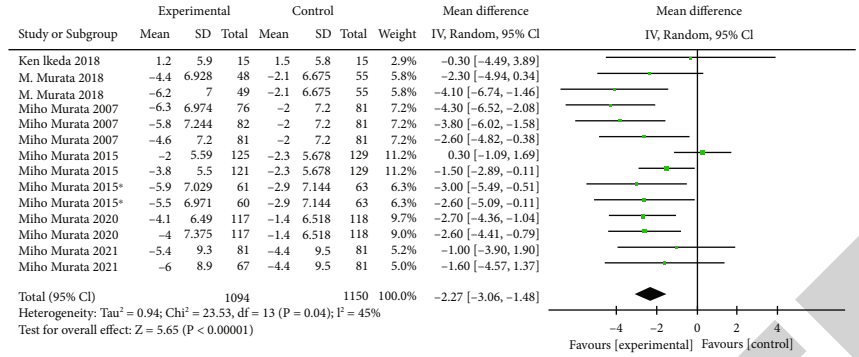
Figure 2: (a, b) Quality assessment of included studies.

1.88], $p = 0.59$). There was no evidence of heterogeneity between studies ($p = 0.64$, $I^2 = 0\%$) (Figure 5(d)).

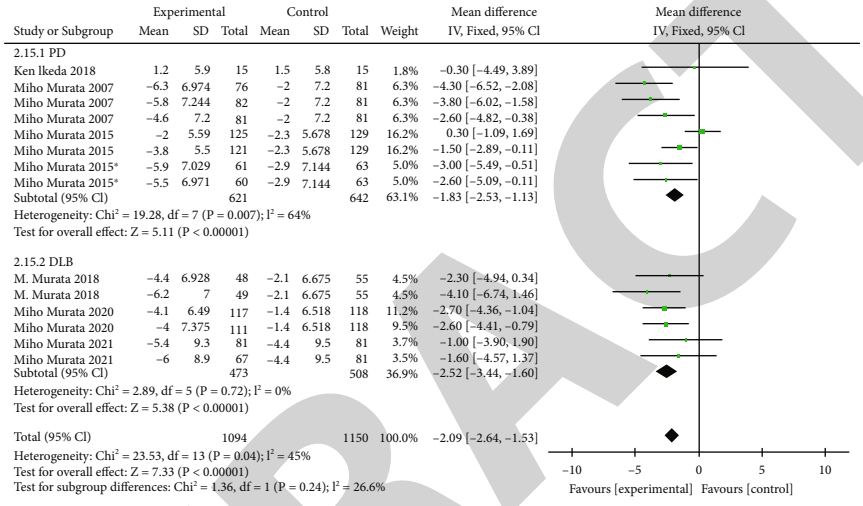
3.8. The Effect of Zonisamide on UPDRS IV, No. 34

3.8.1. Worsened. A total of 1 RCTs reported the UPDRS IV, No. 34 worsened in 375 patients (246 zonisamide users and 129 nonusers). The effect of zonisamine on UPDRS IV, No. 34 worsened was not statistically significant when compared to the control group (OR-0.73 [95% CI: 0.19, 2.72], $p = 0.63$). There was no evidence of heterogeneity between studies ($p = 0.42$, $I^2 = 0\%$) (Figure 6(a)).

3.8.2. Improved. A total of 1 RCTs reported the No. 34 improved in 375 patients (246 zonisamide users and 129 nonusers). The effect of zonisamine on UPDRS IV, No. 34 improved was not statistically significant when compared to the control group (OR-1.57 [95% CI: 0.25, 9.72], $p =$



(a)



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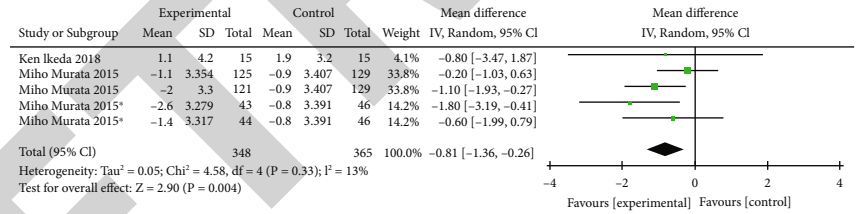

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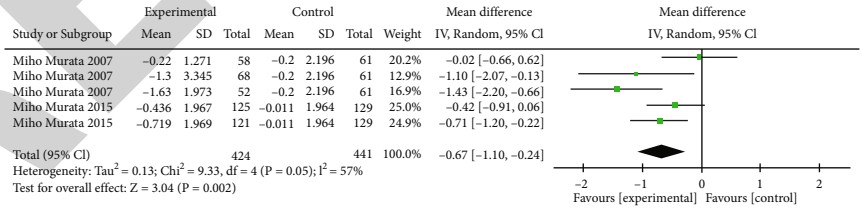
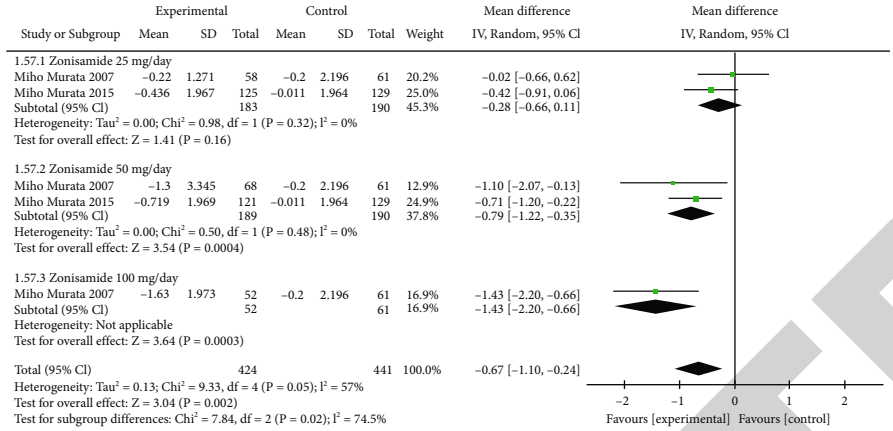


(d)

Figure 3: Continued.



(e)

Figure 3: The effect of zonisamide on UPDRS III total score (a), UPDRS III total score subgroup analysis (b), the effect of zonisamide on UPDRS II "Off" total score (c), the effect of zonisamide on daily "Off" time (d), and daily "Off" time subgroup analysis (e).

0.63). There was no evidence of heterogeneity between studies ($p = 0.70$, $I^2 = 0\%$) (Figure 6(b)).

3.8.3. Unchanged with Scores ≥ 1. A total of one RCTs reported the UPDRS IV, No. 34 unchanged with scores ≥ 1 in 375 patients (246 zonisamide users and 129 nonusers). The effect of zonisamine on UPDRS IV, No. 34 unchanged with scores ≥ 1 was not statistically significant when compared to the control group (OR-2.05 [95% CI: 0.35, 11.96], $p = 0.42$). There was no evidence of heterogeneity between studies ($p = 0.53$, $I^2 = 0\%$) (Figure 6(c)).

3.8.4. Zero (No New Onset). A total of 1 RCTs reported the UPDRS IV, No. 34 zero in 375 patients (246 zonisamine users and 129 nonusers). The effect of zonisamine on UPDRS IV, No.34 zero was not statistically significant when compared to the control group (OR-0.88 [95% CI: 0.32, 2.43], $p = 0.80$). There was no evidence of heterogeneity between studies ($p = 0.26$, $I^2 = 0\%$) (Figure 6(d)).

3.8.5. Adverse Events. Seven RCTs reported the results of a total of 39 adverse events. Six adverse events, including excoriation, rash, restless legs syndrome, hypnagogic hallucination, abnormal behavior, and attention deficit, were not included in the analysis due to incomplete data. A total of 33 adverse events were included in the analysis. In addition, we also performed subgroup analysis for six of them (contusion, somnolence, reduced appetite, constipation, weight loss, and insomnia) because they have been reported in RCTs of both PD and DLB with zonisamide.

4. Contusion

A total of 5 RCTs reported adverse events of contusion loss in 1421 patients (1048 zonisamide users and 373 nonusers) during the trial. Our analysis results showed that compared with the control group, zonisamide significantly increased the occurrence probability of contusion. There was a significant statistical difference (OR-0.59 [95% CI: 0.39, 0.89], $p = 0.01$). There was no significant difference in heterogeneity among included studies ($p = 0.91$, $I^2 = 0\%$) (Figure 7(a)). In addition, further subgroup analysis showed that for DLB patients, compared with the control group, zonisamide also significantly increased the occurrence probability of contusion. The results showed a statistical difference (OR-0.60 [95% CI: 0.38, 0.96], $p = 0.03$). However, for PD patients, there was no statistical difference between the placebo and zonisamide groups (OR-0.45 [95% CI: 0.19, 1.07], $p = 0.07$) (Figure 7(b)).

4.1. Somnolence. A total of 1592 RCTs (1078 zonisamide users and 514 nonusers) reported somnolence adverse events during the trial, and there was no significant difference in somnolence occurrence probability between the zonisamide group and the control group (OR-1.54 [95% CI: 0.96, 2.49], $p = 0.07$). There was low heterogeneity among included studies ($p = 0.33$, $I^2 = 12\%$) (Figure 7(c)). In addition, further subgroup analysis showed that for DLB patients, there was also no statistical difference between the placebo and zonisamide groups (OR-1.08 [95% CI: 0.58, 2.01], $p = 0.81$). However, for PD patients, compared with the control group, the results showed a statistical difference (OR-2.17 [95% CI: 1.25, 3.76], $p = 0.006$) (Figure 7(d)).

4.2. Reduced Appetite. A total of 1751 RCTs (1189 zonisamide users and 562 nonusers) reported reduced appetite and adverse reactions during the trial. There was no significant difference in the incidence probability of reduced appetite between the zonisamide group and the control group (OR-1.16 [95% CI: 0.68, 1.99], $p = 0.58$). There was low heterogeneity among the included studies ($p = 0.06$, $I^2 = 41\%$) (Figure 8(a)) In addition, further subgroup analysis showed that for PD patients, there was also no statistical difference between the placebo and zonisamide groups (OR-0.67 [95% CI: 0.43, 1.05], $p = 0.08$). However, for DLB patients, compared with the control

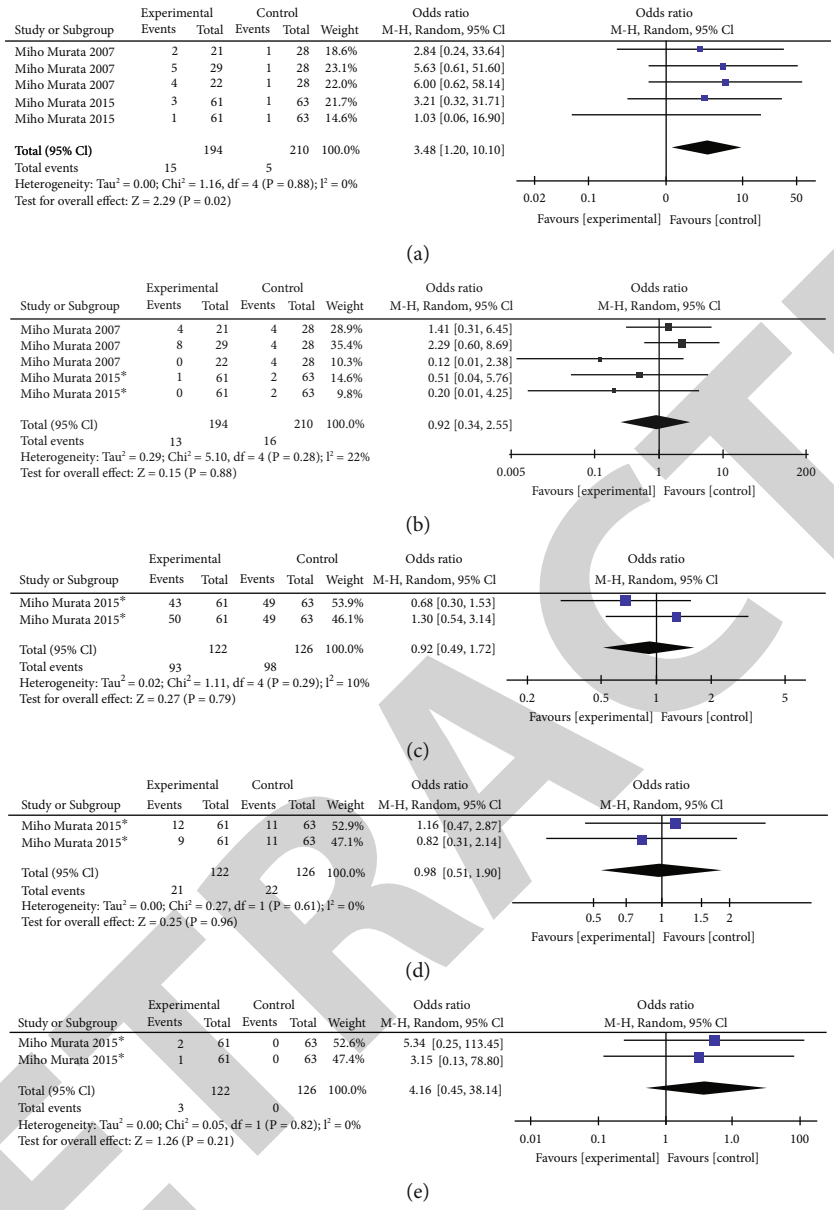


Figure 4: The effect of zonisamide on UPDRS Part IV, No. 32 worsened (a), the effect of zonisamide on UPDRS Part IV, No. 32 improved (b), the effect of zonisamide on UPDRS Part IV, No. 32 no new onset (c), the effect of zonisamide on UPDRS Part IV, No. 32 unchanged with scores ≥ 1 (d), and the effect of zonisamide on UPDRS Part IV, No. 32 new onset (e).

group, the results showed a statistical difference (OR-3.13 [95% CI: 1.61, 6.08], $p = 0.0008$) (Figure 8(b)).

4.3. Weight Loss. A total of 4 RCTs reported adverse events of weight loss in 1012 patients (702 zonisamide users and 310 nonusers) during the trial, and there was no significant difference in the probability of weight loss between the zonisamide group and the control group (OR-1.29 [95% CI: 0.80, 2.09], $p = 0.29$). There was no significant difference in heterogeneity among included studies ($p = 0.53$, $I^2 = 0\%$) (Figure 8(c)). Further subgroup analysis also showed that there was no statistically significant difference in the incidence of weight loss between the zonisamide group and the control group for both PD and DLB patients (PD: (OR-1.01 [95% CI: 0.54, 1.89], $p = 0.98$) DLB: (OR-2.01 [95% CI: 0.85, 4.80], $p = 0.11$) (Figure 8(d)).

4.4. Constipation. A total of 5 RCTs reported 1593 patients (1089 zonisamide users and 504 nonusers) with bouts of constipation during the trial. There was no significant difference in the incidence rate of constipation between the zonisamide group and the control group (OR-0.95 [95% CI: 0.60, 1.53], $p = 0.85$). There was low heterogeneity among included studies ($p = 0.43$, $I^2 = 2\%$) (Figure 9(a)). Further subgroup analysis also showed that there was no statistically

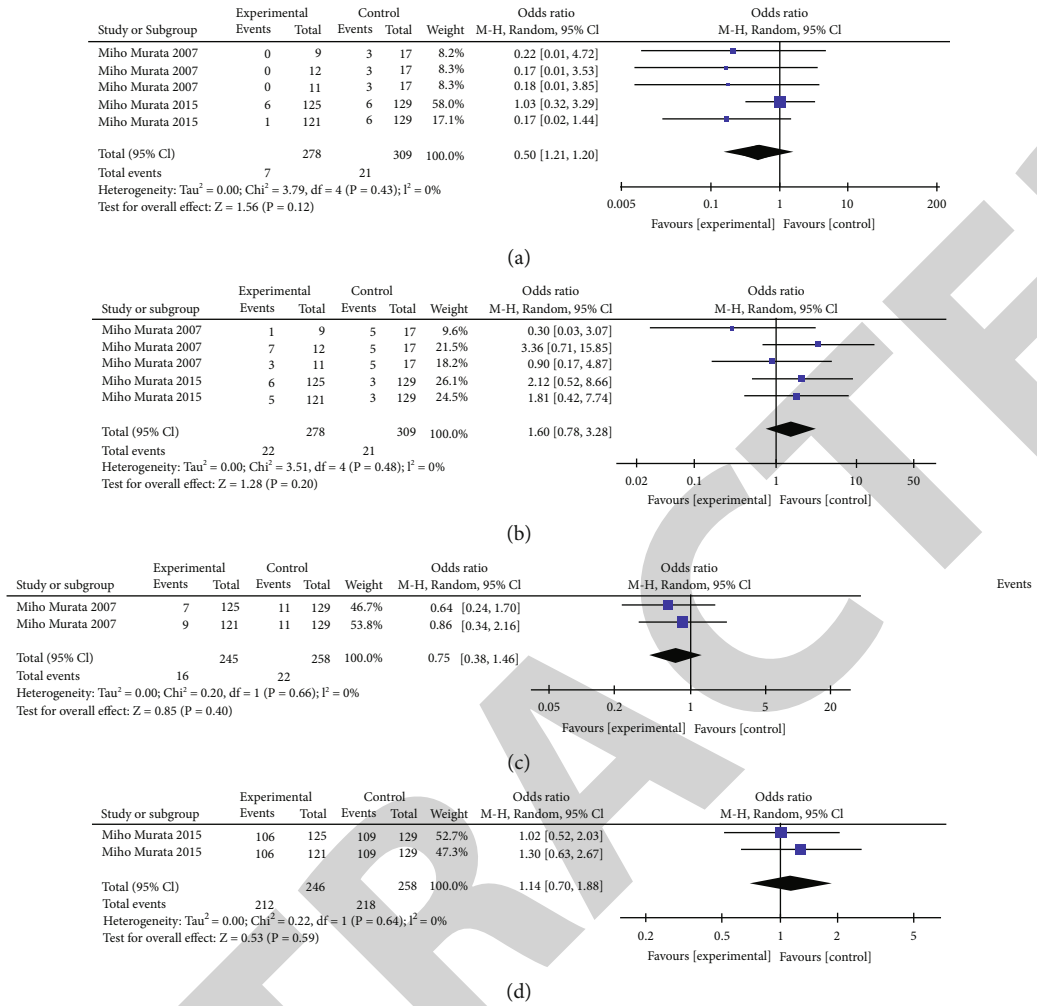


Figure 5: The effect of zonisamide on UPDRS Part IV, No. 33 worsened (a), the effect of zonisamide on UPDRS Part IV, No. 33 improved (b), the effect of zonisamide on UPDRS Part IV, No. 33 unchanged with scores ≥ 1 (c), and the effect of zonisamide on UPDRS Part IV, No. 33 zero (d).

significant difference in the incidence of constipation between the zonisamide group and the control group for both PD and DLB patients (PD: (OR-1.16 [95% CI: 0.64, 2.10], $p = 0.63$), DLB: (OR-0.64 [95% CI: 0.34, 1.22], $p = 0.18$)) (Figure 9(b)).

4.5. Insomnia. A total of four RCTs reported 1263 patients (842 zonisamide users and 421 nonusers) with adverse insomnia during the trial, and there was no significant difference in the probability of insomnia between the zonisamide group and the control group (OR-0.78 [95% CI: 0.43, 1.43], $p = 0.42$). There was no significant difference in heterogeneity among included studies ($p = 0.82$, $I^2 = 0\%$) (Figure 9(c)). Further subgroup analysis also showed that there was no statistically significant difference in the incidence of insomnia between the zonisamide group and the control group for both PD and DLB patients (PD: OR-0.56 [95% CI: 0.26, 1.21], $p = 0.14$), DLB: OR-1.45 [95% CI: 0.51, 4.12], $p = 0.49$) (Figure 9(d)).

In addition, we performed a statistical analysis of the remaining 27 adverse events, and the final results showed that there was no significant difference in the probability of these adverse events between the zonisamide group and the control group, both for PD patients and DLB patients.

5. Discussion

This systematic review and meta-analysis of seven RCTs were conducted to determine the efficacy and safety of zonisamide in the treatment of PD and DLB. The UPDRS III total score was used as the primary outcome indicator to evaluate the effect of zonisamide on PD and DLB treatment. In addition, the UPDRS II total score, daily "off" time, and UPDRS Part IV, Nos. 32, 33, and 34 were also used as secondary outcome indicators to evaluate the therapeutic effect of zonisamide in PD. A total of 33 adverse event datasets were included in the final safety analysis, and we performed a subgroup analysis of the final results to further clarify the differences in the efficacy and safety of zonisamide for PD and DLB treatment.

PD and DLB, as common neurodegenerative diseases, have been a hot topic of research in recent research. In terms

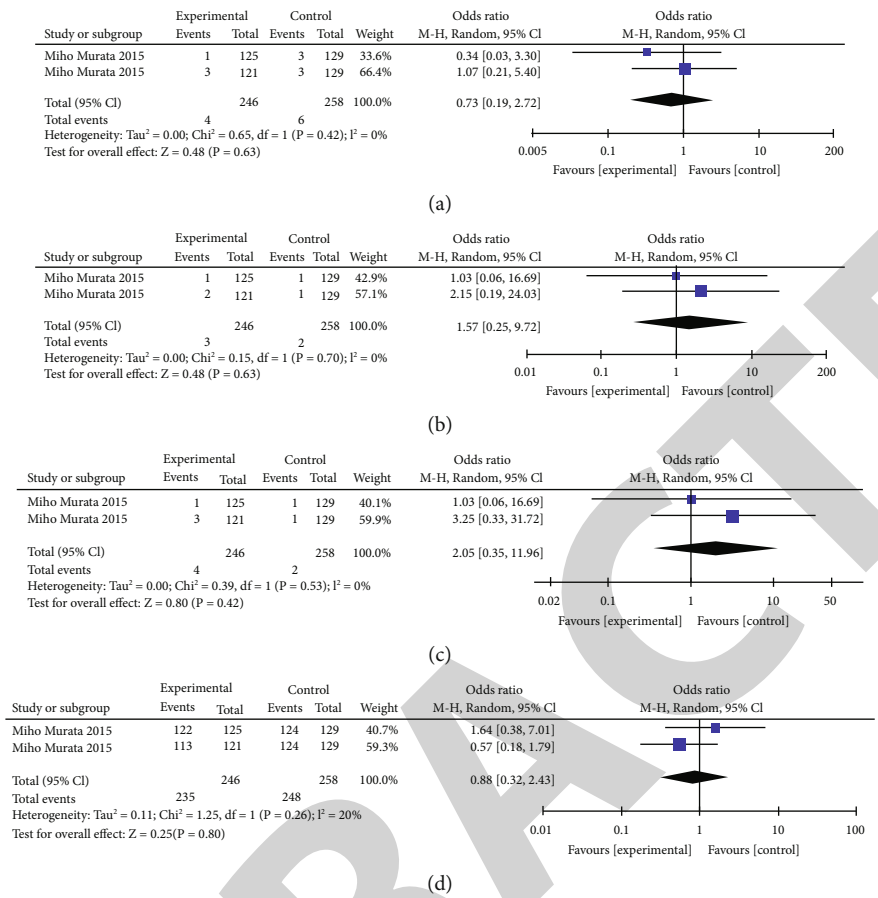
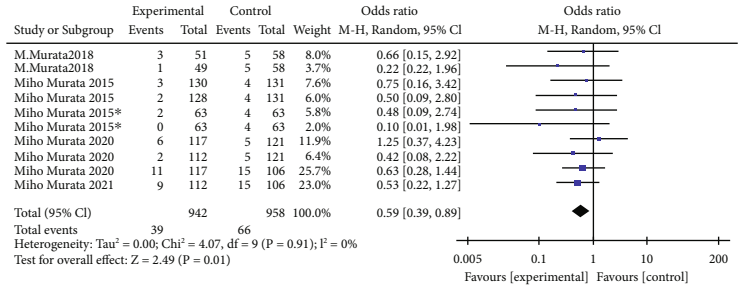


Figure 6: The effect of zonisamide on UPDRS Part IV, No. 34 worsened (a), the effect of zonisamide on UPDRS Part IV, No. 34 improved (b), the effect of zonisamide on UPDRS Part IV, No. 34 unchanged with scores ≥ 1 (c), and the effect of zonisamide on UPDRS Part IV, No. 34 zero (d).

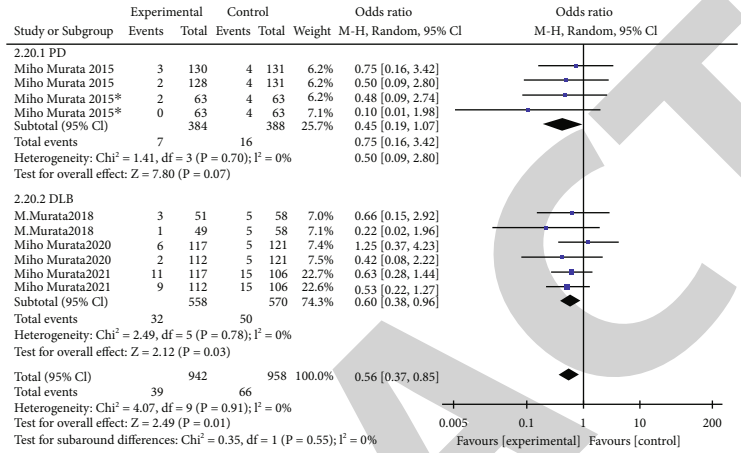
of PD, from a pathophysiological standpoint, depletion of the neurotransmitter dopamine in the basal ganglia causes disruption of connections to the thalamus and motor cortex, resulting in PD [31]. Dopamine replacement therapy, represented by levodopa, is the current gold standard of treatment options for PD. However, the therapeutic efficacy of dopamine begins to wear off as the disease progresses, with the emergence of "off" periods and dopamine-induced dyskinesia [32]. Given that DLB and PD share a similar pathology and that both are considered to be on the same spectrum as Lewy body disease, levodopa is also often considered for the treatment of dyskinesia in patients with DLB [33]. However, due to the nature of the disease itself, people with DLB are vulnerable to adverse effects on their own cognition and behavior and even to psychosis and psychiatric disorders, when treated with dopaminergic therapy [34, 35]. Zonisamide was approved as an antiparkinsonian drug in Japan in 2009, with its pharmacological mechanisms including dopaminergic [36, 37], nondopaminergic [38, 39], and neuroprotective effects [40], which may be associated with the improvement of PD and DLB. However, the exact mechanism of action of zonisamide in improving PD and DLB is still unclear, and more research is needed to clarify it.

The UPDRS (Unified Parkinson's Disease Rating Scale) was used to rate the clinical condition of Parkinson's disease and consists of four main components. The UPDRS Part II displays the self-assessment of patients for activities of daily life, whereas the UPDRS Part III is physician's evaluation of the patient's motor function. The UPDRS Part IV is the patient's evaluation of their own dyskinesia, with subscales 32, 33, and 34 corresponding to the duration of dyskinesia (based on nonsleep time), degree of disability caused by dyskinesia, and the degree of pain provoked by dyskinesia, respectively [41].

In this meta-analysis, our results show that treatment with zonisamide provoked an obvious decrease in both PD and DLB patients' UPDRS Part III total scores. These motor changes measured by the UPDRS Part III also confirm the significant improvement in motor function of zonisamide in PD and DLB patients. In addition, to further clarify whether the effects of zonisamide differed between PD and DLB, a subgroup analysis was performed on the final figures. Our results showed that the improvement in motor function with zonisamide was significant for both PD and DLB. And we also found that the effect of zonisamide in improving the UPDRS III total score appears to be more pronounced for DLB patients by comparing the difference. In animal studies, zonisamide was found to significantly slow the degeneration of nigral dopamine neurons caused by the expression of A53T-



(a)



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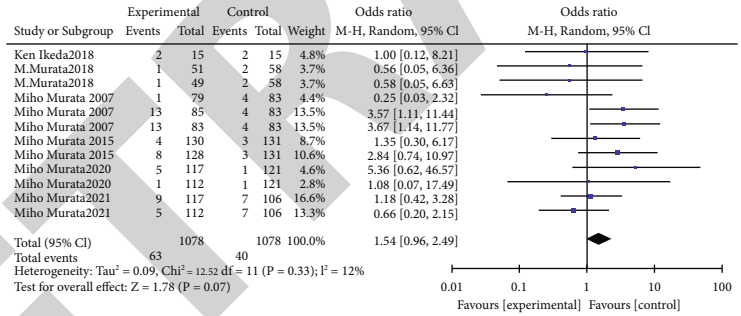

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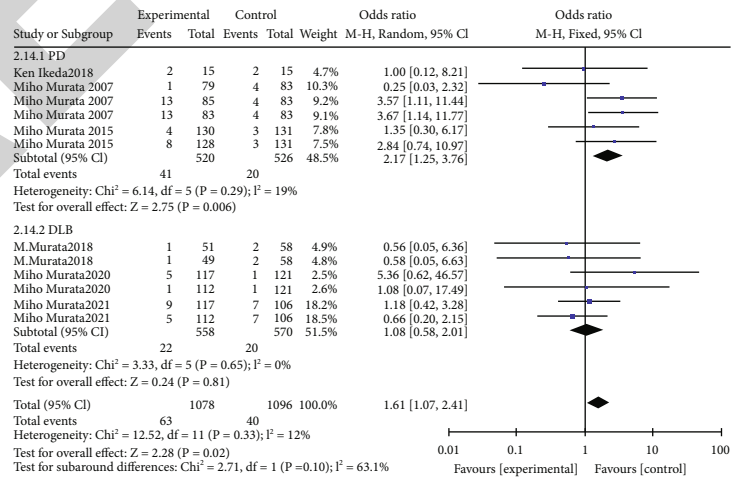
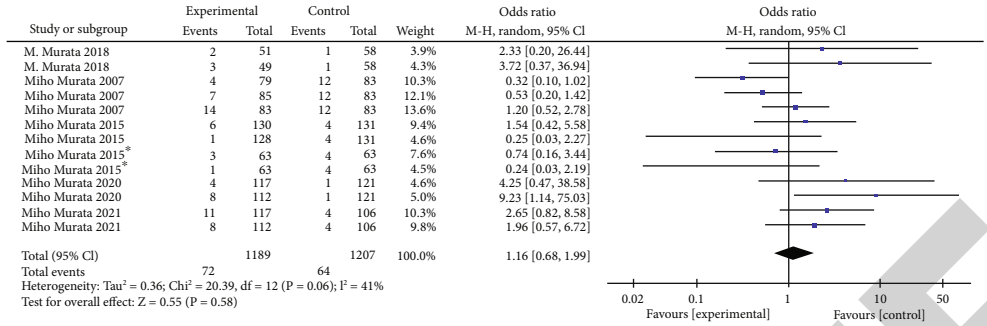


(d)

Figure 7: Contusion (a), contusion subgroup analysis (b), somnolence (c), and somnolence subgroup analysis (d).



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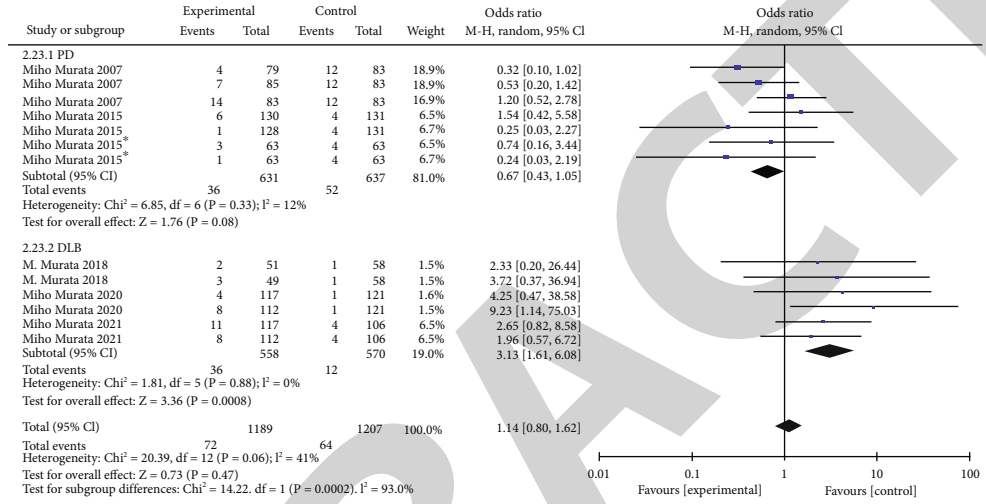

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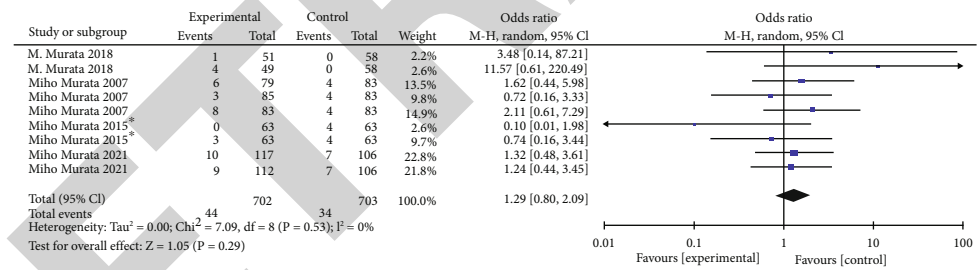

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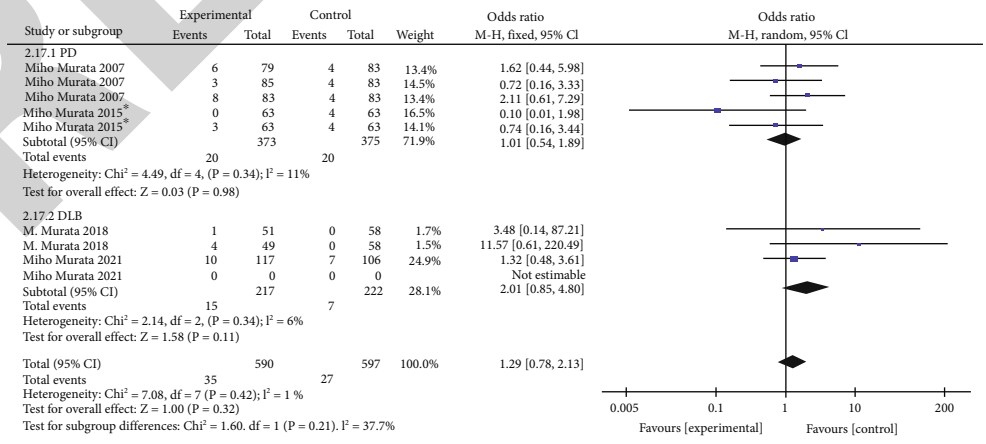
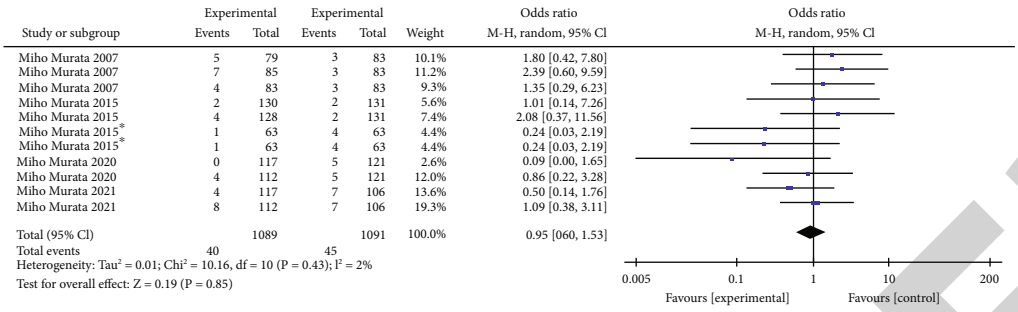
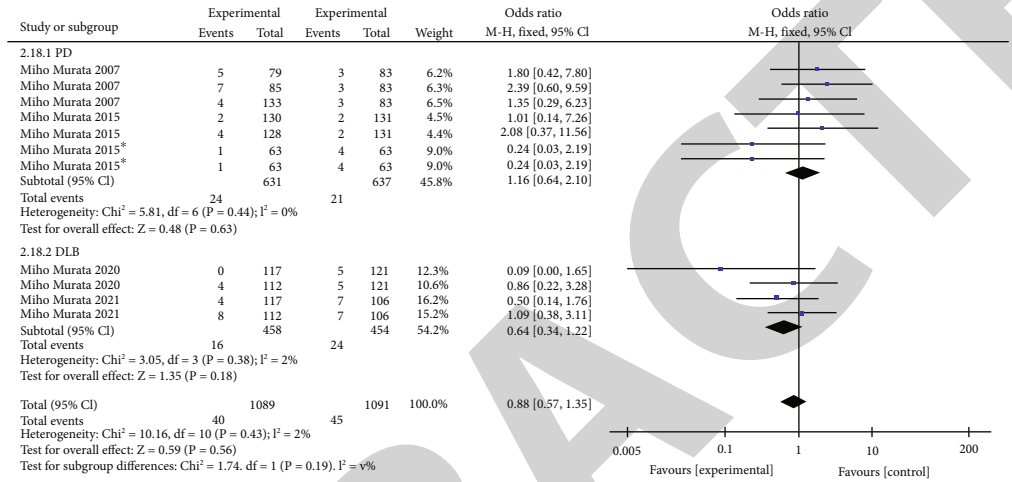


(d)

Figure 8: Reduced appetite (a), reduced appetite subgroup analysis (b), weight loss (c), and weight loss subgroup analysis (d).



(a)



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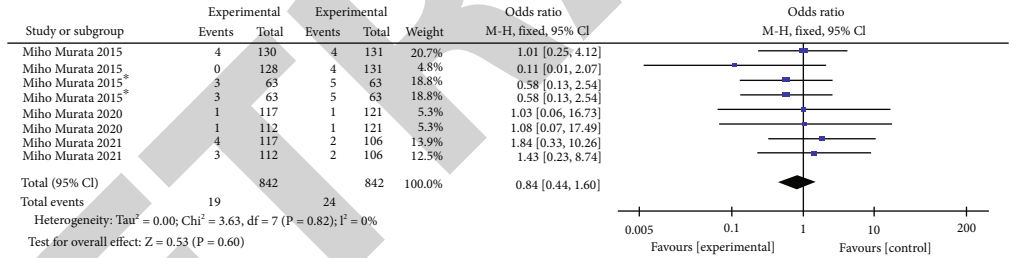

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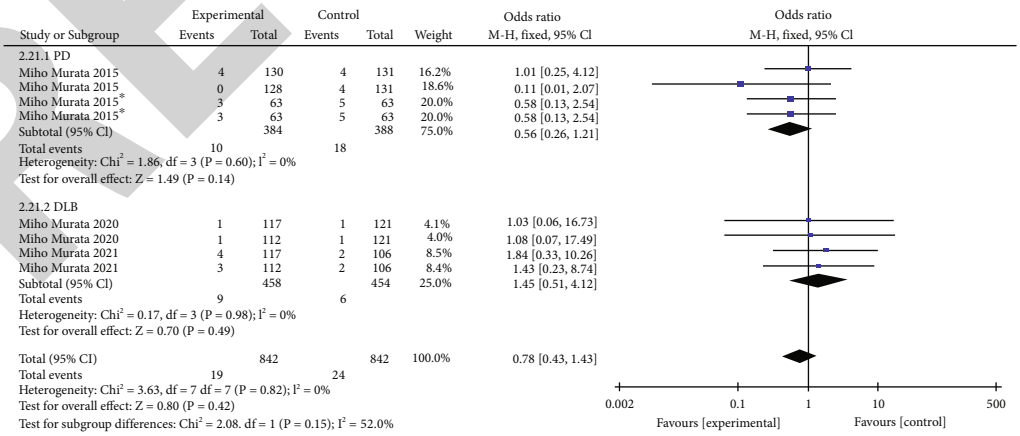

(d)

Figure 9: Constipation (a), constipation subgroup analysis (b), insomnia (c), and insomnia subgroup analysis (d).

synuclein [42]. In a separate study, it was discovered that combining zonisamide with levodopa-carbidopa increased DOPAC levels by 300% when compared to levodopa-carbidopa treatment alone [43]. Zonisamide has also been found to delay degeneration, increase dopamine stores, and enhance dopamine release from striatal nerve endings [44], and we consider that these properties appear to explain the significant improvement in motor function of zonisamide in PD and DLB patients; however, we believe that more studies are still needed to demonstrate the superiority of zonisamide in improving motor function in DLB patients.

In addition, for PD patients, we obtained results showing that treatment with zonisamide also significantly reduced the UPDRS Part II total scores in PD patients. This shows a significant improvement in the function of daily activities in PD patients after treatment with zonisamide, which also seems to indicate that the effect of zonisamide on PD patients is not limited to motor function alone. In three other recent small open-label studies, adjunctive treatment with zonisamide also showed positive improvements in nonmotor symptoms of PD such as impulse control disorder (ICD), binge eating, and refractory anxiety [45, 46]. Therefore, after comprehensive consideration, we conclude that the ameliorative effect of zonisamide on PD is multifaceted, which also needs to be proven by more clinical studies.

For patients with PD, long-term use of levodopa can cause motor complications such as wearing off and dyskinesia. In this meta-analysis, our results showed that zonisamide treatment significantly reduced the daily "off" time, demonstrating that zonisamide could obviously improve wearing off. This may be due to the fact that zonisamide has a half-life of around 60 h, and that its plasma concentration is unaffected by dosing intervals or dosage regimen [47]. For levodopa treatment-induced dyskinesia, our findings showed a significant decrease in UPDRS Part IV, No. 32 worsened after zonisamide treatment. Furthermore, the scores for other items, including improved, no new onset, unchanged with scores ≥ 1, and new onset, to a large extent, also demonstrated improvements of zonisamide on the duration of dyskinesia, although not statistically significant. Additionally, our results showed no statistically significant difference in the effect of zonisamide use on the UPDRS Part IV, Nos. 33 and 34 compared to controls and changes. These parameters suggest that zonisamide appears to improve the duration of dyskinesia. However, its effect on pain and disability caused by dyskinesia needs to be supported by further research data and results.

In terms of safety, our final analysis showed that zonisamide was only statistically significant in terms of increasing the incidence of contusions, and by subgroup analysis, we further found that zonisamide did significantly increase the incidence of contusions in DLB, but the effect of zonisamide on contusions was not statistically significant in the subgroup analysis of PD. In addition, subgroup analysis also showed that zonisamide significantly increased the incidence of reduced appetite in DLB, and that zonisamide significantly increased the incidence of somnolence in PD. However, in the overall analysis, the effect of zonisamide on both reduced appetite and the onset of somnolence was nonsignificant. To summarize the above, in terms of safety, we consider that the use of zonisamide increases the probability of contusion in patients with DLB. In addition to a possible increase in the probability of reduced appetite in patients with DLB and somnolence in patients with PD, which need to be verified by further pilot studies, for patients with DLB, the question of whether therapeutic drugs may have adverse effects on cognitive and psychiatric symptoms is a key safety issue, and, in previous clinical studies of zonisamide in the treatment of epilepsy, it was found that zonisamide use may cause psychiatric and cognitive adverse effects [24]. Based on the above considerations, in a recent 52-week randomized controlled trial, the investigators used the NPI-10 (Neuropsychiatric Inventory) and the MMSE (Mental State Examination Scale) to measure the mental status and cognitive level of patients before and after long-term treatment with zonisamide and did not observe significant changes or deterioration in the mean NPI-10 and MMSE scores [29]. Therefore, zonisamide has a relatively reliable safety profile for the treatment of PD and DLB compared to levodopa.

The above discussion of safety is based on the effects of 25 mg and 50 mg doses of zonisamide in patients with PD and DLB. In the initial clinical study of zonisamide for PD, therapeutic amounts of 100 mg and above have also been used to try. Because the higher dose group was linked to more side effects and a nonsignificant improvement in UPDRS III scores, subsequent researchers reduced the zonisamide dose group to 25 mg and 50 mg in clinical trials [24]. The same dose setting was also used in a clinical study of zonisamide for DLB. We summarized the results of the subsequent clinical trials and discovered that both the 25 mg and 50 mg doses of zonisamide had a significant and comparable effect on motor symptoms in PD patients. However, for the wearing off in PD patients, the ameliorating effect of the 50 mg dose of zonisamide appears to be more pronounced, and PD patients appear to be more responsive to the 50 mg dose of zonisamide. The most recent study concluded that zonisamide 25 or 50 mg/day is effective in the long-term treatment of DLB patients, and that both doses are well tolerated with no new safety concerns [29]. We concluded that 25 mg and 50 mg doses of zonisamide are relatively safe and provide good improvement in the treatment of both PD and DLB, but perhaps more dose options should also be tried in future trials to explore for the highest patient benefit.

In the field of aging medicine, Parkinson's disease and dementia with Lewy bodies are currently hot topics. There are still disadvantages to levodopa therapy that need to be improved. There is currently no meta-analysis of zonisamide in the treatment of PD and DLB. As we all know, this is the first meta-analysis to assess the role of zonisamide in PD and DLB. The advantage of this analysis is that it comprehensively assesses the roles of zonisamide in activities of daily living, motor function, daily "off"

time, duration of dyskinesia, disability caused by dyskinesia, and painful dyskinesia. However, our study has several limitations: (a) seven studies were all carried out on the Japanese population. Other large international multicenter clinical trials with similar reproducible findings are still lacking. (b) The follow-up periods in the included studies were brief, lasting no more than a year. There is no evidence that zonisamide treatment for more than a year results in additional histological benefits. The long-term prognosis and safety of zonisamide are still unknown, and more research is needed. (c) In three RCTs, the subjects of the studies were DLB. Enrolling patients in a long-term trial under double-blind conditions would be difficult due to the progressive nature of DLB and associated caregiver burden and could result in significant study dropouts, especially in the placebo group. (d) Since 2008, the MDS-UPDRS has been used as the new official Parkinson's Disease Rating Scale. However, the UPDRS scale, developed in 1987, was used consistently in all seven RCTs. Because the MDS-UPDRS scale may be more easily understood and answered by patients, it is also possible that differences in the content of the two scales may affect the accuracy of the final data.

6. Conclusions

In conclusion, we completed the current statistical analysis of outcome data on zonisamide in RCTs in PD and DLB. The combined data from RCT studies showed that zonisamide significantly improves the motor function in PD and DLB. Furthermore, in patients with PD, zonisamide has a significant positive impact on the improvement of activities of daily life, wearing off, and duration of dyskinesia. In terms of safety, the use of zonisamide significantly increases the probability of contusion in patients with DLB and may increase the probability of reduced appetite in patients with DLB and somnolence in patients with PD. In order to better guide clinical practice, more RCTs of longer duration and larger sample sizes are needed to determine the efficacy and safety of zonisamide in PD and DLB.

Data Availability

The article/Supplementary Material (available here) contains the original contributions presented in the study. Any additional questions should be directed to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

LK wrote the manuscript after conducting a literature search, information extraction, and information analysis. JX was in charge of data extraction and manuscript review. ZJ HLand XY checked the data and adjusted the structure of the article and organized the pictures. ZW was a part of the review process. All of the authors contributed to the article and approved the final version. Linghui Kong and Jiaqiu Xi contributed equally to this work.

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Supplementary Materials

The supplementary materials are divided into four parts. Supplementary Material 1 is the PRISMA checklist for this meta-analysis. Supplementary Material 2 is the retrieval formula used in database search. Supplementary Material 3 describes the study's characteristics in detail. Supplementary Material 4 contains an analysis of other 27 adverse event datasets. *(Supplementary Materials)*

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Retraction

Retracted: *Astragalus membranaceus* and *Salvia miltiorrhiza* Ameliorate Hypertensive Renal Damage through lncRNA-mRNA Coexpression Network

BioMed Research International

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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] L. Zhou, C. Han, Y. Liu et al., "*Astragalus membranaceus* and *Salvia miltiorrhiza* Ameliorate Hypertensive Renal Damage through lncRNA-mRNA Coexpression Network," *BioMed Research International*, vol. 2022, Article ID 3002353, 14 pages, 2022.

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Research Article

Astragalus membranaceus and *Salvia miltiorrhiza* Ameliorate Hypertensive Renal Damage through lncRNA-mRNA Coexpression Network

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lncRNAs and mRNA are closely associated with hypertensive renal damage, and *Astragalus membranaceus* and *Salvia miltiorrhiza* (AS) have a therapeutic effect; however, the mechanism of AS to ameliorate hypertensive renal damage through the co-expression network of lncRNA-mRNA was unclear. In this study, we investigated the role of AS regulated the coexpression network of lncRNA-mRNA in improving hypertensive renal damage. Sixteen 24-week old spontaneous hypertensive rats (SHRs) were randomly divided into model group (*M*) and drug intervention group (AS, 5.9 g/kg), 8 Wistar Kyoto rats (WKY) of the same age as normal group (*N*). The treatment of rats was 4 weeks. Detecting the change of blood pressure, renal pathology and renal function related indicators, and lncRNA and mRNA sequencing and joint analysis was performed on the kidney. AS reduced blood pressure; decreased urine NAG, urine mALB, serum CysC, and IL-6; and improved renal pathology compared with group M. Simultaneously, AS reversed the disordered expression of 178 differential expression (DE) mRNAs and 237 DE-lncRNAs in SHRs, and their joint analysis showed that 13 DE-mRNAs and 32 DE-lncRNAs were coexpressed. Further analysis of 13 coexpressed DE-mRNAs showed negative regulation of blood pressure and fatty acid beta-oxidation was highly enriched in GO pathways, *PPAR* signaling pathway was highly enriched in KEGG pathways, and the verification related to these pathways was also highly consistent with the sequence. AS can alleviate hypertensive renal damage through the coexpression network of lncRNA-mRNA, of which coexpressed 13 DE-mRNAs and 32 DE-lncRNAs were the important targets, and the pathway negative regulation of blood pressure, fatty acid beta-oxidation, and PPAR signaling pathway play a major regulatory role.

1. Introduction

Hypertensive renal damage, reversible in early stage, is related to hemodynamic changes, inflammation and oxidative stress, excessive renin angiotensin activation, genetic factors, and metabolic factors. Numbers of patients with end stage renal disease (ERSD) due to hypertension are increasing year by year, accounting for about 28% of all ESRD cases [1]. In-depth exploration of the pathogenesis of hypertensive renal damage and intervention measures is of great significance for delaying progress. lncRNA is a noncoding RNA that can directly or indirectly regulate mRNA expression by interacting with mRNA, thereby affecting post transcriptional genes and proteins [2]. lncRNAs are closely associated with hypertension and renal damage. For example, lncRNAs can participate in vascular remodeling by affecting endothelial cell proliferation and phenotypic transformation of vascular smooth muscle [3–6]. lncRNA-p21 enhances autophagy by promoting the transcriptional activity of p53 to prevent endothelial progenitor cells damage

Table 1: Primer sequences.

Gene	Forward primer	Reverse primer
NONRATT028522.2	TGTACGTCTCATAAACCCGAAAGCC	GACCGCTGACAAGTCCTCAATGG
NONRATT028523.2	GGAGCCGCTCACATATACTCACTG	CGCCCACCGAGGTTTCTTGATG
NONRATT016111.2	AGAGTGATGTGGGTGTCAGAGACTG	CAGCCGACTAGCTCAAAGGAAACC
NONRATT026955.2	TTGGATTGCCAGCGGTGATAACTC	CTTCAAGTAGGAGTCAGCACGAACC
NONRATT022172.2	AGTTGCCGTGGAATCTTTCAAAAGC	AAGGTTTCCTCTCTAGGCGACTCTG
ENSRNOT00000083625.1	TCGGAGCCAGTAATGAATGTGAACG	CCTGCACGGTCTGCCTTTTATCG
MSTRG.22291.30	ACATTTCAGAGTGGGCAGCAACC	TAACCAGGGCAGGAACCAGACC
MSTRG.15507.1	TGGGTTTCTCGTCTGGTGAATGATG	TCAGTTGGGCTCCTCCTAGTATGTG
Zbtb16	CGCCACCTTCGCTCACATACAG	ACTTCTTGCCACAGCCATTACACTC
Abcd2	AGCGTCCACCTCTACCACATAGTC	TCGTCCAGCAATGCGTACTTCG
Cnr1	GTGTGCTGCTGCTGTTCATTGTG	CGTGTGGATGATGATGCTCTTCTGG
Adipoq	CGCAGGTGTTCTTGGTCCTAAGG	CCCTACGCTGAATGCTGAGTGATAC
Mapk13	TGAAGACACAGCACCTCAGCAATG	GGTGTTCAGCAGGAGGTTGGAAG
LPl	TTCCAAGGAGGCATTTGAGAAAGGG	TGTAGGGCATCTGAGAGCGAGTC
Fst	CTCCGGCGTACTGCTTGAAGTG	GGTCTTCCTCTTCCTCCTCTTCCTC

caused by AngII [7]. High expression of H19 could down-regulate the expression of fibronectin and destroy the integrity of renal vessels [8], and lncRNA MALAT1 promoted transforming growth factor-β1 (TGF-β1), induced endothelial to mesenchymal transition (EndMT) of endothelial progenitor cells (EPCs), and accelerated renal fibrosis [9, 10]. However, the role of the coexpression network of lncRNAs and mRNAs in hypertensive renal damage has not yet been fully clarified.

In traditional Chinese medicine (TCM), *Astragalus membranaceus* (AM, of the Leguminosa family) has the function of Tonifying Qi. *Salvia miltiorrhiza* (SM, of the Lamiaceae family) could promote blood circulation and remove blood stasis. Previous studies have shown that both AM and SM could relax blood vessels and resist oxidative stress and anti-inflammatory [11–13]. *Astragalus membranaceus* and *Salvia miltiorrhiza* (AS) are often used to treat hypertensive renal damage as a representative of invigorating qi and promoting blood circulation in TCM. We have found that AS can not only reduce blood pressure through intestinal flora-host metabolism [14] but also improve hypertensive renal damage by regulating phosphoinositide 3-kinases (PI3K)/serine-threonine protein kinase 1 (AKT1) and TGF-β1 pathways [15, 16]. However, the mechanism of AS to ameliorate hypertensive renal damage through the coexpression network of lncRNA and mRNA was unclear.

In this study, we mainly investigated the mRNAs and lncRNAs in the kidney of SHRs and the effect of AS on the coexpression profile, so as to clarify the main target and related pathways of AS in the treatment of hypertensive renal damage.

2. Materials and Methods

2.1. Extraction and Identification of AS. AM and SM (AS) were provided by the Affiliated Hospital of Shandong University of TCM. The preparation and quality control of AS were based on our previous research [14, 17]. Briefly, AM and SM were mixed in a ratio of 2 : 1, 10 times the volume of water was added to soak for 1 hour and then decocted for 30 minutes. After filtration and extraction of filtrate, filtrate was extracted from filtrate residue again according to the same procedure, and the two filtrate were mixed to obtain AS solution of 0.59 g crude drug per ml [14]. Finally, the main components of AS were identified and analyzed by UPLC- MS/MS [17].

2.2. Preparation of Animals. Animals were purchased from Vital River Laboratory Animal Technologies Co., Ltd. (no. SCXK (Beijing) 2016-0006). The project has passed the review of ethics committee of Affiliated Hospital of Shandong University of TCM. 16 male SHRS aged 24 weeks were divided into model group (M, $n = 8$) and drug intervention group (AS, $n = 8$) as random, and the control group (N) consisted of 8 age-matched WKY rats. The AS group was given AS (5.9 g/kg, referring to the dose of AS commonly used in clinical patients [14]) by intragastric administration, and the M and N groups were given equal volume of normal saline. The rats were intragastric once daily for 4 weeks.

2.3. Blood Pressure Measurement and Sample Collection. We used a noninvasive sphygmomanometer (ALC-NIBP System, Alcott BioScientific) to measure the blood pressure (BP) of rat caudal artery before and 1, 2, 3, and 4 weeks after intervention. The rats were anesthetized, serum was collected after 4 weeks of intervention, and the serum was centrifuged at a speed of 3000 r/min for 10 minutes and then stored at low temperature (-80°C). Rat kidney tissue was obtained and fixed with formaldehyde for 48 hours. After paraffin embedded, sections in 4 μm thick were cut.

2.4. Biochemical Analysis and Pathological Staining. Automatic biochemical analyzer (Rayto, China, Chemray240)

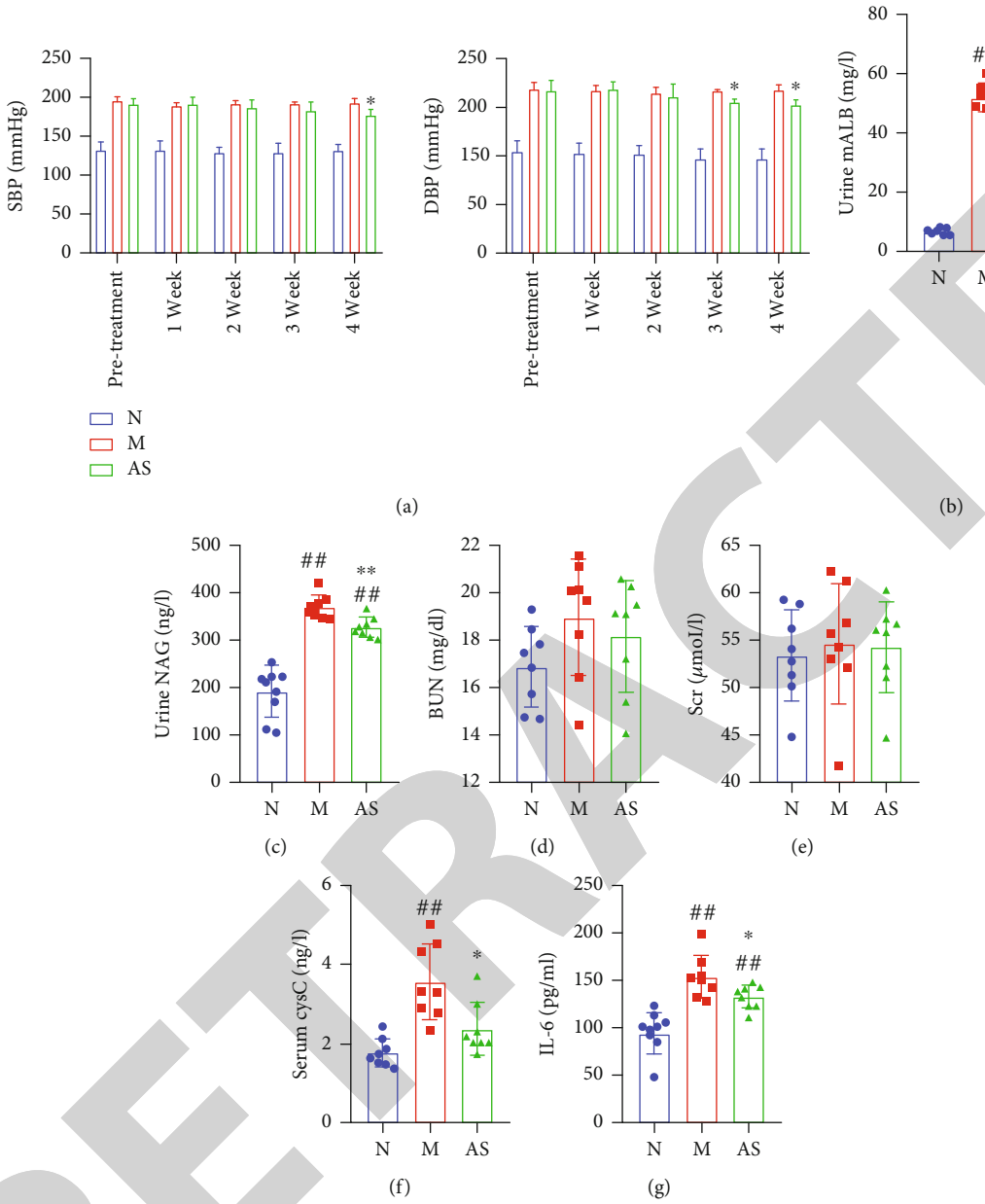


Figure 1: Effects of AS on renal blood pressure and renal function. (a) Systolic blood pressure (SBP) and diastolic blood pressure (DBP). (b) Urine microalbumin (mALB). (c–f) Renal function related indicators: NAG: urine N-acetyl-β-D-glucosidase; BUN: blood urea nitrogen; Scr: serum creatinine; CysC: serum cystatin C. (g) Interleukin-6 (IL-6). Values are the mean ± SD ($n = 8$). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. the N group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. the M group.

was used to determine serum creatinine (Scr) and blood urea nitrogen (BUN) levels. Urine microalbumin (mALB), urine N-acetyl-β-D-glucosidase (NAG), serum cystatin C (CysC), and interleukin-6 (IL-6) were determined by enzyme-linked immunosorbent assay (ELISA), haematoxylin-eosin (HE) staining, and Masson trichrome staining process paraffin sections, which were observed under light microscopic.

2.5. Transcriptome Sequencing and Analysis

2.5.1. Library Construction and Sequencing. The RNeasy mini kits were used to isolate the RNA, and strand-specific libraries were prepared using the VAHTS Total RNA-seq (H/M/R) Library Prep Kit (Vazyme, China). In Brief, RNA was purified after removal of rRNA by magnetic beads. The cleaved RNA fragments, which were segmented with divalent cations(94°C, 8 min), were used to synthesize the first strand cDNA; then, the reverse transcriptase and random primers were used to generate the second strand cDNA. After PCR purification and enrichment, the final cDNA library was generated. Then, Qubit® 2.0 Fluorometer (Life Technologies, USA) was used for quantification, and Agilent 2100 biological (Agilent Technologies, USA) was used for verification, so as to determine the size of the insert

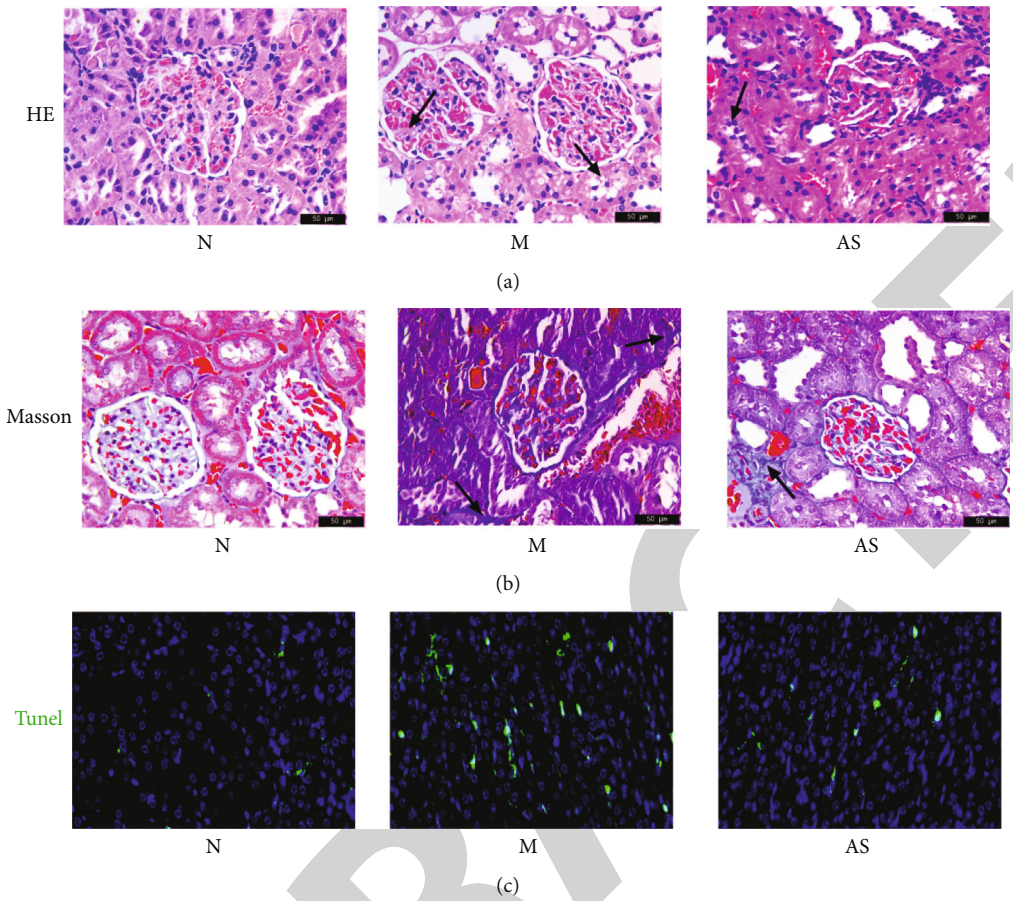


Figure 2: The effect of AS on kidney pathology (scale bars: 50 μm, 400×). (a) HE staining (arrows points to lesions). (b) Masson staining (arrows represents collagen fibres). (c) TUNEL (green represents apoptotic cells).

and calculate the molar concentration. cBot was used for cluster analysis, and Illumina NovaSeq 6000 (Illumina, USA) was sequenced. Shanghai Sinomics Corporation constructed and sequenced the library.

2.5.2. Analysis of lncRNA and mRNA. The offline reading of sequencing was preprocessed. Alignment was performed with Hisat2 software, so clean reads could mapped to the Rnor6.0.91 reference genome. StringTie was then run with a reference annotation to generate FPKM values differentially expressed (DE) lncRNAs and DE-mRNAs. The P value significance thresh for known gene models. Display differences based on fold change (FC) and false discovery rate (FDR). DE-mRNAs and DE-lncRNAs were set to FC > 1.5 or <0.67 and $P < 0.05$, and further combined analysis was shown in the network diagram. Specifically, genes transcribed within 10-kbp window upstream or downstream of the pancreas were considered to be cis-acting targets, and trans-acting target genes were identified by RNAplex software. Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway analysis were used to analyze the functions of the coexpressed DE-mRNAs.

2.6. Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) Analysis of lncRNAs and mRNAs. We used the FastPure total RNA isolation kit (Vazyme, Nanjing, China, RC101) to extract total RNA. PrimeScriptTM RT kits were used to reverse-transcribed, and TB GreenTM Ex TaqTM kits were used to execute the qRT-PCR. RT-PCR was performed using a Light Cycler480 II instrument (Roche, Germany). lncRNAs and mRNAs were normalized using the expression of GAPDH, and the relative RNA levels were analyzed by2-$\Delta\Delta$CT method. Gene-specific primer sequences of genes (Sparkjade, China) were designed and listed that in Table 1.

2.7. Statistical Analysis. Statistical analyses were performed with SPSS 21.0. The data were described as the mean ± standard deviation (SD). Differences between groups were analyzed by one-way ANOVA, and differences were considered significant if P values less than 0.05.

3. Results

3.1. AS Ameliorated Blood Pressure and Renal Function. After 3 weeks, the diastolic blood pressure (DBP) of AS group was significantly lower than the M group ($P < 0.05$). Systolic blood pressure (SBP) and DBP in AS group were both lower than M group ($P < 0.05$) 4 weeks later (Figure 1(a)). In addition, compared to group N, urine

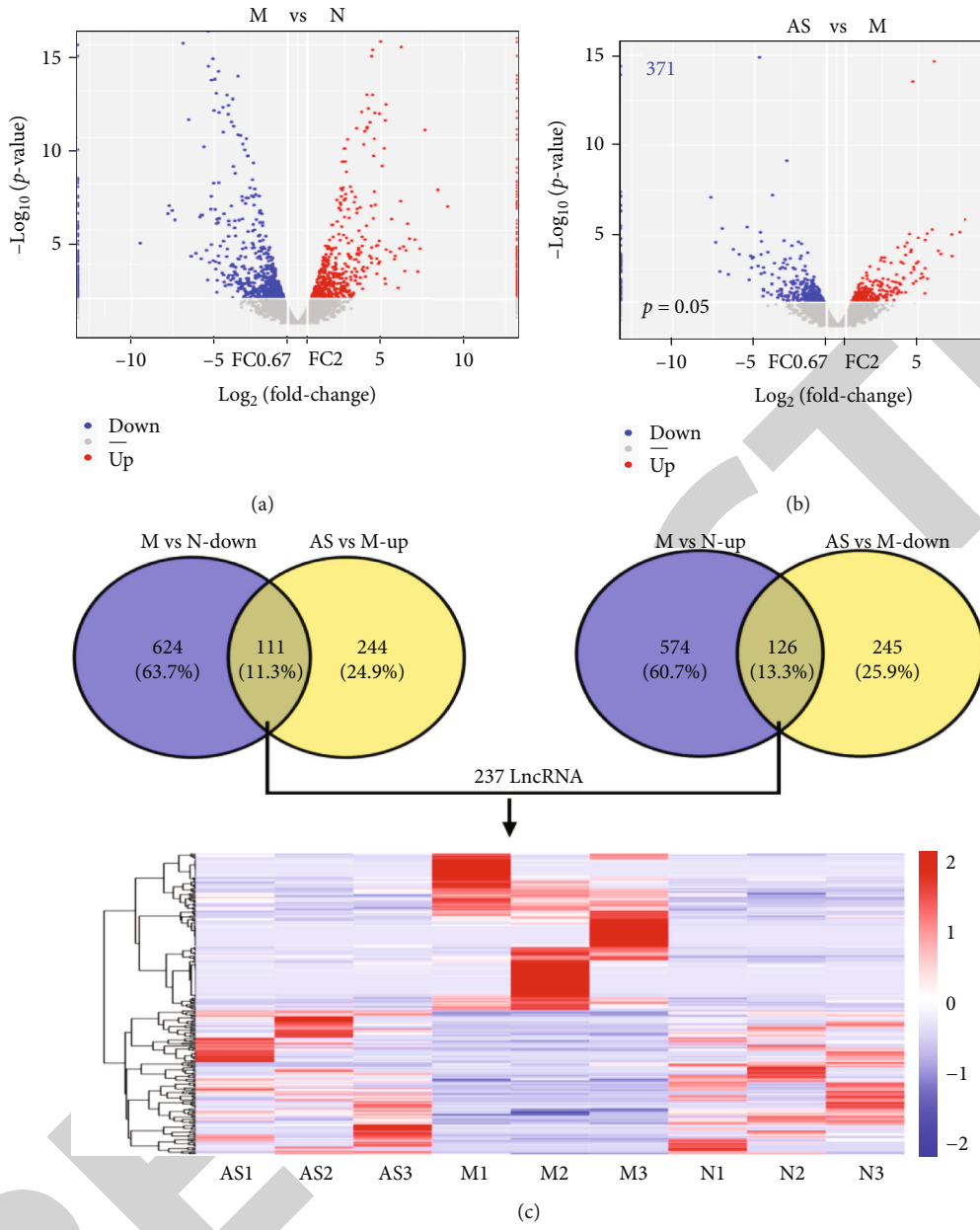


Figure 3: Volcano plots and heat maps of DE-lncRNAs. (a, b) Volcano plots of DE-lncRNAs of *M* vs. *N* and AS vs. *M*. Blue means downregulated genes, red represents upregulated genes, and black represents genes that do not differ significantly. (c) Heat maps of DE-lncRNAs of 3 groups. Red means high expression, and blue means low expression ($n = 3$).

NAG which is reflected to renal tubular injury and urine mALB in response to proteinuria was both increased in *M* group ($P < 0.01$), and both were improved by AS ($P < 0.05$ or $P < 0.01$) (Figures 1(b) and 1(c)). There was no significant change in Scr and BUN among three groups, serum CysC increased in group M, which reflects early renal function injury and was recalled by AS ($P < 0.05$) (Figures 1(d) and 1(f)). Besides, AS decreased IL-6 compared with group *M*, which represented the inflammatory level ($P < 0.05$ or $P < 0.01$) (Figure 1(g)).

3.2. The Effect of AS on Renal Pathology. The renal pathology that may lead to the deterioration of renal function was further explored. HE staining of rats in the M group showed hyaline degeneration of small arteries, dilation of renal tubules, vacuolation of cytoplasm, and tubule atrophy. Masson staining showed that the renal interstitium was widened and fibrotic. TUNEL showed that apoptosis was increased. AS improved the above pathological injury in varying degrees (Figures 2(a)–2(c)).

3.3. AS Modified the Disordered lncRNA Expression Profiles. In the 3 groups, we performed lncRNA sequencing aiming to explore the role of SHRs in renal damages and the intervention targets of AS. Using the Volcano plots to show the lncRNA expression profiles after compared the group *M* to

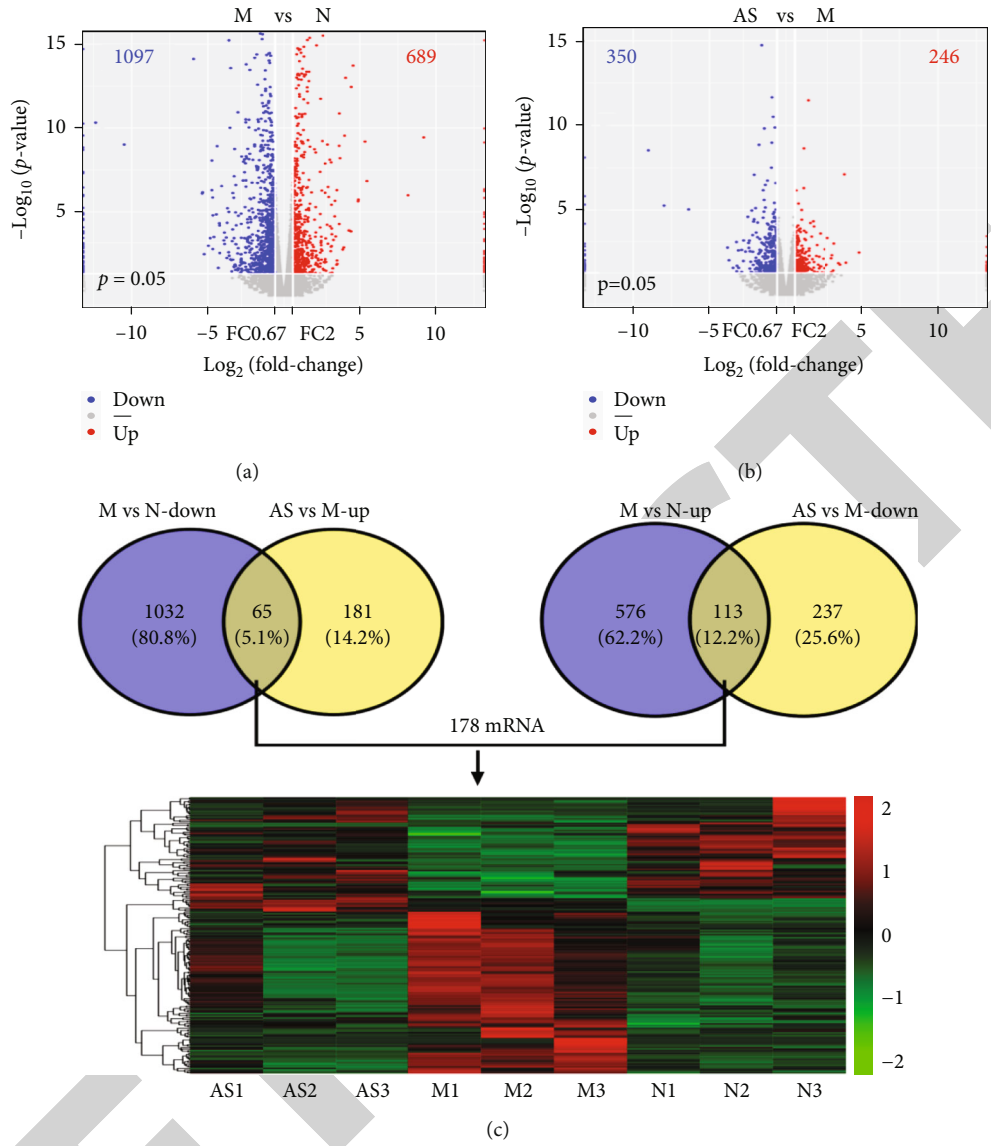


Figure 4: Volcano plots and heat maps of DE-mRNAs. (a, b) Volcano plots of DE-mRNAs of *M* vs. *N* and AS vs. *M*. Blue means downregulated genes, red represents upregulated genes, and black represents genes that do not differ significantly. (c) Heat maps of DE-mRNAs of 3 groups. Red means high expression, and green means low expression ($n = 3$).

the other 2 groups. Among 1435 DE-lncRNAs (*M* vs. *N*), 700 were upregulated and 735 were downregulated (Figure 3(a)). Among 726 DE-lncRNAs (AS vs. *M*), 355 were upregulated and 371 downregulated (Figure 3(b)). 237 DE-lncRNAs were found to be shared and showed the same trend in two comparisons with group *M* after further cluster analysis (Figure 3(c)), suggesting that they are important targets for SHR as to reverse renal injury lncRNAs.

3.4. AS Regulated the Coexpression Network and Pathways of lncRNA-mRNA. SHRs regulated the genetic by further transcriptome sequencing in the same kidney. In group *N*, 1786 DE-mRNAs were found, 1097 were upregulated and 689 downregulated compared to group *M* (Figure 4(a)). In group AS, 596 DE-mRNAs were found, 246 were upregulated and 350 downregulated (Figure 4(b)). 178 DE-mRNAs had a common change trend in the comparison between the other two groups and group *M*, which were displayed by cluster analysis (Figure 4(c)). Furthermore, we performed an association analysis between 237 DE-lncRNAs and 178 DE-mRNAs and constructed a coexpression network of the two. Then, 13 DE-mRNAs were predicted by 32 DE-lncRNAs, and their coexpression network map was further constructed (Figure 5). Finally, we performed KEGG and GO enrichment analysis on 13 DE-mRNAs. Three pathways positive regulation of blood pressure, negative regulation of blood pressure, and fatty acid beta-oxidation were highly enriched in GO analysis. In addition, pathway PPAR signaling pathway was highly enriched in KEGG analysis (Figure 6). Specific information of coexpressed 13 DE-

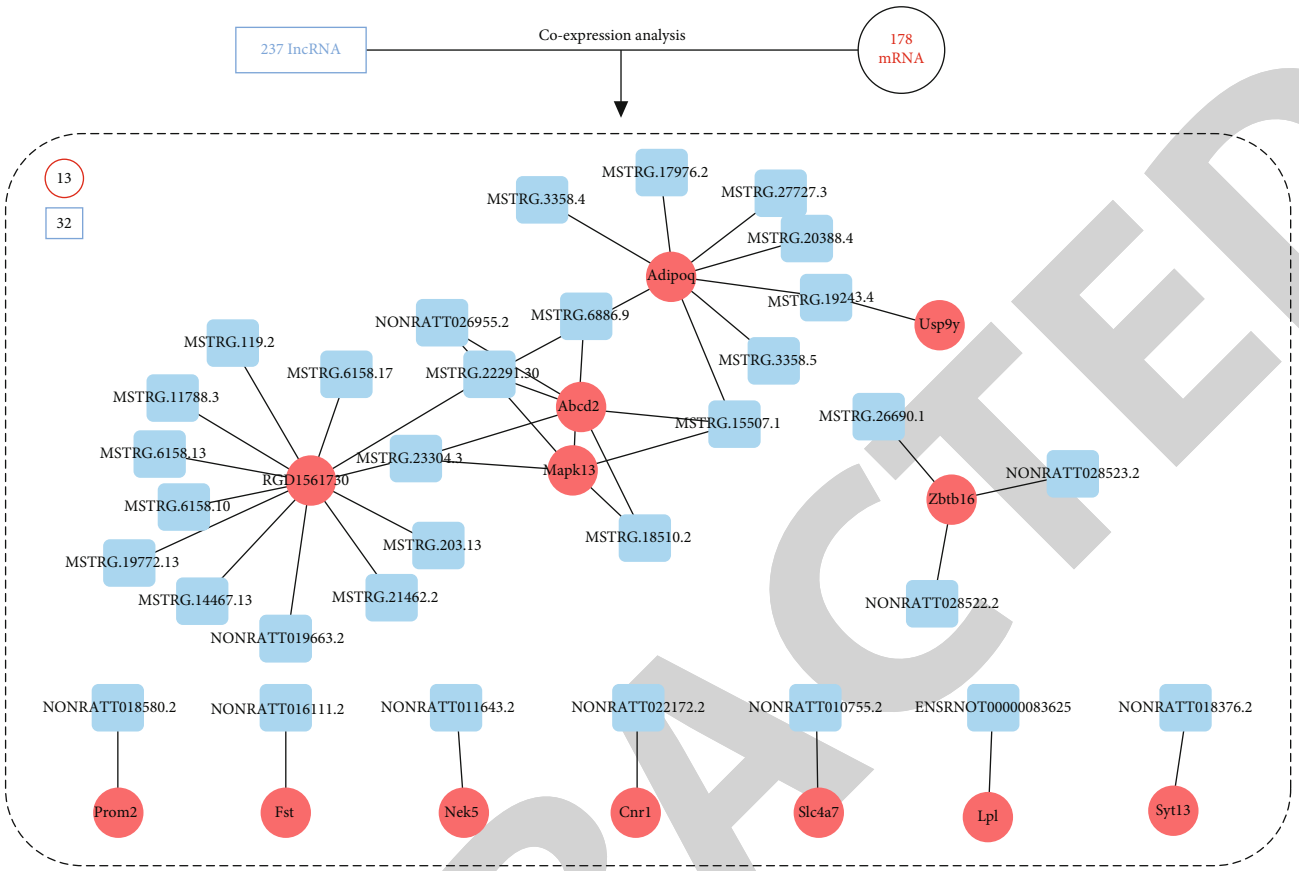


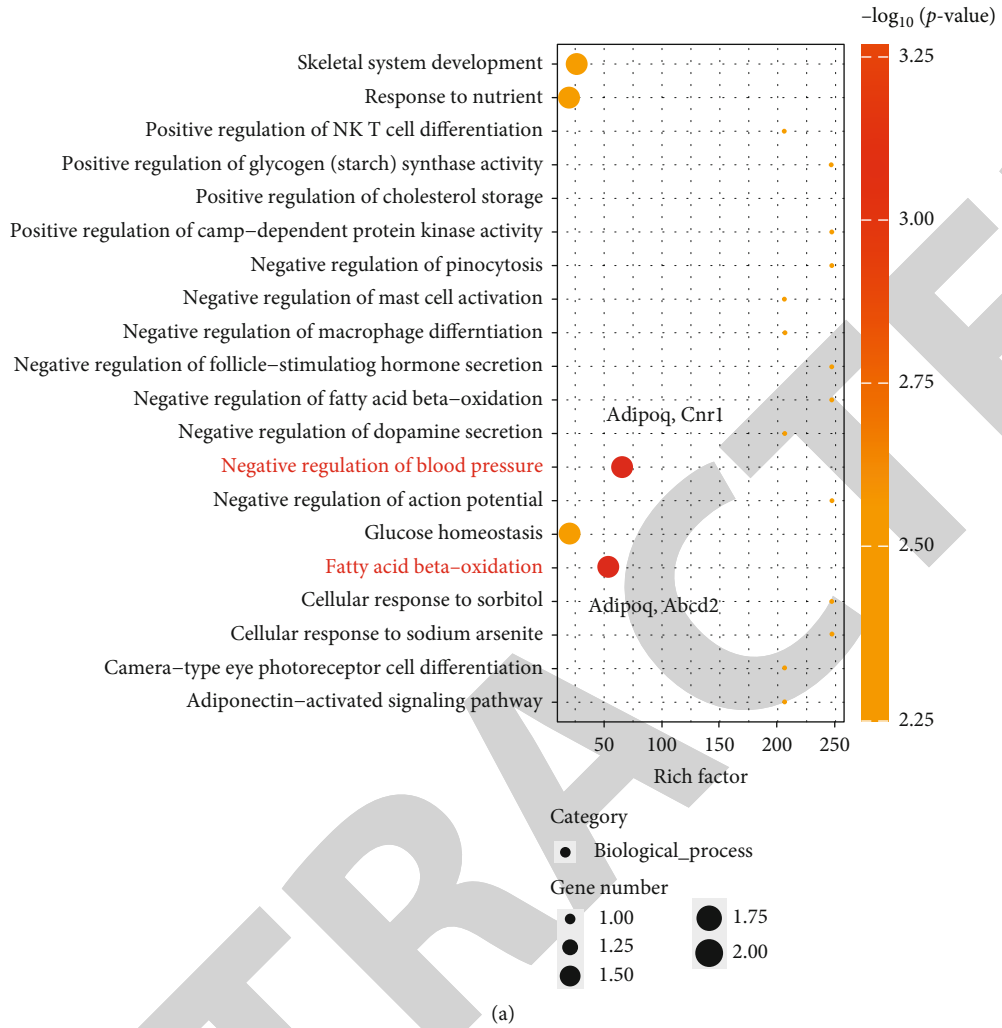
Figure 5: Coexpression of 237 DE-lncRNAs and 178 DE-mRNAs. Finally, 32 DE-lncRNAs and 13 DE-mRNAs have a targeted regulation relationship. The blue square represents DE-lncRNAs, and the red circle represent their targeted DE-mRNAs.

mRNAs and 32 DE-lncRNAs among the three groups is listed in Table 2.

3.5. Validation of Coexpression of DE-lncRNAs and DE-mRNAs Regulated by AS. 8 coexpressed DE-lncRNAs were further verified. The expression of NONRATT028523.2, NONRATT028522.2, MSTRG.22291.30, NONRATT022172.2, and ENSRNOT00000083625 increased in *M* group and decreased in varying degrees after AS intervention. At the same time, the expression of NONRATT026955.2, NONRATT016111.2 and MSTRG.15507.1 in *M* group decreased, which was also recalled by AS (Figures 7(a)–7(h)). We further verified 7 coexpressed DE-mRNAs. The expression of Adipoq and Abcd2 decreased, and the expression of Lpl, Cnr1, Fst, Mapk13, and Zbtb16 increased in *M* group, which were reversed by AS (Figures 8(a)–8(g)). All the verification were consistent with the sequencing results.

4. Discussion

Our study showed that AS could not only lower blood pressure steadily but also improve the damage of renal structure and function in SHRs. Specifically, on the one hand, AS reduced the levels of urine NAG, urine mALB, serum CysC, and IL-6 and increased the level of SOD, which indicated that AS can effectively abate proteinuria, relieve the damage of early renal function, and regulate the level of inflammation and oxidative stress as a whole. On the other hand, AS improved glomerular basement membrane thickening, renal tubular dilatation, and vacuolar degeneration in SHRs, which was consistent to our previous study [15, 16]. Furthermore, we found for the first time that AS inhibits collagen fibroplasia and apoptosis in renal tissue to some extent. Then, we further searched for the mechanism of AS to lower blood pressure and improve renal damage from the coexpression network of mRNAs and lncRNAs. AS reversed the disordered expression of 237 DE-lncRNAs and 178 DE-mRNAs in SHRs found in sequencing. lncRNAs can directly regulate mRNA and participate in the process of hypertension or kidney damage. Therefore, we conducted an association analysis on 237 DE-lncRNAs and 178 DE-mRNAs, and the results showed that 13 DE-mRNAs and 32 DE-lncRNAs were coexpressed, which were important targets of AS. Further analysis of 13 coexpressed DE-mRNAs indicated that PPAR signaling pathway was highly enriched in KEGG pathways, and negative regulation of blood pressure and fatty acid beta-oxidation was highly enriched in GO pathways.



(a)

Figure 6: Continued.

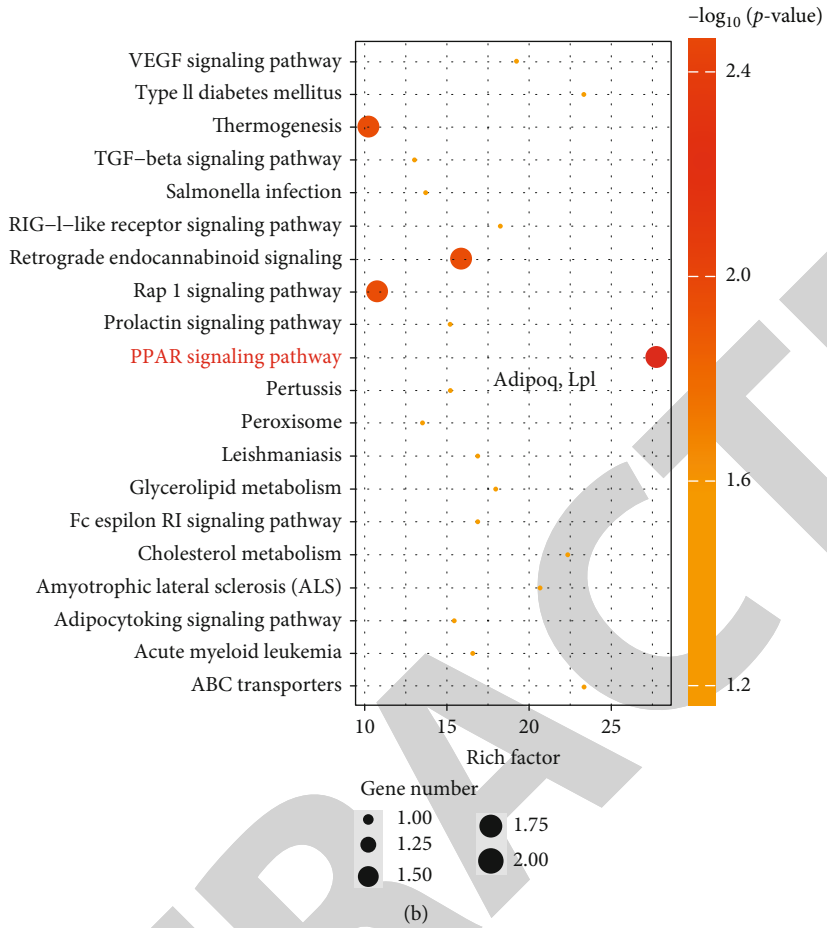


Figure 6: KEGG and GO enrichment analysis of 32 DE-lncRNAs targeted 13 DE-mRNAs. (a) The top 20 pathways in GO enrichment. (b) The top 20 pathways in KEGG enrichment. The red-labeled pathway is the pathway with the highest impact factor (TOP 2 in GO pathway and TOP 1 in KEGG pathway), and the labeled genes are the corresponding DE-mRNAs.

Our previous studies *in vitro* found that PPAR signaling pathway and renin-angiotensin system were highly involved in Ang II induced injury of renal arterial endothelial cells (RRAECs) by integrative analysis of miRNA-mRNA sequencing [18]. This study *in vivo* found that PPAR signaling pathway was also closely involved in the regulation of AS on BP and renal damage in SHRs. PPARs have key regulatory roles in metabolism, hypertension, and vascular function and comprise three subtypes, PPAR α, γ, and β/δ. PPAR γ could inhibit the oxidative stress of vascular endothelial cells and antagonize the renin-angiotensin system of vascular smooth muscle cells to relax blood vessels during hypertension [19]. In hypertensive nephropathy, gastrin normalized blood pressure, reduced renal tubular cell apoptosis, and increased macrophage endocytosis by activating PPAR α [20], and PPARβ/δ-dependent vasodilator pathway can selectively control renal blood flow [21]. Our sequencing results showed that Adipoq and lipoprotein lipase(Lpl), the important downstream effectors of PPAR α, γ and β/δ, were decreased in SHRs and were recalled by AS. Adipoq, which was the target gene of 8 DE-lncRNAs such as MSTRG.15507.1 and MSTRG.22291.30, played a role of renal protective agent by inhibiting renal inflammation, oxidative stress, reducing albuminuria and kidney fibrosis as an endogenous bioactive polypeptide or protein secreted by adipocytes in DCA + Ang II-induced CKD mice [22, 23]. Serum Adipoq levels in patients with pregnancy-induced hypertension were negatively correlated with albuminuria [24]. In addition, Lpl, the target gene of ENSRNOT00000083625, not only aggravated the early development of type 1 diabetic nephropathy in mice but also resulted in lipid accumulation in nephrotic syndrome and CKD [25, 26]. We verified by PCR that AS increased the expression of Adipoq and MSTRG.15507.1 and decreased the expression of Lpl, MSTRG.22291.30, and ENSRNOT00000083625. This was highly consistent with the sequencing results and may be important targets for AS to improve hypertensive renal damage through PPAR signaling pathway.

Positive regulation of blood pressure, negative regulation of blood pressure, and fatty acid beta-oxidation were the top 3 pathway in go enrichment. Sequencing results showed that Cannabis receptor 1 (Cnr1), the target gene of NONRATT022172.2, which belongs to positive

Table 2: Specific information of coexpressed 13 DE-mRNAs and 32 DE-lncRNAs among the three groups.

DE-mRNAs	log2FC		*P* value		Change trend	Coexpressed DE-lncRNAs and change trend (M : N/AS : M)
	M/N	AS/M	M/N	AS/M	(M : N/AS : M)	
Adipoq	-1.068117924	0.662296394	0.001175196	0.014328704	Down/up	MSTRG.27727.3 (down/up); MSTRG.15507.1 (down/up); MSTRG.20388.4 (up/down); MSTRG.22291.30 (up/down); MSTRG.19243.4 (up/down); MSTRG.3358.4 (up/down); MSTRG.17976.2 (up/down); MSTRG.3358.5 (down/up)
Lpl	0.794905651	-0.853559676	1.40585E-05	0.001316594	Up/down	ENSRNOT00000083625 (up/down)
Cnr1	1.356438499	-1.094538823	2.75E-09	0.000440588	Up/down	NONRATT022172.2 (up/down)
Abcd2	-1.158263739	1.597586728	0.049047871	5.70E-05	Down/up	MSTRG.15507.1 (down/up); MSTRG.22291.30 (up/down); MSTRG.6886.9 (up/down); MSTRG.23304.3 (down/up); NONRATT026955.2 (down/up); MSTRG.18510.2 (down/up)
Fst	0.894560311	-1.715392735	0.030006981	0.002178484	Up/down	NONRATT016111.2 (up/down)
Prom2	0.677685369	-0.600170925	5.42E-05	0.000422686	Up/down	NONRATT018580.2 (up/down)
RGD1561730	1.805761687	-1.190334966	0.00210257	0.037622436	Up/down	MSTRG.14467.13 (up/down); MSTRG.6158.10 (up/down); MSTRG.22291.30 (up/down); NONRATT019663.2 (down/up); MSTRG.203.13 (down/up); MSTRG.19772.13 (up/down); MSTRG.23304.3 (down/up); MSTRG.6158.17 (up/down); MSTRG.6158.13 (up/down); MSTRG.21462.2 (up/down); MSTRG.119.2 (down/up); MSTRG.11788.3 (up/down)
Syt13	1.55842082	-1.496316284	3.18E-12	2.80E-05	Up/down	NONRATT018376.2 (up/down)
Mapk13	0.777767762	-0.60268267	0.000106259	0.00169343	Up/down	MSTRG.15507.1 (down/up); MSTRG.22291.30 (up/down); MSTRG.6886.9 (up/down); MSTRG.23304.3 (down/up); NONRATT026955.2 (down/up); MSTRG.18510.2 (down/up)
Zbtb16	2.132334028	-1.354103129	1.17E-15	3.23E-07	Up/down	MSTRG.26690.1 (up/down); NONRATT028523.2 (up/down); NONRATT028522.2 (up/down)
Usp9y	Inf	-6.369845576	5.86E-07	9.01E-06	Up/down	MSTRG.19243.4 (up/down)
Slc4a7	1.327084846	-1.494267287	8.17E-14	6.66E-07	Up/down	NONRATT010755.2 (up/down)
Nek5	1.105543899	-1.069217283	5.11E-07	0.001094649	Up/down	NONRATT011643.2 (up/down)

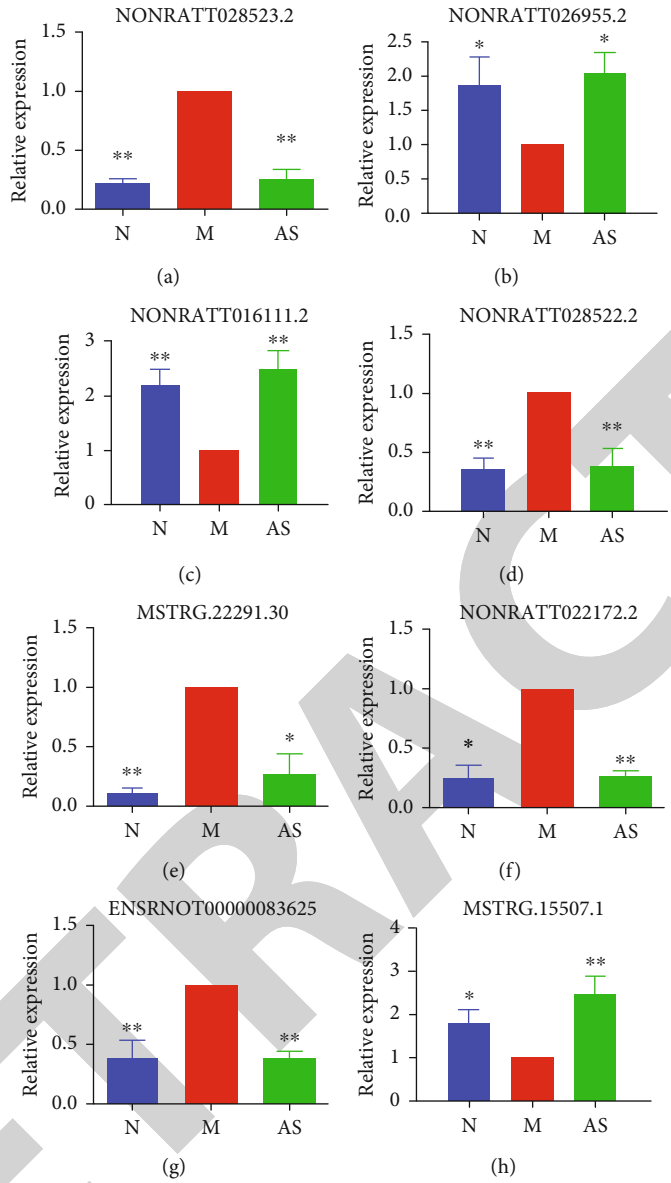


Figure 7: The recovery effect of AS on the lncRNAs co-expression profiles. (a–h) qRT-PCR verification of NONRATT028523.2, NONRATT026955.2, NONRATT016111.2, NONRATT028522.2, MSTRG.22291.30, NONRATT022172.2, ENSRNOT00000083625, and MSTRG.15507.1. Columns are mean ± SD ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. group M.

regulation of blood pressure, negative regulation of blood pressure pathway, increased in SHRs. Related studies have found that Cnr1 was expressed in many cell types of normal kidneys. Inhibiting its expression can not only regulate blood pressure by maintaining water and sodium balance but also delay the fibrosis of metabolic and nonmetabolic nephropathy [27]. Consistent with the results of sequence, AS reduced the expression of Cnr1 and NONRATT022172.2 by PCR, and the regulation of these two may be an effective mechanism for reducing the blood pressure of SHRs and protecting the kidneys. Fatty acid oxidation, especially β-oxidation of fatty acids in peroxisomes and mitochondria, was the main energy source for renal tubular epithelial cells. In CKD, the lack of key genes such as acyl-Coenzyme A oxidase (Acox) and phosphoenolpyruvate carboxy kinase (PCK) for fatty acid β-oxidation can directly induce ATP depletion, apoptosis, and lipid accumulation ultimately lead to epithelial-mesenchymal transition (EMT) and renal fibrosis [28, 29]. Sequencing results revealed that ATP binding cassette subfamily D member 2 (Abcd2), which was the target gene of 5 DE-lncRNAs such as NONRATT026955.2 and involved in peroxisomal import of fatty acids and/or fatty acyl-CoAs in the organelle [30], had a decreased expression in SHRs and was recalled by AS. Consistent with the sequence, AS increased Abcd2 and NONRATT026955.2 in the PCR verification, which may also contribute to the inhibition of renal tissue apoptosis by AS.

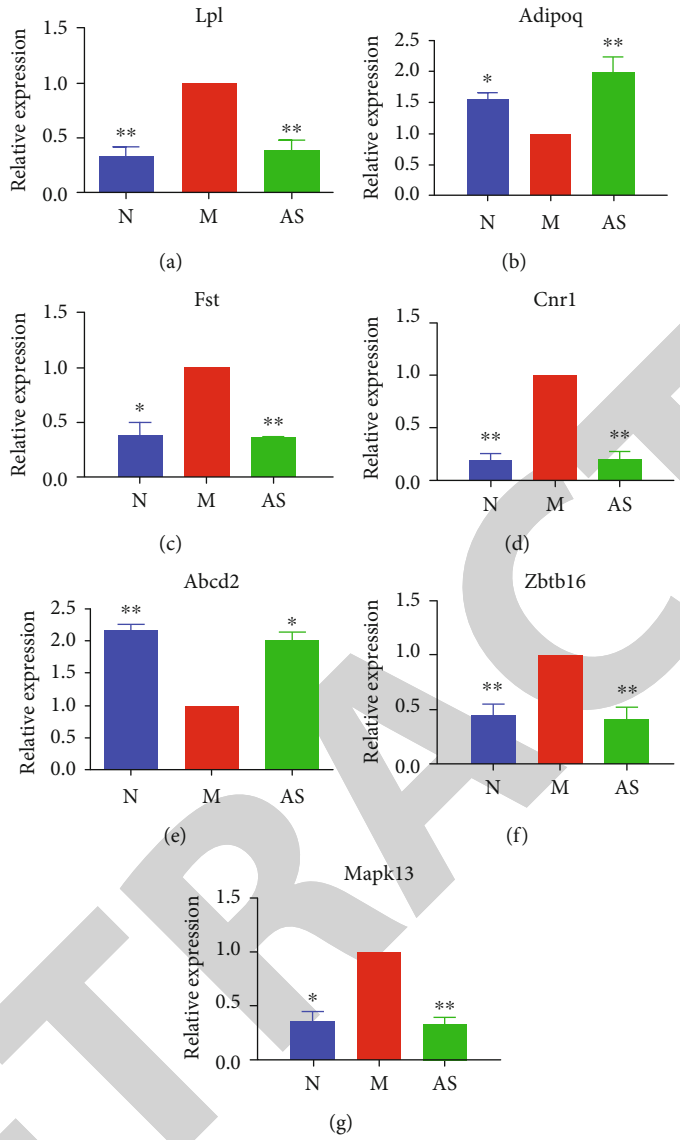


Figure 8: The recovery effect of AS on the mRNAs coexpression profiles. (a–g) qRT-PCR verification of Adipoq, Lpl, Abcd2, Cnr1, Fst, Mapk13, and Zbtb16. Columns are the mean ± SD ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. group M.

In addition, sequencing results also found that the expression of Fst, Prom2, RGD1561730, Syt13, Mapk13, Zbtb16, Usp9y, Slc4a7, and Nek5 in SHRs was disordered and recalled by AS. These genes were found to be related to the improvement of hypertensive renal damage by AS for the first time. The target gene Fst of NONRATT016111.2 belongs to the TGF-β signaling pathway, associated with renal fibrosis [31]. Zbtb16 is the target gene of NONRATT028523.2 and NONRATT028522.2 in the positive regulation of NK T cell differentiation pathway, whose overexpression can promote white fat production and accelerate lipid accumulation [32]. Our verification was highly consistent with sequencing and found that AS decreased the expression of Fst, Zbtb16, NONRATT016111.2, NONRATT028523.2, and NONRATT028522.2. In particular, the coexpression network confirms the molecular communication between genes. For example, Adipoq, Abcd2, and Mapk13 are regulated by MSTRG.15507.1 and MSTRG.22291.30 at the same time. Abcd2 and Mapk13 are also target genes of NONRATT026955.2. The mutual communication of coexpression differences may contribute to the improvement of hypertensive renal damage by AS.

In conclusion, the results of this study demonstrated that AS had good antihypertensive and renal protective effects, which may be mediated by the coexpression network of lncRNA-mRNA. This study provided new insights for *Astragalus membranaceus* and *Salvia miltiorrhiza* to improve hypertensive renal damage.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

All authors declare that there is no potential conflicts of interest referring to this study.

Authors' Contributions

Le Zhou and Cong Han contributed equally to this work and should be considered as co-first authors.

Acknowledgments

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Retraction

Retracted: Effect of Exercise Intervention on Internet Addiction and Autonomic Nervous Function in College Students

BioMed Research International

Received 11 July 2023; Accepted 11 July 2023; Published 12 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] W. Zhang and R. Xu, "Effect of Exercise Intervention on Internet Addiction and Autonomic Nervous Function in College Students," *BioMed Research International*, vol. 2022, Article ID 5935353, 7 pages, 2022.

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Research Article

Effect of Exercise Intervention on Internet Addiction and Autonomic Nervous Function in College Students

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Objective. To investigate the effects of 12-week physical exercise (jogging, basketball, and outdoor training) on sleep quality, harmful mood, and heart rate variability (HRV) in college students with Internet addiction. *Methods.* 46 college students with Internet addiction were chosen and then randomly assigned to the Internet addiction group (IA, $n = 23$) and the Internet addiction exercise group (IA+EX, $n = 23$). The subjects in the IA+EX group underwent physical exercise for 12 weeks (three times per week), and the IA group did not perform regular physical exercise during the experiment. Then, the degree of Internet addiction, depression, and sleep quality were evaluated by using Young's Internet Addiction Test (IAT) scale, Center for Epidemiologic Studies Depression (CES-D) scale, and Pittsburgh sleep quality index (PSQI); HRV were measured by using Polar Team 2 before and after physical exercise intervention. *Results.* (1) After the 12-week exercise, compared to preexercise intervention, the scores of IAT, CES-D, and PSQI significantly decreased ($t = 12.183$, 9.238, 5.660; $P < 0.01$) in the IA+EX group; compared with the IA group, the scores of IAT, CES-D, and PSQI significantly decreased ($t = 2.449$, 3.175, 4.487; $P < 0.05$, $P < 0.01$) in IA+EX group college students with Internet addiction. (2) After the 12-week exercise, compared to preexercise intervention, LFn and the ratio of LF/HF significantly decreased ($t = 5.650$, 3.493; $P < 0.01$) and HFn significantly increased ($t = -2.491$, $P < 0.05$) in the IA+EX group; there were no significant differences in the above indexes before and after the experiment in the IA group ($P > 0.05$). Compared with the IA group, HFn significantly increased ($t = 3.616$, $P < 0.01$) and the ratio of LF/HF significantly decreased ($t = 2.099$, $P < 0.01$) in IA+EX group college students with Internet addiction; there was no significant difference in LFn between the two groups. *Conclusion.* Long-term physical exercise could significantly reduce the degree of Internet addiction and depression, improve sleep quality, and balance sympathetic parasympathetic function of college students with Internet addiction, indicating that exercise-based intervention might be an effective way to alleviate or even eliminate Internet addiction.

1. Introduction

According to the 2019 report of the China Internet Network Information Center, the number of Internet users in China reached 854 million, most of which are teenagers and young adults [1]. Although the Internet has brought great convenience to our lives, poor network usage can lead to impaired mental health, academic failure, decline in job performance, and especially Internet addiction. Internet addiction is a type of behavioral addiction, which refers to the uncontrolled online impulse under the influence of nonaddictive substances and manifests as a significant decline in social and psychological functions due to excessive use of the Internet [2]. Moreover, Internet addiction has been considered a serious mental disorder, which may lead to attention deficit, social phobia and impulsivity, depression, anxiety, and obsessive-compulsive disorder [3]. The investigation of Younes et al. [4] showed that Internet addiction could significantly affect the sleep quality, emotional disturbance, and self-esteem of college students, hindering their learning and affecting long-term career goals, which have produced extensive and harmful consequences for the whole society. Nowadays, these serious problems have attracted widespread attention in society and the research on the underlying

mechanisms of Internet addiction and mood disorders is urgently needed. Studies have shown that Internet addiction is closely related to autonomic dysfunction. The heart rate variability (HRV) is an effective noninvasive measure to assess autonomic function by analyzing the frequency and time components of heart rate changes over time. Lin et al. [5] found that the HRV decreased in children with Internet addiction, which was manifested as a significant increase in low-frequency power (LF) and a significant decrease in high-frequency power (HF) and total power (TP) which was associated with sleep disturbances in children with Internet addiction. And Kim et al. [6] found that adolescent autonomic dysfunction was related to depression caused by Internet addiction. In addition, Wang et al. [7] also found that the scores of the addiction scale for Internet addicts were positively correlated with LF and LF/HF ratio of HRV and negatively correlated with HF, which suggested that HRV can be used to assess whether adolescents are addicted to the Internet and is an important reference indicator of the severity of Internet addiction.

Meta-analysis shows that drug treatment (bupropion, methylphenidate, etc.), cognitive behavioral therapy, family group therapy, and active physical exercise have good effects on Internet addiction [8], among which exercise intervention is the low-cost and simple intervention method that has attracted much attention. Studies have shown an inverse relationship between physical activity levels and the severity of video game-related problems and Internet addiction [9]. And Cerrillo-Urbina et al. [10] found that physical exercise interventions can reduce inattention, hyperactivity, and impulsivity, as well as improve anxiety, executive function, and social skills in people with ADHD. In addition, Cao [11] found that yoga can improve the anxiety and depression of obese female college students by regulating the level of autonomic nervous function and promoting the physical and mental development of college students. And physical exercise can produce a series of pleasant feelings to the body, which can better eliminate the anxiety and depression of the body, make the body produce a great sense of happiness, and improve the mental health of the body. Based on the above literature, it can be seen that physical exercise intervention may have a positive effect on Internet addicts, but whether the effect of exercise on Internet addiction, bad mood, and sleep quality of college students with Internet addiction is related to the autonomic function needs to be confirmed by research. Therefore, the current study investigates the effect of a 12-week exercise intervention (jogging, basketball exercise, and outreach training) on sleep quality, negative emotions (anxiety and depression levels), and HRV in college students with Internet addiction, so as to provide a theoretical basis for exercise intervention on Internet addiction.

2. Objects and Methods

2.1. Research Objects. Based on G power calculation, 46 college students with Internet addiction were consulted in the psychological counseling room of Zhengzhou University and randomly divided into two groups, the Internet addiction group (IA; $n = 23$) and the Internet addiction exercise group (IA+EX; $n = 23$). There were 20 males and 12 females in the IA group, with an average age of 19.61 ± 1.19 years and the net age of 3.96 ± 1.07 years. There were 18 males and 14 females in the IA+EX group, with an average age of 19.39 ± 1.73 years and the net age of 4.04 ± 1.11 years. There was no statistical significance in the comparison of basic information such as age, gender, and Internet age among the two groups of college students by independent samples t-test ($P > 0.05$).

The inclusion criteria are as follows: ① those who have been diagnosed as Internet addicts by standardized clinical interview and Internet addiction test and ② no history of taking psychotropic drugs in the 1ast month. Exclusion criteria are as follows: ① those with a history of serious physical or psychological problems, including other addiction disorders, psychotic disorders, and major depressive disorders; ② those with serious physical illnesses; and ③ students who are using drug therapy and are receiving psychological therapy. Before the intervention, all subjects filled out the informed consent form and the research purpose, process, benefits, and possible inconveniences are explained in detail to the subjects, and it was approved by the ethics committee of the university.

2.2. Methods

2.2.1. Exercise Intervention Program. From September to November 2020, exercise intervention was implemented in Zhengzhou University for 12 weeks (3 times/week, 60 min/time). Each exercise includes 10 minutes of warmup, 10 minutes of relaxation exercises (jogging and stretching), and 40 minutes of aerobic exercise, including jogging, basketball exercise, and outreach training (exercise intensity: 60%-65% HRmax). In order to ensure the safety during exercise, the Polar Sports tester monitors the exercise intensity of the subjects. The control group was sedentary at the same time, and the members of the experimental group recorded their feelings of daily exercise.

2.2.2. Adolescent Internet Addiction Scale. Before and after the exercise intervention, all subjects were used to assess the severity of compulsive Internet use by the Young's Internet Addiction Test (IAT) which is widely used in international studies, and its validity and reliability have been proved in previous studies. The scale included 5 components and 20 items and is scored on a 5-point Likert scale (1 is hardly ever, 2 is occasionally, 3 is sometimes, 4 is often, and 5 is always); the total score is 100 points, 40-60 is mild Internet addiction, 60-80 is moderate Internet addiction, and 80-100 is severe Internet addiction. This scale has high reliability and validity; Cronbach's alpha coefficient is 0.90 [12].

2.2.3. CES-D Self-Rating Depression Scale. The CES-D scale is used to evaluate depressive symptoms in the general population and to screen people at high risk for depression. The scale has been tested in Chinese adolescents and achieved good reliability and validity. The scale contains a total of 20 items and is used to measure the frequency of depressive symptoms in the past week. The scale uses a 4-point scoring system (0 is hardly ever, 1 is sometimes, 2 is often, and 3 is

most of the time), and the overall score ranges from 0 to 60 points, with higher scores for depression the higher the degree. A score of 0-15 indicates no depression, a score of 16-20 indicates mild depression, a score of 21-30 indicates moderate depression, and a score greater than 30 indicates severe depression. Cronbach's alpha coefficient of this scale is 0.86 [13].

2.2.4. Pittsburgh Sleep Quality Index (PSQI). Before and after the exercise intervention, the sleep status of the subjects within one month was assessed using a standard and valid questionnaire of the PSQI scale. The scale consists of 19 items, of which 18 items generated seven components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunctions), each of which is scored on a 0-3 scale (0 means very good, 1 means good, 2 means bad, and 3 indicates very poor), and the total score is 0-21 points. A total score of <5 indicates satisfactory sleep quality, and ≥5 indicates poor sleep quality. Cronbach's alpha coefficient is 0.74 [14].

2.2.5. HRV Measurement. The HRV of subjects was measured using a Polar Team 2 team before and after exercise intervention. In order to avoid the influence of circadian rhythm on autonomic function, HRV measurement was scheduled at 8:00-10:00 am, the test environment humidity was 55-65%, and the temperature was 25 ± 1°C. Before the test, the experimenter should wear a chest strap, lie down, and rest for 10 minutes. The Polar 2 software for data collection was opened and gathered for 10 minutes when the subjects breathe calmly. *Test indicators include* low-frequency power (low frequency (LF), 0.04-0.15 Hz), high-frequency power (high frequency (HF), 0.15-0.4 Hz), and low-frequency/high-frequency (LF/HF) ratio.

2.3. Statistical Analysis. All experimental data are represented by $\bar{x} \pm s$, and the data was analyzed using SPSS 21.0 statistical software package. Normal distribution was analyzed using the Shapiro-Wilk test; since LF and HF do not obey normal distribution, statistical analysis is performed after logarithmic transformation (Ln). Paired t-test was used to compare the experimental data before and after exercise intervention within the group (groups IA and IA+EX). Independent samples t-test was used to analyze the differences between groups in IAT, CES-D, and PSQI scores and HRV indexes before and after exercise intervention, and $P < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1. The Effect of Exercise Intervention on Internet Addiction and Depression in College Students with Internet Addiction. As shown in Table 1, compared with preexercise, the scores of IAT and CES-D of college students in the IA+EX group significantly decreased (t values were 12.183 and 9.238; $P < 0.01$), and the decrease was 10.35% and 8.74%, respectively; there was no significant difference in the above indicators in the IA group before and after the experiment (all $P > 0.05$). Before the exercise intervention, there was no significant difference in the scores of Internet addiction and depression between the college students in the IA+EX group and the IA group (t values were -0.502 and -0.434, $P > 0.05$); after the exercise intervention for 12 weeks, compared with the IA group, the scores of Internet addiction and depression level of college students in the IA+EX group significantly decreased (t values were 2.449 and 3.175; $P < 0.05$ and $P < 0.01$).

3.2. The Effect of Exercise Intervention on the Sleep Quality of College Students with Internet Addiction. As shown in Table 2, after 12 weeks of exercise intervention, compared with preexercise, the scores of subjective sleep quality, sleep latency, sleep disturbance, and daytime dysfunction in college students with Internet addiction significantly decreased (t values were 2.577, 2.313, 2.152, 2.472, and 5.660; $P < 0.05$ and $P < 0.01$); there was no significant change in sleep persistence, habitual sleep efficiency, and hypnotic drug dependence before and after intervention in the IA+EX group (t values were 1.367, 1.447, and 1.000; $P > 0.05$); all the above indexes in the IA group had no significant changes before and after the experiment ($P > 0.05$). Before exercise intervention, there were no significant differences in the scores of 7 components of sleep quality and PSQI between the IA group and the IA+EX group ($P > 0.05$). Except the scores of subjective sleep quality, sleep latency, sleep disturbance, daytime dysfunction, and PQSI significantly decreased (t values were 2.275, 2.053, 2.065, 2.655, and 4.487; $P < 0.05$ and $P < 0.01$). There was no significant difference in the scores of habitual sleep efficiency and hypnotic drug dependence when compared with the IA group (t values were 1.164, 1.026, and -0.321; $P > 0.05$).

3.3. Effect of Exercise Intervention on HRV of College Students with Internet Addiction. As shown in Table 3, after 12 weeks of exercise intervention, compared with preexercise, the LFn and LF/HF of college students with Internet addiction in the IA+EX group significantly decreased (t values were 5.650 and 3.493; both $P < 0.01$); the decrease was 3.87% and 34.45%, respectively; HFn significantly increased by 2.25% ($t = -2.491$, $P < 0.05$); there was no significant difference in all the above indexes before and after the experiment in group IA ($P > 0.05$). There were no significant differences in LFn, HFn, and LF/HF between the IA group and the IA+EX group before exercise intervention (t values were -0.216, 0.435, and 0.471; $P > 0.05$); after 12 weeks of exercise intervention, compared with the IA group, the HFn of IA+EX college students with Internet addiction increased significantly ($t = 3.616$, $P < 0.01$), and the LF/HF ratio decreased significantly ($t = 2.099$, $P < 0.05$). There was no significant difference in LFn between the two groups ($t = 2.099$, $P < 0.05$; $t = -0.792$, $P > 0.05$).

4. Discussion

4.1. The Effect of Exercise Intervention on Internet Addiction, Depression, and Sleep Quality of College Students with Internet Addiction. The Internet has become a key resource in society and everyday life, and Internet addiction is

Table 1: Results of IAT and CES-D scores in college students with Internet addiction before and after the exercise interventions ($\bar{x} \pm s$).

Group	Before and after	n	Value	CES-D	IAT
IA group	Before	23		26.78 ± 5.63	66.83 ± 6.26
	After	23		27.83 ± 5.72	67.91 ± 7.12
			t value	−1.850	−1.150
			P value	0.078	0.262
IA+EX group	Before	23		26.96 ± 4.80	68.09 ± 10.29
	After	23		24.17 ± 5.47$^{**\#}$	62.14 ± 8.81$^{**\#}$
			t value	9.238	12.183
			P value	0.000	0.000

Note: $^{*}P < 0.05$ and $^{**}P < 0.01$, significant difference before vs. after program; $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$, the IA group vs. the IA+EX group.

Table 2: Results of PSQI scores in college students with Internet addiction before and after the exercise interventions ($\bar{x} \pm s$).

Sleep quality (score)	Group	n	Before	After	t value	P value
Subjective sleep quality	IA	23	1.26 ± 0.45	1.30 ± 0.55	-0.569	0.575
	IA+EX	23	1.30 ± 0.70	0.96 ± 0.47$^{*\#}$	2.577	0.017
Sleep latency	IA	23	1.17 ± 0.72	1.22 ± 0.67	-1.000	0.328
	IA+EX	23	1.13 ± 0.63	0.86 ± 0.46$^{*\#}$	2.313	0.030
Sleep persistence	IA	23	0.91 ± 0.59	1.00 ± 0.60	-1.447	0.162
	IA+EX	23	0.96 ± 0.47	0.83 ± 0.39	1.367	0.816
Habitual sleep efficiency	IA	23	0.35 ± 0.48	0.30 ± 0.47	1.000	0.328
	IA+EX	23	0.30 ± 0.47	0.22 ± 0.42	1.447	0.162
Sleep disturbance	IA	23	1.22 ± 0.67	1.35 ± 0.71	-1.817	0.083
	IA+EX	23	1.13 ± 0.63	0.96 ± 0.56$^{*\#}$	2.152	0.043
Hypnotic drug dependence	IA	23	0.22 ± 0.42	0.26 ± 0.45	-0.569	0.575
	IA+EX	23	0.35 ± 0.49	0.30 ± 0.47	1.000	0.328
Daytime dysfunction	IA	23	1.39 ± 0.58	1.52 ± 0.59	-1.817	0.083
	IA+EX	23	1.30 ± 0.56	1.09 ± 0.51$^{*\#}$	2.472	0.022
PSQI	IA	23	6.52 ± 1.41	6.82 ± 1.44	-2.077	0.050
	IA+EX	23	6.47 ± 1.23	5.17 ± 1.03$^{**\#\#}$	5.660	0.000

Table 3: Results of HRV parameters in college students with Internet addiction before and after the exercise interventions ($\bar{x} \pm s$).

HRV	Group	Before	After	t value	P value
LFn	IA	3.91 ± 0.17	3.93 ± 0.15	-1.849	0.060
	IA+EX	3.88 ± 0.18	3.73 ± 0.23**	5.650	0.000
HFn	IA	3.55 ± 0.31	3.59 ± 0.28	-2.019	0.056
	IA+EX	3.57 ± 0.29	3.64 ± 0.30$^{*\#\#}$	-2.491	0.021
LF/HF	IA	2.59 ± 1.58	2.62 ± 1.50	-0.208	0.837
	IA+EX	2.38 ± 1.42	1.56 ± 1.70$^{**\#}$	3.493	0.002

another worldwide public health problem. Internet addiction has also been considered as a psychological escape mechanism to avoid real-world problems and has been proven to be associated with both mental and physical symptoms. Examples are the higher risk of Internet addition, inferior mental health outcomes, suicidal ideation, depression, and anxiety [15]. Meta-analysis shows that the global prevalence of Internet addiction is 1.6%-18% [16], while

the prevalence of Internet addiction among Chinese college students is 11.3% [17]. The negative impact of Internet addiction on physical and mental health has been a major public concern. It is reported that Internet addiction is significantly associated with mood disorders, poor sleep quality, low self-esteem, impulsivity, suicide, low levels of physical activity, and health problems (migraines, back pain, and obesity), and the prevalence of poor sleep quality, depression, and anxiety symptoms is high among college students worldwide [18]. In addition, college students with sleep problems are more likely to have symptoms of depression. In recent years, physical exercise as an alternative or adjunctive treatment for Internet addiction has been extensively studied. Meta-analysis showed that exercise intervention significantly improved various dimensions of the Internet addiction scale and psychopathological symptoms, especially the improvement of Internet addiction symptoms [19]. In addition, Internet addiction is related to decreasing physical activity by the Internet addiction scale. Compared with physical inactive peers, physical active young people tend to get more satisfaction from sleep and are less likely to develop Internet addiction [20]. And Kocak [21] found that regular exercise (12 weeks, 3-5 times/week, at least 45 min/time) can reduce college students' Internet addiction and Internet time and help to prevent the psychosocial, physical, and psychological negative effects induced by Internet addiction, which suggested that regular physical exercise can reduce and prevent college students' Internet addiction. The research of Zheng et al. [22] suggested that exercise intervention has a positive effect on the treatment of smartphone addiction and should be regarded as an alternative nondrug method for the treatment of smartphone addiction patients. In addition, Wang et al. [23] thought that at least 12 weeks of physical exercise can lead to the adaptation of key brain structures involved in reward and inhibitory control and improve Internet addiction symptoms. And physical exercise especially moderate-intensity comprehensive sports intervention (basketball, badminton, sports games, etc.) has been confirmed to be better improvement in the prevention and treatment of Internet addiction [24]. Therefore, the current study implemented a 12-week exercise intervention (including jogging, basketball, and expansion sports) for the Internet addicts. The results showed that compared with the IA group, the scores of Internet addiction and depression levels of college students in the IA+EX group significantly decreased, and the sleep quality significantly improved, indicating that exercise intervention may be an effective way to alleviate or even eliminate Internet addiction. However, Gao et al. [25] found that an 8-week exercise intervention has a good effect on the mental health correction in mild Internet addicts, but the treatment effect is not ideal for moderate and severe patients. The current study mainly recruited mild and moderate Internet addicts, and further research needs to conduct exercise intervention studies on Internet addicts with different degrees.

4.2. The Effect of Exercise Intervention on HRV of College Students with Internet Addiction. The substantial association between both Internet addiction and depression and sleep quality and social support may shed insights to our understanding about the mechanism. HRV is directly controlled by the central nervous system and the autonomic nervous system, and it is one of the important indicators of the human body's adaptation process, but there are few reports on the effects of Internet addiction on autonomic nervous function. The results of this study found that college students with Internet addiction had higher sympathetic nerve activity and lower parasympathetic nerve activity and overall autonomic nerve activity, which suggested that long-term, excessive use of the Internet is at risk of reducing HRV levels. Studies have shown that HRV is an effective tool for measuring and regulating emotional responses, and the reduction in HRV indicates autonomic dysregulation and lack of flexibility in response to stimuli, which can lead to physical and psychological disorders (emotional dysregulation and decreasing social engagement) [26]. In the treatment of patients with anxiety and depression, Kircanski et al. [27] found that patients with high HRV have a better prognosis, while those with low HRV have a poorer prognosis, indicating that HRV has broad application prospects in evaluating the prevention of psychosomatic and mental dysfunction/the therapeutic effect of intervention. Therefore, it can be considered that the depression level of college students with Internet addiction in this study may be related to the reduction of HRV. However, the mechanism of the reduction of HRV in the college students with Internet addiction is still unclear. Kim et al. [6] thought that Internet addiction can change the sleep-wake schedule, so excessive use of the Internet will deprive sleep time of people, which results in poor sleep quality and exerts adverse effects on autonomic nervous system function. And Lin et al. [28] found that Internet addiction is associated with higher sympathetic nerve activity and lower parasympathetic nerve activity, and lack of sleep (less sleep time and poor sleep quality) can activate the stress system and increase the catecholamine, norepinephrine, and epinephrine levels, thereby increasing sympathetic nerve activity, which suggests that the autonomic dysregulation associated with Internet addiction may be partly due to poor sleep quality. This study is a cross-sectional study and cannot confirm a causal relationship between Internet addiction, sleep quality, and the autonomic nervous system. In conclusion, the effect of Internet addiction on the autonomic nervous system function may be a comprehensive effect of psychological, physiological, and behavioral changes accompanying Internet overuse, and the mechanism of autonomic dysregulation associated with Internet addiction needs to be further elucidated.

Long-term physical activity has been shown to induce resting bradycardia with reducing sympathetic and/or elevated parasympathetic activity [29]. In addition, there is growing evidence that regular physical activity may enhance physical and mental health and relieve stress states by optimizing HRV and improve well-being [30]. Toni et al. [31] found that the combination of long-term physical exercise and the antidepressant sertraline could significantly increase HRV in elderly patients with depression and had an antidepressant effect by regulating the cardiac autonomic function. And Tseng et al. [32] found that 12 weeks of moderate-

intensity exercise training had a beneficial effect on sleep quality and cardiac autonomic function; middle-aged and elderly people with poor sleep quality should be encouraged to perform moderate-intensity aerobic exercise to improve their cardiac autonomic function. In addition, Zhang et al. [33] found that 24-week aerobic exercise can reduce drug addiction of drug addicts by regulating the autonomic nervous function of compulsory drug addicts. However, there are few related reports on the effect of exercise on the HRV of college students with Internet addiction. The results of this study found that compared with the IA group, after 12 weeks of exercise intervention, the HFn increased significantly and the LF/HF ratio decreased significantly of college students with Internet addiction in IA+EX, indicating that long-term physical exercise may improve the excitability of the vagus nerve and promote sympathetic-parasympathetic balance, which can improve the cardiac autonomic function of college students with Internet addiction to a certain extent. In addition, it was previously reported that low HRV was significantly associated with self-regulation ability and craving for Internet use [34]. Therefore, the improvement of long-term physical exercise on Internet addiction in college students with Internet addiction is related to the increase of HRV and the balance of sympathetic-parasympathetic nerve function.

5. Summary

The increase of HRV can enhance the emotion regulation ability and improve the level of depression and sleep quality of the college students with Internet addiction, and the specific mechanism needs to be further studied.

Data Availability

The experimental 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 to report regarding the present study.

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Retraction

Retracted: A Rehabilitation Model Conducive to Postoperative Recovery of Endometrial Cancer Patients after Laparoscopy

BioMed Research International

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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] L. Yang and F. Han, "A Rehabilitation Model Conducive to Postoperative Recovery of Endometrial Cancer Patients after Laparoscopy," *BioMed Research International*, vol. 2022, Article ID 9910841, 7 pages, 2022.

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Research Article

A Rehabilitation Model Conducive to Postoperative Recovery of Endometrial Cancer Patients after Laparoscopy

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Although collaborative care is increasingly being implemented in the treatment of various diseases, there are currently no related studies on its effects in endometrial cancer patients after laparoscopic treatment. Thus, this study is aimed at investigating the significance of an integrated medical and nursing care model for women with gynecologic malignant tumors who underwent laparoscopic treatment. The patients were randomly divided into a medical-nursing integrated nursing group (study group) and a general nursing group (control group). Their serum carbohydrate antigen 19-9 (CA19-9), human epididymal protein 4 (HE4), CA15-3, and CA125 levels were measured at admission, 7 and 15 days after admission, and 30 days after discharge. Their first postoperative flatulence time, eating time, and hospitalization duration were recorded, and the self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were used to evaluate the psychological state of the patients. A questionnaire survey was also used to evaluate their satisfaction with nursing. Adverse events within 2 years of follow-up were recorded. The results showed that the clinical performance of the study group was significantly better than that of the control group. Further, the study group demonstrated significantly lower serum tumor marker levels, SAS score, SDS score, and incidence of adverse events at 7 and 15 days after admission and 30 days after discharge and higher nursing satisfaction than the control group. Thus, the collaborative nursing mode might be more conducive to the recovery of women who have underwent laparoscopic treatment for gynecologic malignant tumors than normal routine nursing.

1. Introduction

Endometrial cancer is the most common gynecological malignancy with a growing incidence [1]. It led to approximately 320,000 new cases and 76,000 deaths in 2012 [2]. According to statistics, it is the sixth most common cancer worldwide and the 14th leading cause of cancer death in women [3]. At present, hysterectomy and the removal of the fallopian tubes and ovaries are considered the standard treatment for women with endometrial cancer, while radiotherapy and chemotherapy are regarded as common auxiliary treatments [4]. Ben-Hur and Phipps described the first laparoscopic-assisted vaginal hysterectomy in 1989 [5]. With the advancement in cancer research, minimally invasive treatment such as laparoscopic surgery has been increasingly used and started to replace the traditional open surgery in endometrial cancer treatment [6]. However, it was recently reported that the incidence of laparoscopic-associated adverse events, such as lymphedema, neuropathy, and wound infection rates, for endometrial cancer was quite high, at ~21%, and might even reach 33% in some settings [7]. Therefore, postoperative care for endometrial cancer patients is particularly important to timely identify and treat complications and enhance their recovery.

The postoperative recovery of patients was found to be closely associated with the methods and mode of nursing. Collaborative care is a complex intervention for depression developed in the United States. Specifically, collaborative care has advantages like combined multiprofessional approaches to patient care, structured management plans, scheduled patient follow-up, and enhanced interprofessional communication [8]. The collaborative care model has been

recognized as pivotal in improving the management of various chronic diseases [9]. In addition, collaborative care has been shown to improve the short- and long-term depression outcomes more effectively than standard care. Further, incremental evidence shows that collaborative care can improve the prognosis and recovery of patients with long-term chronic diseases such as diabetes [10], significantly reduce the length of hospital stay of patients with gastrointestinal cancer, and improve patients' quality of life [11]. Thus, based on existing literature, we believe that collaborative care would also benefit patients with reproductive system cancer.

However, there are currently no studies on the effects of integrated nursing involving doctors and nurses under a collaborative care model for the laparoscopic treatment of endometrial cancer patients. To fill this gap, we performed this study to compare the effects of collaborative care versus general care on women who underwent laparoscopic treatment for endometrial cancer to provide an effective theoretical basis for potentially improving the treatment and outcomes of endometrial cancer patients.

2. Materials and Methods

2.1. Study Subjects. The data of 1144 patients with endometrial cancer who underwent laparoscopic treatment in our hospital from March 2018 to February 2021 were collected. Inclusion criteria are as follows: (1) patients diagnosed with endometrial cancer based on comprehensive clinical diagnosis and treated by laparoscopy; (2) surgery naïve patients, older than 18 years old; (3) could communicate normally and complete the study survey in oral or written form; and (4) patients and their families were informed and signed the informed consent form, agreeing to participate in the study. Exclusion criteria are as follows: (1) patients with other malignant tumors; (2) presence of severe liver and kidney function damage, cardiovascular disease, or other serious organ and tissue diseases; (3) patients with severe mental illness, severe cognitive impairment, or language problems; and (4) contraindications to study treatment. After admission, the patients were divided into a study group ($n = 572$) and a control group ($n = 572$) according to different nursing methods at the treating physician's discretion. The study group adopted integrated nursing with doctors and nurses based on a collaborative care model, mainly including (1) establishment of a consultation group based on the collaborative care model; (2) primary evaluation of admitted patients by the consultation group; (3) ward round by the consultation group; (4) patient care during admission and guidance by the consultation group; and (5) provided psychological care to the patients. Routine nursing was applied in the control group, mainly comprising examination on admission, guidance on diet, exercise and drugs after admission, and general health assessment and guidance. The general data of all patients were recorded, including age, gender, height, weight, education, age of onset, disease duration, tumor stage, pathological type, past medical history, complications, and follow-up time. Informed consent was obtained from all patients, and this study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (No. 2022PS147K).

2.2. Detection of Serum Tumor Markers. All patients were drawn 4 ml of peripheral venous blood on an empty stomach at admission, 7 and 15 days after admission, and 30 days after discharge. After standing for 20 min, the blood was centrifuged at 3000 r/min for 10 min. Then, the supernatant was aspirated and stored at -20°C. The level of carbohydrate antigen 19-9 (CA19-9), human epididymis protein 4 (HE4), carbohydrate antigen 15-3 (CA153), and carbohydrate antigen 125 (CA125) in serum was measured with an automatic biochemical analyzer (Mindray, China).

2.3. Evaluation of Psychological Status. All patients were graded using a self-rating anxiety scale (SAS) and self-rating depression scale (SDS) before nursing, 7 and 15 days after nursing, and 30 days after discharge. Then, according to the score, the psychological status of patients in the two groups before and after nursing was evaluated.

2.3.1. SAS Score. Each item was graded on a level of 1-4 according to the sensation in the last week, and the cumulative score of each item was regarded as the total SAS score. The SAS standard score was defined as follows: less than 50, no anxiety; 50-59, mild anxiety; 60-69, moderate anxiety; and greater than 70, severe anxiety [12].

2.3.2. SDS Score. It ranged from 1 to 4 levels. The score for each item was then calculated to obtain the overall score, which was classified as follows: less than 50, no depression; 50-59, mild depression; 60-69, moderate or high depression; and greater than 70, severe depression [12]. The criterion score = overall score* 1.25.

2.4. Evaluation of Clinical Indicators during Hospitalization. To determine the significance of the collaborative nursing mode during hospitalization, the following postoperative recovery-associated indicators were recorded and assessed: time taken to first postoperative exhaust, time taken to first postoperative food-taking, and overall hospital stay (from admission to discharge).

2.5. Evaluation of Satisfaction with Care. A self-made satisfaction questionnaire (total points, 100) was used to assess the two groups' satisfaction with nursing care. The scoring criteria were as follows: unsatisfactory, 0-59 points; satisfactory, 60-89 points; and very satisfactory, 90-100 points.

2.6. Postoperative Follow-Up. Patients in both groups were followed up for 2 years after surgery, and adverse events or complications during follow-up were recorded.

2.7. Statistical Analysis. SPSS 25.0 software was used for data analysis. The measurement data with normal distribution was expressed as mean ± standard deviation (SD). The mean of multiple groups was compared by one-way ANOVA, and pairwise comparison was performed by *t*-test. The categorical data was described by frequency (n) and percentage (%), and the difference between groups was assessed by using chi-

square test or Fischer's exact test. $P < 0.05$ indicated statistical significance.

3. Results

3.1. General Information of Patients. The basic characteristics of the study and groups are shown in Table 1. The mean age of patients in the two groups was around 61 years (study vs. control group, 61.00 ± 9.54 vs. 61.69 ± 6.86), and the age of onset was around 55 years. There was a relatively higher proportion of patients for tumor stage 1. There were no significant differences between the two groups in gender, age, height, weight, histological classification, past medical history, and complications (Table 1), indicating the two groups of patients were comparable.

3.2. Collaborative Care Effectively Reduced the Level of Serum Tumor Markers at Different Periods and Improved the Mood of Patients. The levels of serum tumor markers, CA19-9, HE4, CA153, and CA125, were determined at the indicated time. The results showed no significant difference in serum tumor marker levels at admission between the two groups. However, after admission, the level of serum tumor markers of patients in both groups gradually decreased, with patients in the study group demonstrating a significantly greater decrease than the control group at 7 and 15 days after admission and 30 days after admission (Figure 1(a)). Similarly, the two groups had no significant difference in SAS and SDS scores at admission, but after admission, a decrease in SAS and SDS scores was observed in both groups. We observed that the SAS and SDS scores of patients in the study group were significantly lower than those of the control group at 7 and 15 days of admission and 30 days of admission (Figure 1(b)). The above results suggested that collaborative care was more effective than routine care in the recovery of patients with endometrial cancer.

3.3. Collaborative Care Can Effectively Reduce Relevant Clinical Indicators of Patients during Hospitalization. The relevant clinical indicators during hospitalization were compared between the two groups. The results showed a significantly shortened time to first postoperative exhaust (4.52 ± 1.10 days), postoperative food-taking (5.46 ± 1.70 days), and hospital stay (24.85 ± 4.42 days) in the study group compared with the control group (Table 2).

3.4. Collaborative Care Can Improve Patients' Satisfaction with Nursing. The satisfaction rate of nursing care in the two groups was also evaluated. The results indicated that the satisfaction rate of patients with nursing care in the study group was mostly "very satisfied" ($n = 347$), while that in the control group was mostly "satisfied" ($n = 240$). In addition, there were 19 "dissatisfied" cases with nursing care in the study group, while in the control group, the number of "dissatisfied" cases was 99. Overall, the patients' satisfaction with nursing care in the study group was as high as 96.67%, which was significantly higher than that in the control group (82.69%) (Table 3).

3.5. Collaborative Care Can Significantly Reduce the Incidence of Postoperative Adverse Events in Patients. After 2 years of follow-up in both groups, adverse events and complications were recorded. The results revealed that the main complications of patients in the study group included fever, lymphocele, and intestinal obstruction. The control group contained 13 cases with urinary retention, 13 cases with pulmonary embolism, and 11 cases with ureteral fistula, while patients in the study group had no such complications. In addition, there was only one case of poor healing of vaginal stump and brain obstruction in the study group, while the control group had more than 10 cases of complications. The above result displayed that patients in the study group had a distinctly lower incidence of adverse events and complications than those in the control group (Table 4).

4. Discussion

In this study, using a large cohort of 1144 patients, we investigated the significance of a rehabilitation model via collaborative nursing consisting of doctors and nurses for endometrial cancer patients after laparoscopy compared with routine nursing care. The results showed that collaborative care was associated with a significantly faster reduction in serum tumor marker, an improved mood of patients, faster in-hospital postoperative recovery, greater satisfaction with the nursing offered, and reduced risk of postoperative adverse events. An important strength of this study was that the patients from both groups were well balanced in terms of age, education level, tumor stage, histological classification, past medical histories, and major complications such as hemorrhage, infection, and intestinal problems, which might have otherwise significantly affected the recovery of the patients, thereby biased this study's important indicators such as changes in tumor markers and in-hospital postoperative recovery.

Collaborative care interventions were designed to provide more individualized support and care coordination to patients across the continuum of care. For example, in such settings, dedicated health care professionals are able to timely assess, treat, and monitor patient conditions throughout the whole hospitalization period and even after discharge. Collaborative care interventions have been confirmed to be effective in chronic disease care [13, 14]. A recent meta-analysis of 37 collaborative care intervention studies on 12,355 patients found that depression was improved at 6-month follow-up, and long-term benefits up to 5 years were also observed [15]. Besides, Dwight-Johnson et al. reported significantly reduced depression and good prognosis in samples of patients with breast and cervical cancer after applying collaborative care approaches [16]. Similarly, this study found that collaborative care intervention was superior to routine care.

Collaborative care enhances the interactions between patients and healthcare professionals via the identification of multiple physical, psychological, social, and spiritual needs of the patients and the implementation of evidence-based supportive care interventions flexibly and responsively in the context of a collaborative multidisciplinary approach to care, to achieve optimal health outcomes for the patients

Table 1: Basic characteristics of patients from the study and control groups.

Characteristics	Study group ($n = 572$)	Control group ($n = 572$)	t/χ^2	P^*
Age (years)	61.00 ± 9.54	61.69 ± 6.86	1.402	0.161
Height (cm)	158.64 ± 5.82	158.47 ± 5.70	0.488	0.626
Weight (kg)	61.66 ± 7.18	62.27 ± 5.80	1.581	0.114
Education background, *n* (%)			2.172	0.338
Elementary school	384 (67.1)	407 (71.2)		
Senior high school	127 (22.2)	112 (19.6)		
College and above	61 (10.7)	53 (9.4)		
Age of onset (years)	55.51 ± 9.54	55.21 ± 7.09	1.393	0.164
Tumor staging, *n* (%)			2.219	0.528
Stage 1	295 (51.6)	288 (50.4)		
Stage 2	96 (16.8)	95 (16.6)		
Stage 3	116 (20.2)	134 (23.4)		
Stage 4	65 (11.4)	55 (9.6)		
Histological classification, *n* (%)			1.850	0.174
Endometrioid adenocarcinoma	524 (91.6)	536 (93.7)		
Other types of cancer	48 (8.4)	36 (6.3)		
Past medical history, *n* (%)			2.386	0.122
Related cases	480 (83.9)	460 (80.4)		
Unrelated cases	92 (16.1)	112 (19.6)		
Complications, *n* (%)			2.092	0.554
Hemorrhage	340 (59.4)	329 (57.5)		
Infection	168 (29.4)	179 (31.3)		
Intestinal problems	31 (5.4)	24 (4.2)		
Other	33 (5.8)	40 (7.0)		

*P value vs. control group.

[17, 18]. Thus, based on this interactive guidance and continuous support, the patients in the study group demonstrated faster time to exhaust and oral food intake and shorter hospital stays. Further, these also led to a significantly greater degree of satisfaction in the study group compared with this control group (study vs. control group, 96.67% vs. 82.69%), especially considering that the patients had more psychological support and guidance by the treating hospital staff members. These findings also indicate that collaborative care-based services could be of high value in regulating patients' physical and mental states, especially for those with cancer.

We also observed that the study group had a significantly lower risk of postoperative complications such as poor healing of wounds, urinary retention, and lung infections, among others. The major sequelae after endometrial cancer surgery include symptoms similar to menopause as well as sexual dysfunction [19]. Although some studies have pointed out that laparoscopic surgery can improve the above adverse effects compared to open surgery [20], some other studies have also shown that there is some consequential amount of abdominal bleeding despite laparoscopic surgery [20], and the incidence of bladder injury [21] and vascular injury reaches 1% [22]. Interestingly, in this study, we found that collaborative care could significantly reduce the incidence of symptoms such as blood loss, bladder injury, vascular injury, and ureteral injury. We believe that the main reasons could be as follows. First, the interventions (i.e., changing of dressings and vital sign assessment) for patients with conventional care are mainly performed by students or nurses alone, while the managing physicians are mainly responsible for major systemic treatment, and there might be a lack of timely and direct communication between them resulting in lack of adequate attention to factors that might have potentially led to these complications [23]. The collaborative care-based nursing can effectively avoid the above-mentioned shortcomings as it integrates the medical and nursing personnel to form an intervention team, which improves the standardization and systematization of treatment and results in better treatment outcomes for the patients [24].

Further, the adoption of multidisciplinary team-based nursing care not only led to decreased complications but might have also directly affected the reduction of serum tumor levels, SAS score, and SDS score. Postoperative complications can be described as a deviation from the normal postoperative course and can be classified in terms of severity or infective/noninfective etiology [25]. Although the patients were well balanced in several demographics and clinical characteristics, the significantly faster decrease in serum tumor markers needs further investigation. We hypothesize that there may be a relationship between

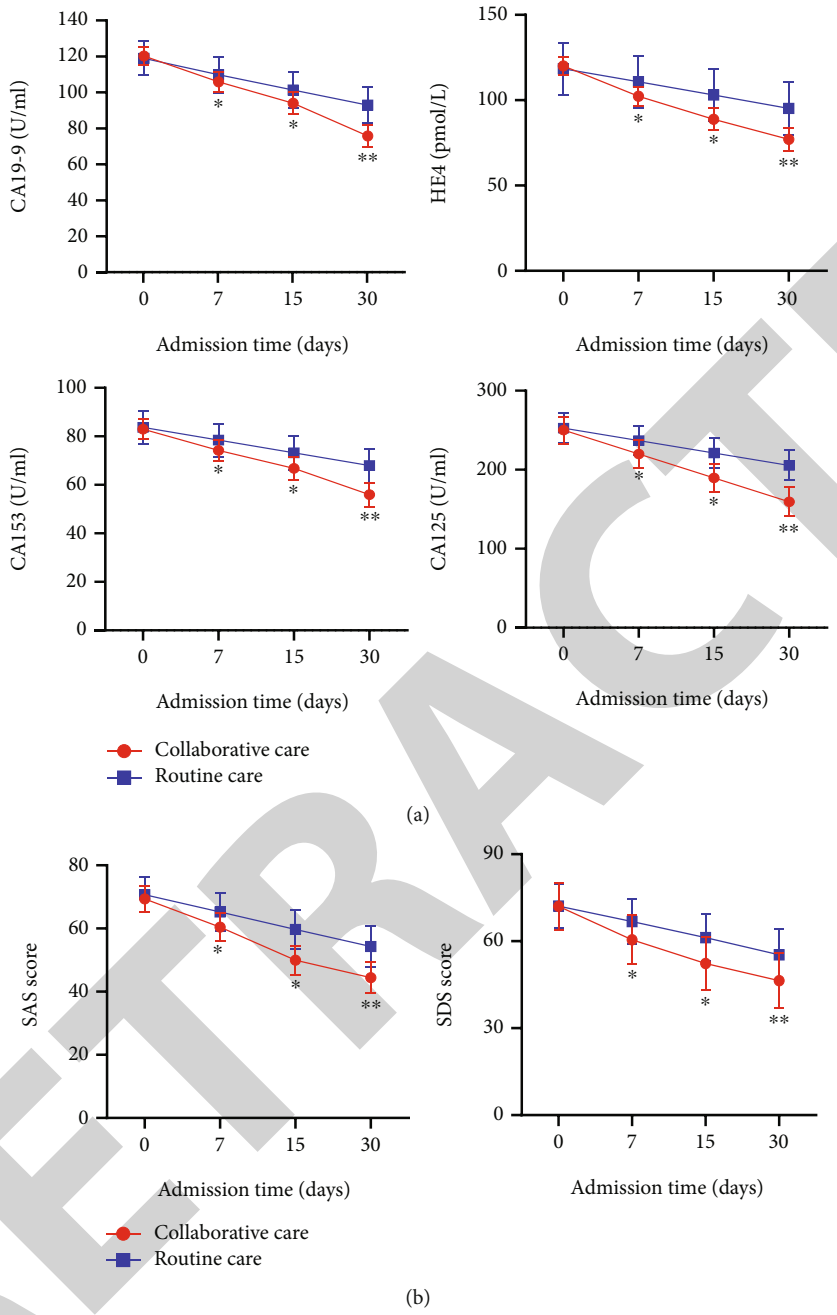

Figure 1: Comparison of serum tumor marker level and psychological scores between the collaborative and routine care groups. (a) Serum level of CA19-9, HE4, CA153, and CA125 of the two groups at different admission periods. (b) Comparison of SAS and SDS scores of the two groups at different admission periods. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. routine care group.

Table 2: Comparison of relevant clinical indicators during hospitalization between the two groups.

Variables	Study group (days)	Control group (days)	t	P^{*}
Time to first postoperative exhaust time	4.52 ± 1.10	7.88 ± 1.96	35.713	<0.001
Time to first postoperative food-taking	5.46 ± 1.70	6.44 ± 1.10	11.544	<0.001
Hospital stay	24.85 ± 4.42	29.18 ± 2.60	20.163	<0.001

$^{*}P$ value vs. control group.

Table 3: Comparison of patients' satisfaction between the two groups.

Variables	Very satisfied, *n* (%)	Satisfied, *n* (%)	Dissatisfied, *n* (%)	Degree of satisfaction
Study group	347 (60.7)	206 (36.0)	19 (3.3)	96.67%
Control group	233 (40.7)	240 (42.0)	99 (17.3)	82.69%
χ^2				60.475
P				<0.001*

Note: a satisfaction score of 80 or above is considered very satisfied, a score of 60 to 79 (including 60 and 79) is considered satisfied, and a score of less than 60 (exclusive) is considered unsatisfied. *P value vs. control group.

Table 4: Comparison of the incidence rate of adverse events and complications after 2-year follow-up between the two groups.

Variables	Study group, *n*	Control group, *n*	t/χ^2	P^*
Fever	26	85	34.730	<0.001
Lymphocele	21	61	21.019	<0.001
Intestinal obstruction	19	75	36.348	<0.001
Poor healing of vaginal stump	1	11	8.422	0.004
Poor healing of abdominal incisions	2	16	11.063	0.001
Urinary retention	0	13	13.149	<0.001
Abdominal bleeding	2	25	20.066	<0.001
Vesicovaginal fistula	3	26	18.716	<0.001
Lung infection	2	34	29.369	<0.001
Brain obstruction	1	15	12.242	<0.001
Pulmonary embolism	0	13	13.149	<0.001
Ureteral fistula	0	11	11.107	<0.001

*P value vs. control group.

patients' tumor markers, other biochemistry markers, complications, and immunity. Patients in the study group received greater attention and care by an intervention team, which led to timely identification of issues in biochemistry markers, such as white blood cell, neutrophil and hemoglobin counts, and levels of C-reactive protein (CRP), albumin, and interleukin-6 (IL-6), and therefore possibly faster treatment compared with the control group. Thus, lesser aggravation in the condition of the patients from the study group might have contributed to a faster decrease in tumor markers and lesser interference with other biochemical markers compared with the control group. In addition, the better SAS and SDS scores observed in the study could be attributed to the lower physical stress and emotional and financial burden compared to the control group.

Despite the interesting findings observed in this study, there were several limitations worth mentioning. First, this was a single-center retrospective study; therefore, the presence of some bias might have been inevitable. However, considering that many of the important characteristics between the two groups of patients were well-balanced (Table 1), we believe this might not have significantly affected the overall study results. Second, the association between serum tumor markers and other serological markers (i.e., inflammatory and nutritional) was not assessed; therefore, the faster decrease in tumor marker levels in the study group requires further investigations. Lastly, longer follow-up might be needed to determine the possible association of collaborative care in terms of patients' survival and tumor recurrence risk compared with routine nursing.

5. Conclusions

In summary, compared with routine nursing, collaborative care can enhance the rehabilitation of patients with endometrial cancer and improve their psychological status and satisfaction with nursing. Moreover, collaborative care can improve the outcomes of laparoscopic treatment of endometrial cancer. The results of this study provide preliminary support for the application of collaborative care in the treatment of endometrial cancer, especially after laparoscopy, and should be further validated in larger cohort of patients with multicenter prospective clinical settings.

Data Availability

Data and material are available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (No. 2022PS147K).

Consent

Informed consent was obtained from all patients.

Conflicts of Interest

All authors declare that they have no competing interests.

Authors' Contributions

All authors contributed to the study design and preparation of study materials. Li Yang contributed to the data collection. Feng Han contributed to the data analysis and writing of the manuscript. All authors reviewed the manuscript. Li Yang and Feng Han contributed equally to this work.

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Retraction

Retracted: Effect of Core Stability Training on Correction and Surface Electronic Signals of Paravertebral in Adolescent Idiopathic Scoliosis

BioMed Research International

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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] H. Weng and Q. Li, "Effect of Core Stability Training on Correction and Surface Electronic Signals of Paravertebral in Adolescent Idiopathic Scoliosis," *BioMed Research International*, vol. 2022, Article ID 1819606, 6 pages, 2022.

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Research Article

Effect of Core Stability Training on Correction and Surface Electronic Signals of Paravertebral in Adolescent Idiopathic Scoliosis

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Objective. To observe the effect of 12-week core stability training on Cobb angle and the ratios of AEMG (averaged EMG) and IEMG (integral EMG) of paravertebral electromyography in thoracic and lumbar segments in adolescent idiopathic scoliosis (AIS) patients and offer a practical-based evidence for the rehabilitation treatment for AIS patients. *Methods*. 31 AIS female middle school students were randomly divided into an exercise group ($n = 16$, 12 weeks of core stability training, 3 times/week) and AIS group ($n = 15$). In addition, 15 female secondary school students without scoliosis were included as the normal group (the AIS group and normal group did not perform any regular physical exercise throughout the trial period and only receive regular evaluation and guidance). Before and after the experiment, the digital diagnostic equipment of Philips was used to examine the Cobb angle and Noraxon was used to measure the surface EMG signals of the back thoracic and lumbar paravertebral muscles. *Results*. Compared with that before training, after 12 weeks of core stability training, the Cobb angle in the exercise group significantly decreased, and the ratio of AEMG (convex/concave) and IEMG (convex/concave) of paravertebral muscles in the thoracolumbar segment significantly decreased ($P < 0.01$, respectively); there was no significant difference in the above indicators in the AIS group before and after the experiment ($P > 0.05$, respectively). After 12 weeks of core stability training, compared with the AIS group, the Cobb angle decreased significantly ($P < 0.01$), and the ratio of AEMG (convex/concave) and IEMG (convex/concave) of paravertebral muscles in thoracolumbar segment decreased significantly ($P < 0.01$, $P < 0.05$). Compared with the normal group, the ratio of AEMG and IEMG of paravertebral muscles in thoracolumbar segment significantly increased ($P < 0.01$) in the AIS group ($P < 0.01$, respectively). *Conclusions*. The core stability training can significantly reduce the Cobb angle of AIS and correct the bad posture of scoliosis patients, which may be related to the balance of the electromyographic activities (convex concave side) of paravertebral muscles in AIS patients.

1. Introduction

Scoliosis is a kind of skeletal muscle disease with spinal deflection or rotation, which often occurs in the period of sudden growth before puberty. The etiology of most scoliosis patients is unclear. It is called idiopathic scoliosis in medicine, and approximately 80% of scoliosis patients are adolescent idiopathic scoliosis (AIS) [1]. Worldwide, the prevalence of AIS ranges from 0.93% to 12%, and the incidence and severity of spinal curvature in girls are higher than those in boys [2]. With the development of the body, the degree of spinal deformity in AIS patients is increasing, which makes the patients show abnormal posture, such as stooping, hunchback, and high and low shoulders. These images reflect that AIs may have certain effects on clavicular angle, pelvic inclination angle, Cobb angle, and ankle movement angle and even affect the patient's lung function [3]. At present, the pathogenesis of AIS mainly focuses on genetic, biochemical, mechanical, neural, muscular, and physical factors [4]. Recently, some scholars believe that AIS patients have muscle imbalance on both sides of the spine, which can aggravate the development of scoliosis. In addition, the study of Mahaudens and Mousny [5] showed that the

activity of convex paravertebral muscle decreased significantly after spinal fusion, but the effect on concave paravertebral muscle was not obvious. And Liu et al. [6] found that electroacupuncture can improve the spine morphology of IS patients by adjusting the paravertebral muscle electromyographic activity. Based on the above literature, the imbalance of paravertebral muscle activity on both sides of the spine may play an important role in the progression of AIS scoliosis.

At present, the treatment methods for IS are usually divided into two types. According to the degree of Cobb angle, surgery is recommended for patients with a Cobb angle > 40°, and conservative treatment is adopted for AIS patients with a Cobb angle less than 40°, which includes wearing auxiliary devices (brace treatment), spinal adjustment treatment, and exercise treatment [7]. However, ensuring the quality of daily life of AIS patients and choosing a more appropriate treatment method have become a problem for more doctors. The rise of exercise therapy also provides a new idea for the conservative treatment of AIS. It is considered to be an important method to maintain spinal function and can effectively prevent the development of scoliosis. For mild patients with a Cobb angle less than 25°, exercise rehabilitation intervention should be carried out as soon as possible [8]. Recent studies have found that compared with traditional training, core stability training is more effective in reducing rotation deformity and pain in AIS patients, suggesting that core stability training is an effective method for early treatment of AIS [9]. In addition, it is reported that 12-week core stabilization exercise significantly reduces the Cobb angle and improves lumbar muscle strength in AIS patients [10]. Therefore, it can be considered that core stability training may have a more positive impact on spine morphology and back muscle strength balance in AIS patients. Based on the above assumptions, the current study compared the changes of the Cobb angle and EMG (electromyography) signals (the ratios of AEMG and IEMG) of thoracic and lumbar paravertebral muscles in AIS patients after 12 weeks of core stabilization exercise and explored the impact of core stability training on back EMG signals (convex/concave) of AIS patients, so as to provide a theoretical basis for core stabilization exercise intervention in AIS patients.

2. Object and Method

2.1. Research Object. Thirty-one AIS female middle school students with thoracolumbar double curvature were selected and were randomly divided into an exercise group ($n = 16$) and AIS group ($n = 15$, only receiving regular evaluation and guidance); another 15 female middle school students without scoliosis were selected as the normal group. Inclusion criteria were as follows: (1) meet the diagnostic criteria for scoliosis of the international society of spine surgery; (2) Cobb angle (10°-20°); (3) have not received surgical treatment and have no plans for brace treatment in the near future; (4) no motor organ disease; (5) informed consent to this study, voluntary participation, and signing of informed consent. Exclusion criteria were as follows: (1) nonidiopathic scoliosis; (2) there are growth and development disorder; history of nerve, muscle, and bone infection; spirit; etc; (3) obvious deformity of the lower limbs and feet; and (4) had a history of major surgery. All participants signed the informed consent before the trial (in addition, 2 participants stopped the rehabilitation plan for personal reasons and 14 AIS patients in the EG group). There was no significant difference among the three groups before the exercise intervention in terms of age, height, and weight by one-way ANOVA ($P > 0.05$). Table 1 shows the basic information of the subjects.

2.2. Research Methods

2.2.1. Core Stability Training Program. The core stability training program [11] is designed on the basis of previous studies; all participants performed the core stability training for 12 weeks (3 sessions per week, 60 min each session). Each session includes 10 minutes of warm-up and 5 minutes of relaxation (both stretching and posture exercises of large muscle groups) and 45 minutes of core stability exercise intervention. All movements are carried out under the supervision of professional teachers to ensure that all movements are accurate.

Core stability exercises include unstable equipment exercises (such as balance pad and Swiss ball), back bridge exercise, side bridge exercise, prone two-point support, supine bending and supine leg lifting, trunk curling, and cat camel stretching exercises; each type of exercise was conducted in 3 sets of 12 repetitions. During exercise, the polar table monitors the exercise intensity at any time.

2.2.2. Cobb Angle Measurement. The digital diagnostic equipment of Philips was used to examine the whole spine X-ray plain film (posterior anterior position and lateral position) of 44 subjects before and after exercise intervention. For the posterior-anterior position, the patient stands naturally, feet shoulder-width apart, eyes looks straight ahead, and hands are naturally hanging at the sides of the body; for the lateral position, the patient stands naturally, hip and knee joints are fully extended, elbows are fully flexed, hands are making a fist on the clavicle on the same side and avoid it when shooting limbs overlap with the spine.

Cobb angle was measured using Cobb method. The end vertebrae that were the most tilted toward the concave side of the curvature to be measured were determined at the upper and lower ends of the curvature. One line was drawn above the upper end of the vertebra, and the other line was drawn below the lower end of the vertebra. A line was drawn perpendicular to each line, and the angle in which the lines meet was obtained. The Cobb angle was measured by a specialist in rehabilitation medicine.

2.2.3. Paravertebral Electromyography Measurement. Telemetry myoelectric instrument (Noraxon 16) was used to monitor the surface myoelectric activity of paravertebral muscles of patients. The room temperature was required to be 26°C. No strenuous exercise was performed for 24 hours, and no drugs were used one week before the measurement. The patients were familiar with the measurement process and could complete the specified actions as required. The procedure is as follows: the patients take the prone position

Table 1: Physical characteristics of subjects ($x \pm s$).

	n	Age (year)	Height (m)	Weight (kg)
Normal group	15	13.34 ± 1.08	1.56 ± 0.02	47.76 ± 2.13
AIS group	14	13.87 ± 0.96	1.57 ± 0.01	48.02 ± 1.25
Exercise group	15	13.15 ± 0.47	1.56 ± 0.03	48.32 ± 1.98

and paste the electrode and place arms at the sides of the torso in a relaxed state before the experiment. In patients with thoracolumbar double bending AIS, electrode pairs 1 and 3 shall be pasted at 2 cm from the left and right side of the midline of the spine to the corresponding top vertebral plane of the maximum Cobb angle, and electrode pairs 2 and 4 shall be pasted at 2 cm from the left and right side of the midline of the spine to the corresponding top vertebral plane of the minimum Cobb angle; the reference electrodes are placed 6.5 cm away from the parallel outer side of the corresponding test electrode pair. Each patient recorded 4-lead sEMG signals at the same time.

In this study, BST (Biering Sorensen test) was used to measure the paravertebral muscle function of subjects. The BST is the earliest and widely used research method to evaluate the paravertebral muscle function of the lumbar back. The specific operations are as follows: the patient's upper body is exposed in a prone position, and the lower limbs are fixed on the treatment bed with bandages after sticking the electrode sheet. The patient places his arms on the side of the body and his upper body outside the treatment bed. The patient actively exerts force and backs up to the maximum until the patient is tired after hearing the command. Then, the test is stopped and the surface EMG() signal is recorded. Input the surface EMG signal obtained from the test into software (MR3.10) for signal processing, extract the surface EMG index RMS of paravertebral muscle, calculate the ratios of IEMG and AEMG (convex/concave side), and finally carry out statistical analysis.

2.3. Statistical Analysis. All experimental data were presented as mean ± standard deviation. SPSS 21.0 statistical software was used for statistical analysis. Paired sample t -test was used for the data of the normal group, AIS group, and exercise group before and after the experiment. One-way ANOVA was used for the difference between the groups before and after exercise. The significance level (α) was set to $P < 0.05$.

3. Results

3.1. Effect of Core Stability Training on Paravertebral Electromyography in Patients with AIS

3.1.1. Effect of Core Stability Training on Thoracic Paravertebral Electromyography in Patients with AIS. Table 2 shows that after 12 weeks of core stability training, compared with that before the intervention, the ratio of AEMG (convex/concave) in the thoracic segment in the exercise group significantly decreased by 13.25% ($P < 0.01$), and the ratio of IEMG (convex/concave) significantly decreased by 11.94% ($P < 0.01$). Compared with that before the intervention, the imbalance of concave convex side increased to some extent, but there was no significant difference in the AIS group (the ratio of AEMG: $P > 0.05$; the ratio of IEMG: $P > 0.05$) and there was no statistical difference between the left and right EMG signals in the normal group before and after the experiment (the ratio of AEMG: $P > 0.05$; the ratio of IEMG: $P > 0.05$).

One-way ANOVA showed that before the intervention, there were significant differences among the three groups (AEMG ratio: $F = 176.978$, $P = 0.000$; IEMG ratio: $f = 100.342$, $P = 0.000$). Compared with the normal group, the ratios of AEMG and IEMG were significant higher in the AIS group and exercise group ($P = 0.000$, $P = 0.000$); compared with the AIS group, there was no significant difference in the ratios of AEMG and IEMG in the exercise ($P = 0.895$, $P = 0.930$). After 12 weeks of exercise intervention, there were still significant differences among the three groups (the ratio of AEMG: $F = 147.547$, $P = 0.000$; the ratio of IEMG is as follows: $F = 86.020$, $P = 0.000$). Compared with the normal group, the ratios of AEMG and IEMG were significantly higher ($P = 0.000$, respectively) in the AIS group and exercise group, but compared with the AIS group, the ratios of AEMG and IEMG were significantly lower ($P = 0.000$, respectively) in the exercise group.

3.1.2. Effect of Core Stability Training on Lumbar Paravertebral Electromyography in Patients with AIS. Table 3 shows that after 12 weeks of core stability training, compared with that before the intervention, the ratio of AEMG (convex/concave) of the lumbar segment in the exercise group decreased significantly by 7.97% ($P < 0.01$), and the ratio of IEMG (convex/concave) decreased significantly by 12.12% ($P < 0.01$). In the AIS group, the imbalance of concave convex side increased to some extent, but there was no significant difference (the ratio of AEMG: $P > 0.05$; the ratio of IEMG: $P > 0.05$). Compared with the normal group before the experiment, there was no significant difference between the left and right muscle electrical signals (the ratio of AEMG: $P > 0.05$; the ratio of IEMG: $P > 0.05$).

One-way ANOVA showed that before the exercise intervention, there were significant differences among the three groups (the ratio of AEMG: $F = 56.436$, $P = 0.000$; the ratio of IEMG ratio: $F = 45.687$, $P = 0.000$). Compared with the normal group, the ratios of AEMG and IEMG (convex/concave) in the AIS group and exercise group increased significantly ($P = 0.000$, respectively). Compared with AIS group, there was no significant difference in the ratios of AEMG and IEMG between the exercise group and AIS group ($P = 0.554$, $P = 0.108$). After 12 weeks of core stability training, there were significant differences among the three groups (AEMG ratio: $F = 43.479$, $P = 0.000$; IEMG ratio: $F = 48.612$, $P = 0.000$). Compared with the normal group, the ratios of AEMG and IEMG (convex/concave) in the AIS group and exercise group significantly increased ($P = 0.000$, respectively). Compared with the AIS group, the ratios of AEMG and IEMG (convex/concave) in the exercise group significantly decreased ($P = 0.024$, $P = 0.003$).

Table 2: Changes of sEMG signal in thoracic paravertebral muscle of AIS patients in BST ($x \pm S, \mu V/s$).

sEMG	Group	Before	After	t	P
The ratio of AEMG (convex/concave)	Exercise group	$1.51 \pm 0.08^{**}$	$1.32 \pm 0.10^{\#\#**\Delta\Delta}$	7.893	0.000
	AIS group	$1.48 \pm 0.11^{**}$	$1.50 \pm 0.08^{**}$	-0.575	0.576
	Normal group	1.02 ± 0.04	1.01 ± 0.03	0.503	0.623
The ratio of IEMG (convex/concave)	Exercise group	$1.39 \pm 0.08^{**}$	$1.19 \pm 0.11^{\#\#**\Delta\Delta}$	11.037	0.000
	AIS group	$1.37 \pm 0.12^{**}$	$1.38 \pm 0.09^{**}$	-0.595	0.562
	Normal group	1.00 ± 0.04	1.01 ± 0.05	-0.321	0.576

Note: $^{\#\#}P < 0.01$ comparison before and after experiment; $^{**}P < 0.01$ vs. normal group; $^{\Delta\Delta}P < 0.01$, vs. the AIS group.

Table 3: Changes of sEMG signal in the lumbar paravertebral muscle of AIS patients in BST ($x \pm S, \mu V/s$).

sEMG	Group	Before	After	t	P
The ratio of AEMG (convex/concave)	Exercise group	$1.38 \pm 0.10^{**}$	$1.27 \pm 0.13^{\#\#**\Delta}$	4.119	0.001
	AIS group	$1.33 \pm 0.14^{**}$	$1.37 \pm 0.12^{**}$	-1.836	0.089
	Normal group	1.01 ± 0.05	1.00 ± 0.03	1.424	0.176
The ratio of IEMG (convex/concave)	Exercise group	$1.32 \pm 0.12^{**}$	$1.16 \pm 0.10^{\#\#**\Delta\Delta}$	5.520	0.000
	AIS group	$1.26 \pm 0.12^{**}$	$1.29 \pm 0.08^{**}$	-0.880	0.395
	Normal group	1.00 ± 0.03	1.01 ± 0.04	-0.269	0.792

Note: $^{\#\#}P < 0.01$, comparison before and after experiment; $**P < 0.01$, vs. the normal group; $^{\Delta\Delta}P < 0.01$ vs. the AIS group.

3.2. Effect of Core Stability Training on Cobb Angle in AIS Patients. Table 4 shows that after 12 weeks of core stability training, compared with that before exercise, the Cobb angle in the exercise group decreased significantly by 27.97% ($P < 0.01$); but there was no significant difference in the AIS group compared with that before the experiment ($P > 0.05$). There was no significant difference in the Cobb angle between the two groups before exercise ($P > 0.05$). After 12 weeks of core stability training, the Cobb angle in the exercise group decreased significantly compared with that in the AIS group ($t = 3.700$, $P = 0.001$).

4. Discussion

4.1. Effect of Core Stability Training on Cobb Angle in AIS Patients. Core muscle strength training refers to the training of the muscle strength and control ability at the core of the human body, and the core generally refers to the areas below the shoulder and above the hip, including the spine and pelvis. As early in the 1990s, scholars from the United States and other western countries surveyed the trunk muscles; they conducted in-depth research on the trunk muscles from different angles such as sports anatomy and sports biomechanics, put forward the concept of "core muscle group," and recognized the important role of core muscle strength in maintaining spinal stability and normal posture [12]. Whether a person is in motion or at rest, core muscle strength is considered as a muscle band to enhance the stability of the spine [13]; some scholars also mentioned the definition of core strength, which means that the body attached to the spine, pelvis, hip, and other bones can maintain basic posture, posture stability, and balance regardless of whether the body is at rest or in the motion [14].

The double curvature type AIS patients are selected in this study and the average Cobb angle is15.27 ± 2.66 degrees, which belong to mild AIS patients. The AIS patients are subject to 12 weeks of core stability training; during the core muscle strength training, the patients are always in a normal position, and the muscle strength training of the trunk is balanced as far as possible. Therefore, the spine can be ensured to be on the correct force line and can also make the spine in a more stable state through effective core muscle strength training. Research suggests that the transverse abdominal muscle and internal oblique abdominal muscle can not only enhance the stability of the spine and pelvis but also increase the abdominal pressure [13], which can not only change the scoliosis state but also peel off the adhesion of the ligament soft tissue, improve the muscle blood supply, and enhance its elasticity, and the soft tissue and ligament can also be softened. The results of this study showed that after 12 weeks of core stability training, the Cobb angle of AIS patients in the exercise group decreased significantly, and the results are consistent with that of previous scholars [11]. In addition, this study also found that during the 12 weeks of experiment, the Cobb angle of the AIS group increased from 15.71 ± 2.70 degrees to 16.07 ± 2.95, suggesting that AIS patients were at risk of aggravating spinal deformity without any treatment. However, the duration of exercise intervention is very important. Some scholars suggest that exercise therapy for AIS patients should last for at least 6 months or longer, which will have a greater impact on the Cobb angle [15]. Therefore, the follow-up study should extend the intervention time of core stability training and verify the duration of the rehabilitation effect of core stability training on AIS patients.

Table 4: Results of Cobb angle pre and post the core stabilization training in AIS ($x \pm s$).

Group	n	Before	After	t value	P value
AIS group	14	15.71 ± 2.70	16.07 ± 2.95	-1.161	0.266
Exercise group	15	14.87 ± 2.64	$12.40 \pm 2.47^{\#\#\Delta\Delta}$	6.788	0.000

Note: $^{\#\#}P < 0.01$, comparison before and after experiment; $^{\Delta\Delta}P < 0.01$, vs. the control group.

4.2. Effect of Core Stability Training on sEMG Signal of Paravertebral Muscle in Patients with AIS. SEMG is called a biometric technology to test the neuromuscular response during various activities. SEMG signals represent the characteristics of muscle function, provide information about muscle activities, and can be used as an important reference for formulating treatment plans for muscle function diseases [16]. Biopsy study showed that paravertebral muscle structure, protein synthesis, and muscle fiber type composition were abnormal in AIS patients [17]. In the study of the cause and mechanism of scoliosis, the theory of paravertebral muscle abnormality is controversial. However, in the etiological study of AIS, the abnormal distribution of paravertebral muscle electromyography has been confirmed by most scholars that the back muscle activity between the concave and convex sides of the spine is obviously asymmetric. The increase of convex side electromyogram activity and the decrease of concave side electromyogram activity are one of the risk factors for the aggravation of spinal curvature [18]. SEMG can be used as one of the objective examinations to evaluate the back electromyographic activity of scoliosis [19]. Xu et al. [20] found that the proportion distribution of muscle fiber types in paravertebral muscles of AIS patients was unbalanced through the analysis of electromyographic signals of paravertebral muscles on the concave convex side in the back of adolescent scoliosis patients. The larger the Cobb angle, the greater the difference of back muscle strength on the concave convex side, and the more obvious the imbalance. At the same time, Zheng et al. [21] found that there was no significant difference in the EMG activity of the convex/concave side between the younger age group (7-10-year-old group) and the control group, while there were more differences between the older age group (11-14-year-old group) and the control group, which mainly manifested in the convex side. Therefore, they believed that the EMG changes of the paravertebral side were the main results of scoliosis. And the older the age, the longer the course of disease, the greater the Cobb angle, and the greater the load of the convex side muscle to maintain body balance, so the difference of EMG activity is more obvious. Cheung et al. [22] found that the EMG ratio of convex/concave side of scoliosis patients in sitting and standing posture significantly increased, which suggested that the EMG activity of paravertebral muscles might have important reference value for predicting scoliosis. The current study found that the ratios of AEMG and IEMG in the left and right of the back thoracic and lumbar segments in the normal group of female middle school students were close to 1, which showed that the muscle strength of both sides was basically symmetrical. While the ratios of AEMG and IEMG(convex/concave) in the thoracolumbar of 29 AIS patients significantly increased (greater than 1) which indicated that the muscle strength of paravertebral muscles on the concave convex side in the back thoracolumbar segment of AIS female middle school students was unbalanced, which was consistent with the research results of the above scholars.

Previous studies have confirmed that scoliosis interventions can improve the spinal morphology of scoliosis patients by balancing paravertebral muscle electromyography. Liu et al. [6] found that after the electroacupuncture plus chiropractic intervention, the motor potential amplitude of scoliosis patients increased in concave side and decreased in convex side (before the intervention, the concave side decreased and the convex side increased), and the Cobb angle significantly improved, which suggested that electroacupuncture chiropractic treatment has a significant adjustment effect on scoliosis patients. In addition, Ko et al. [23] found that asymmetric spinal stability exercises can significantly increase the average RMS and peak amplitude of the concave side in the paravertebral muscle, and the Cobb angle of the patients significantly decreased. They believed that asymmetric spinal stability exercises can improve the severity of scoliosis by strengthening the concave paravertebral muscle. BST is the earliest and widely used research method to evaluate the function of lumbar paravertebral muscle [20]. Through the BST experiment, the current study found that after 12 weeks of core stability training, the ratios of IEMG and AEMG (convex/concave) in paravertebral muscles of thoracic and lumbar segments in the exercise group significantly decreased, but the ratio was still higher than 1, and there was still significant difference compared with the normal control group, which indicated that 12 weeks of core stability training can effectively balance the EMG activity in the convex concave side of AIS patients, but it cannot be completely improved; future research needs to extend the intervention time of core stability training to verify its effect. It is believed that the imbalance of paravertebral muscle electromyographic activity is one of the risk factors for the aggravation of spinal curvature [24]. Therefore, the core stability training to balance the EMG activity(convex/concave) of paravertebral muscles may be beneficial to the improvement of spinal deformity in patients with scoliosis in this study may be related to the decrease of Cobb angle in AIS patients, and the specific mechanism needs to be further studied.

5. Summary

12-week core stabilization training can effectively improve the spinal deformity of AIS patients and balance the EMG activity of the convex and concave sides of patients which may be related to the release of the back muscles and the activation of the weak side muscles by core stabilization training in patients with AIS, but it cannot be completely improved. In order to verify its effect, later studies need to extend the core stabilization training intervention time.

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Retraction

Retracted: Cell Division Cycle-Associated Protein 3 (CDCA3) Is a Potential Biomarker for Clinical Prognosis and Immunotherapy in Pan-Cancer

BioMed Research International

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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] Y. Xu, M. Shen, Y. Peng et al., "Cell Division Cycle-Associated Protein 3 (CDCA3) Is a Potential Biomarker for Clinical Prognosis and Immunotherapy in Pan-Cancer," *BioMed Research International*, vol. 2022, Article ID 4632453, 28 pages, 2022.

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Research Article

Cell Division Cycle-Associated Protein 3 (CDCA3) Is a Potential Biomarker for Clinical Prognosis and Immunotherapy in Pan-Cancer

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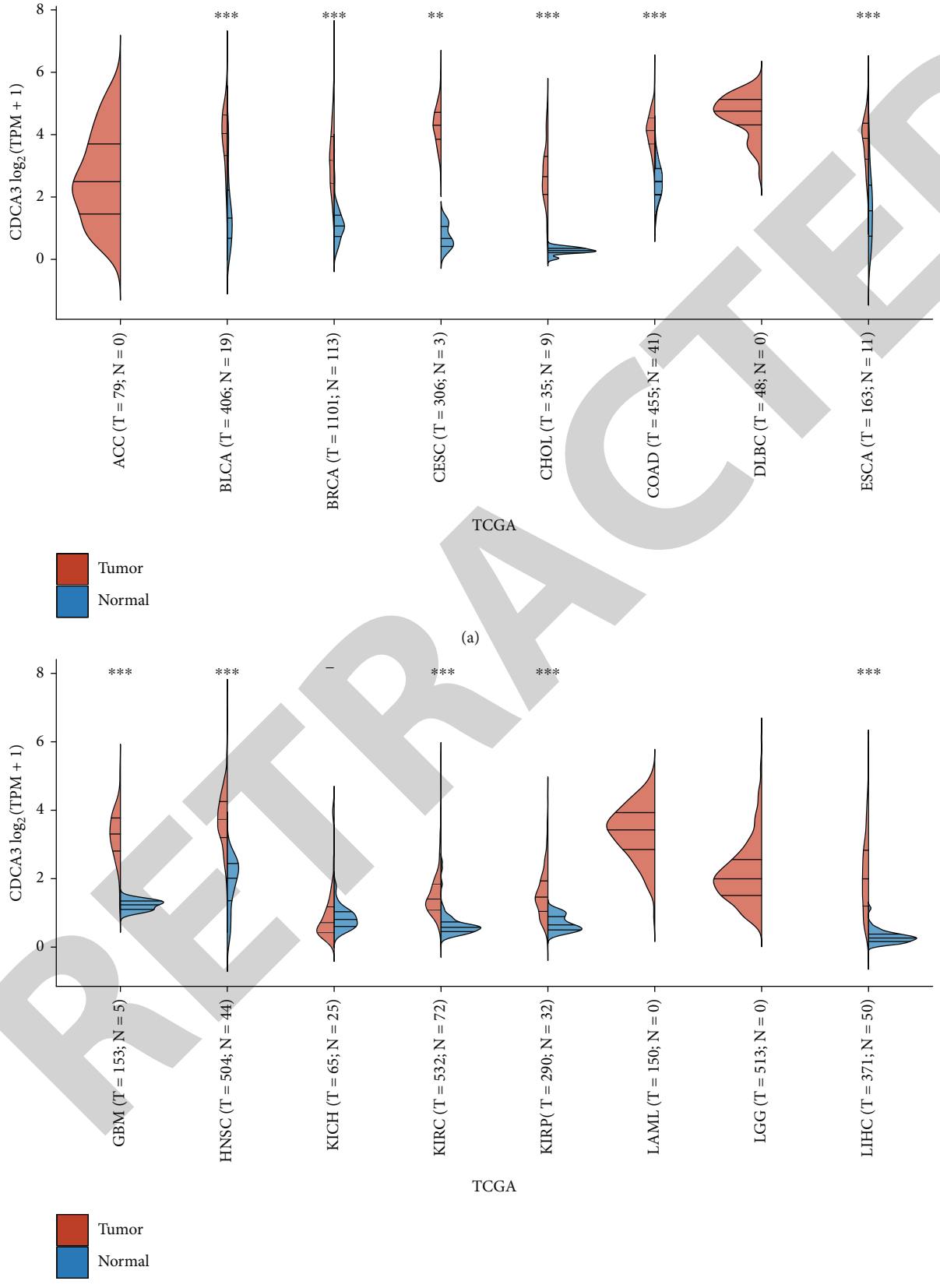
CDCA3 is an essential regulator in cell mitosis and can regulate many physiological and pathological processes in the human body by stimulating certain proteins such as cell cycle regulatory proteins, transcription factors, and signal transduction molecules. Although several studies have shown that dysregulation of CDCA3 is a common phenomenon in human cancers, no systematic pan-cancer analysis has been performed. In this study, we comprehensively investigated the role of CDCA3 in 33 human cancer types by utilizing multiple cancer-related databases and bioinformatics analysis tools, including TCGA, GTEx, GEPIA, TIMER, STRING, Metascape, and Cytoscape. Evidence from bioinformatics databases shows that CDCA3 is overexpressed in almost all human cancer types, and its overexpression is significantly associated with survival in patients with more than ten cancer types. CDCA3 expression positively correlates with immune cell infiltration levels in multiple human cancer types. Furthermore, the results of the GSEA analysis revealed that overexpression of CDCA3 may promote the malignant progression of cancer by activating various oncogenic signaling pathways in human cancers. In conclusion, our pan-cancer analysis provides a comprehensive overview of the oncogenic role of CDCA3 in multiple human cancer types, suggesting that CDCA3 may serve as a potential therapeutic target and prognostic biomarker in multiple human cancer types.

1. Introduction

With the changes in the disease spectrum, cancer has become a major threat and challenge to human health, and morbidity and mortality have increased yearly, bringing a heavy burden to global public health [1–3]. Worldwide, more than 28.4 million new cancer cases will occur by 2040, a 47 percent increase from 2020 [4]. Early diagnosis and treatment of cancer patients are the most important means to improve the cure rate and survival rate of cancer patients. Compared with pathological biopsy, in early cancer screening, cancer markers have the advantages of noninvasiveness, low cost, convenience, and speed. At the same time, the presence of quantitative changes in cancer markers can indicate the nature of cancer, understand the occurrence, cell differentiation, and function of cancer, and play a vital role in the diagnosis, classification, prognosis, recurrence, and treatment of cancer. As research progresses, researchers have discovered that cancer is a complex genomic disease with multiple forms depending on its location and cellular origin [5]. Although emerging therapies and various targeted drugs are developed for cancer treatment, cancer cannot be cured entirely. Therefore, there is an urgent need to discover early diagnostic tools, predictive biomarkers, and more reliable treatments to improve cancer patients' cure and survival rates [6–10]. The significance of pan-cancer research is to apply diagnosis and treatment to more cancers through cross-cancer similarity [11, 12]. Therefore, identifying



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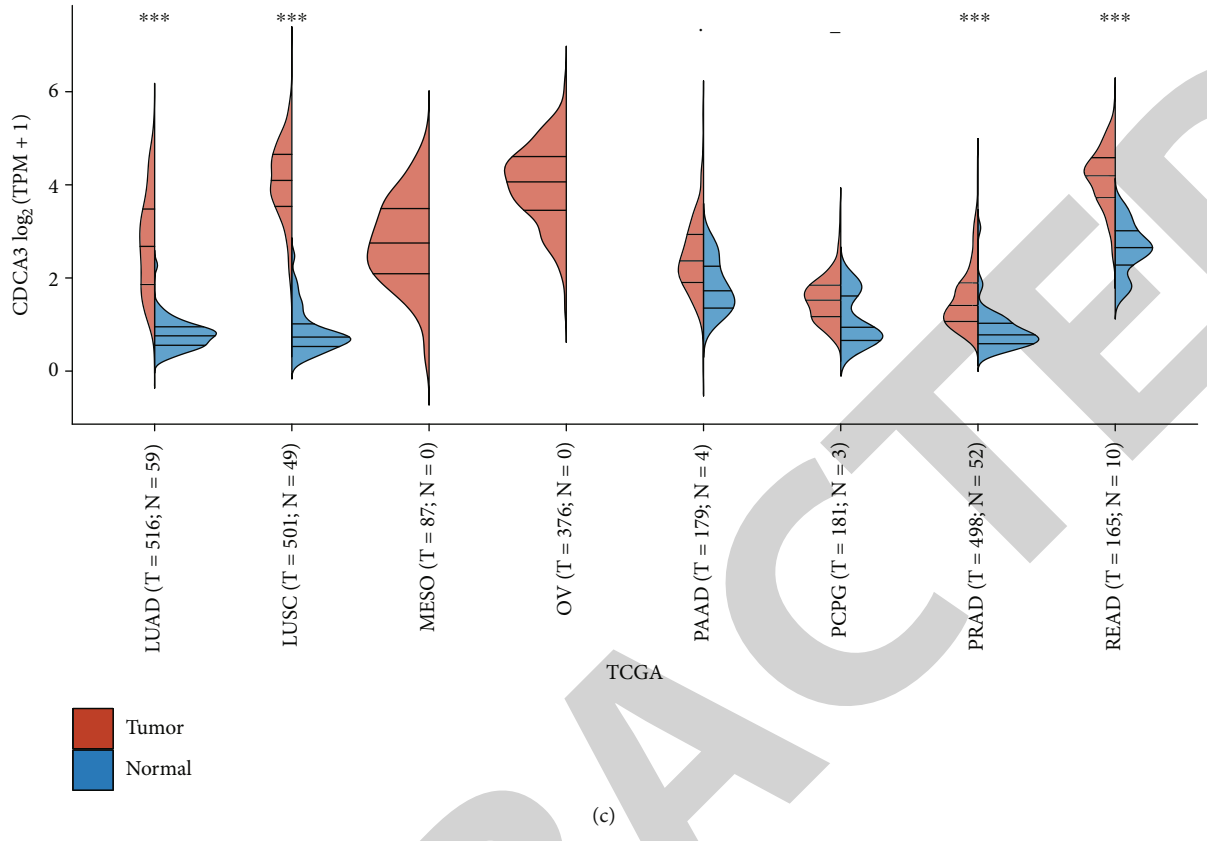

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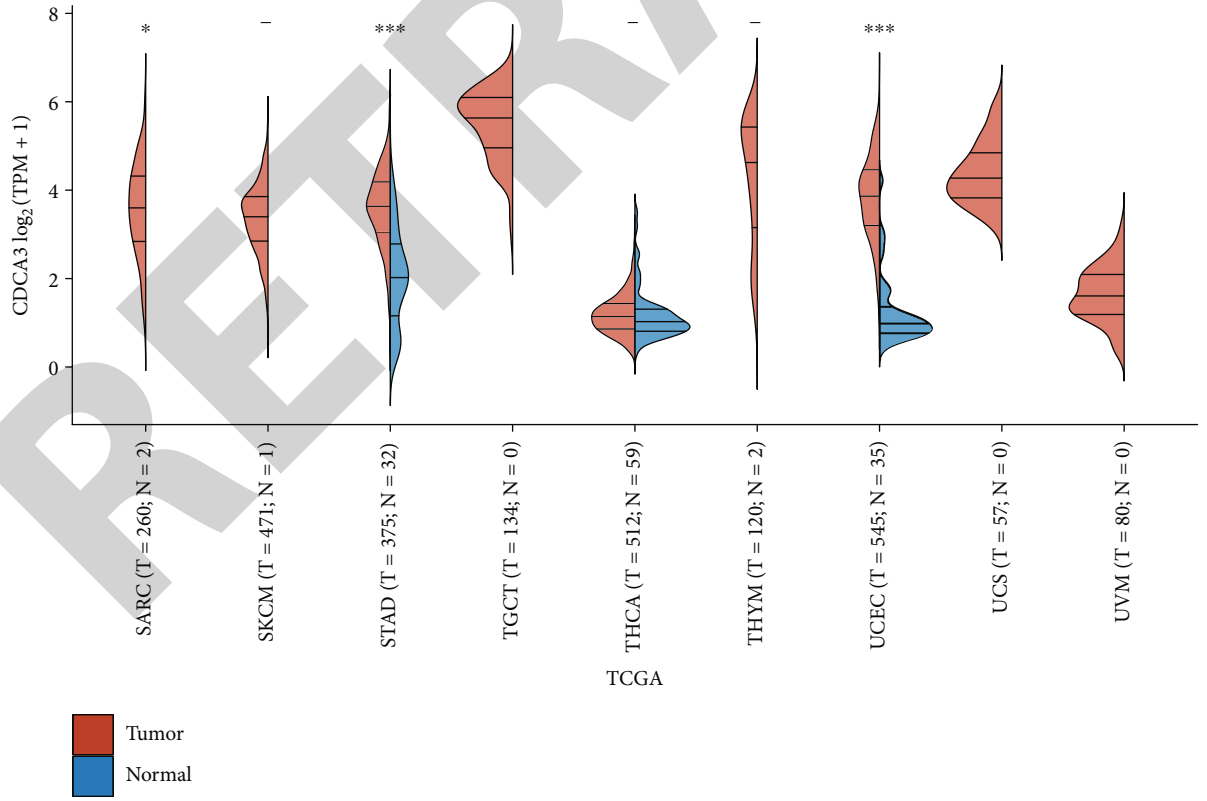

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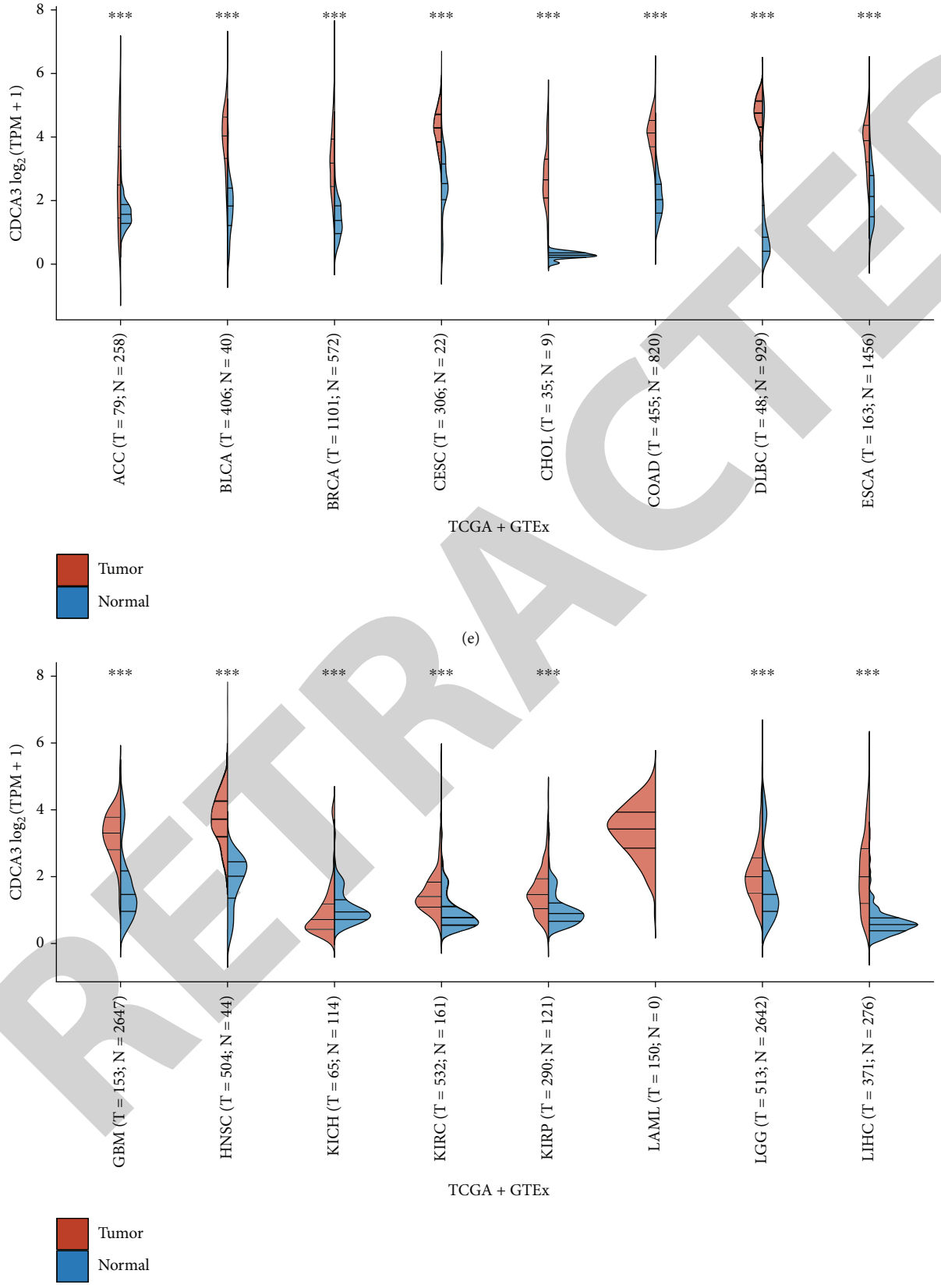

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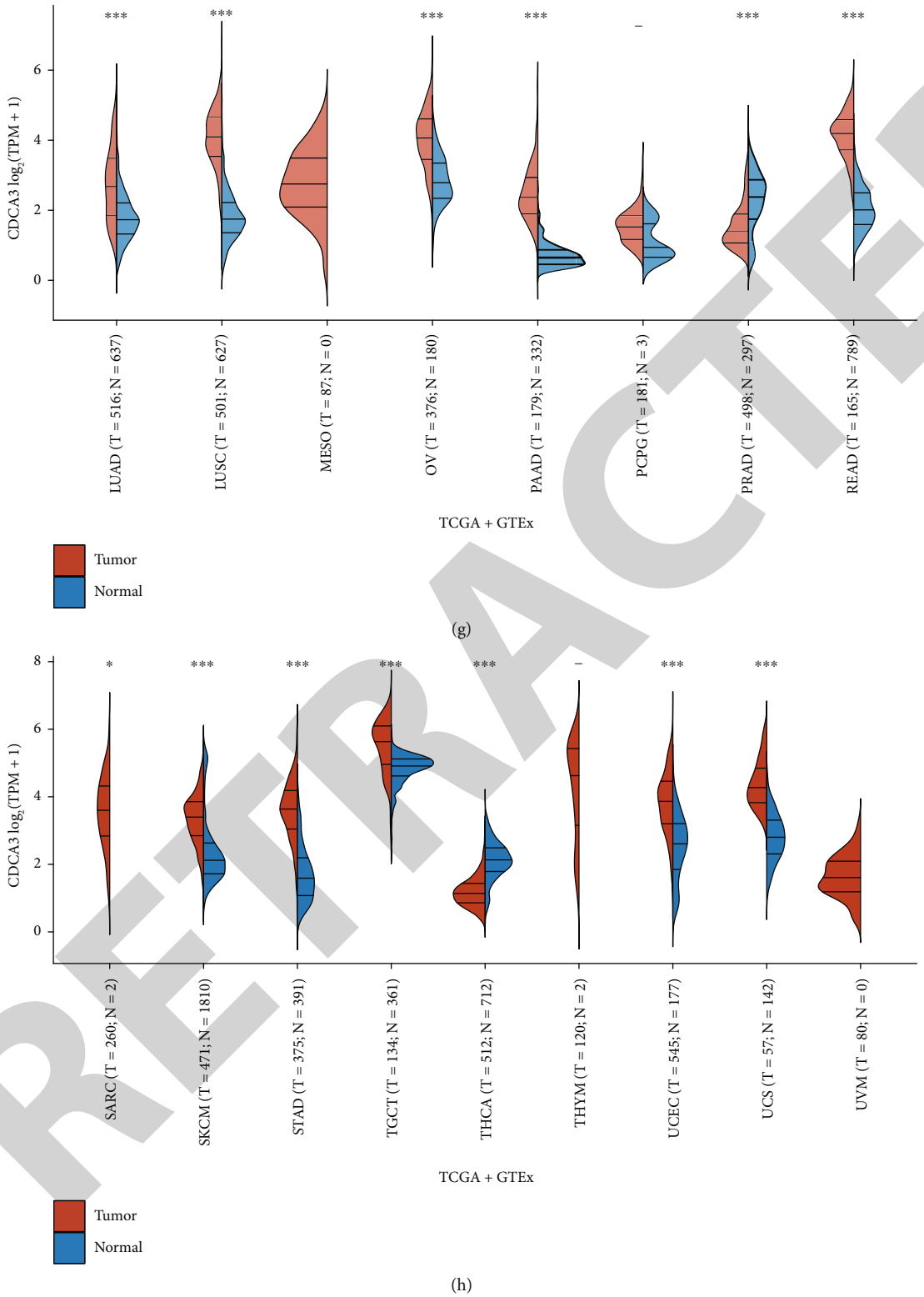
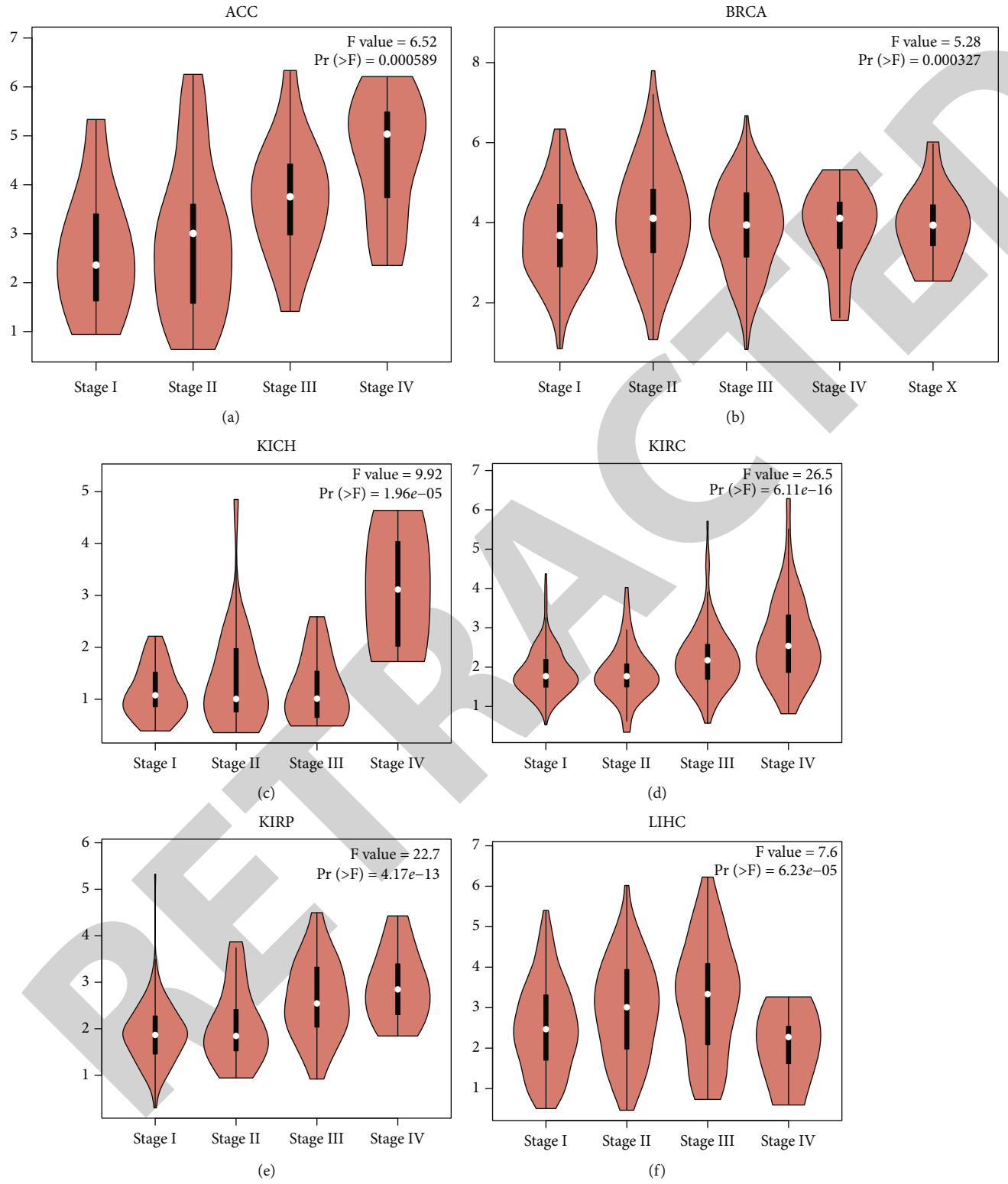


Figure 1: Expression distribution of CDCA3 in pan-cancer. (a–d) Violin plots show the expression distribution of CDCA3 gene in various tumor tissues and normal tissues based on the TCGA database. (e–h) Combining TCGA and GTEx databases, violin plots show the expression distribution of CDCA3 gene in various tumor tissues and normal tissues. The abscissa represents different tumor tissues, the ordinate represents the gene expression distribution, red represents the tumor group, and blue represents the normal group. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.



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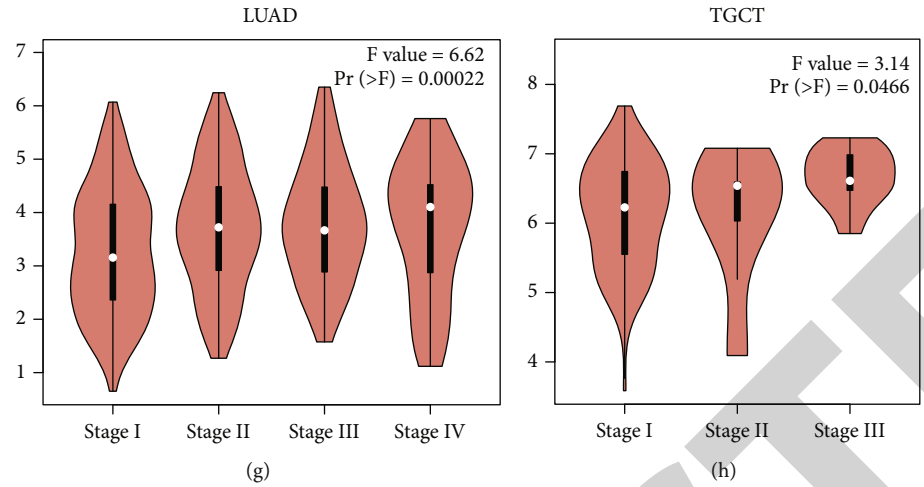


Figure 2: Violin plots show the expression of CDCA3 in different stages of various tumors. (a) ACC, (b) BRCA, (c) KICH, (d) KIRC, (e) KIRP, (f) LIHC, (g) LUAD, and (h) TGCT.

cancer markers between different cancer types is helpful for cancer diagnosis and treatment.

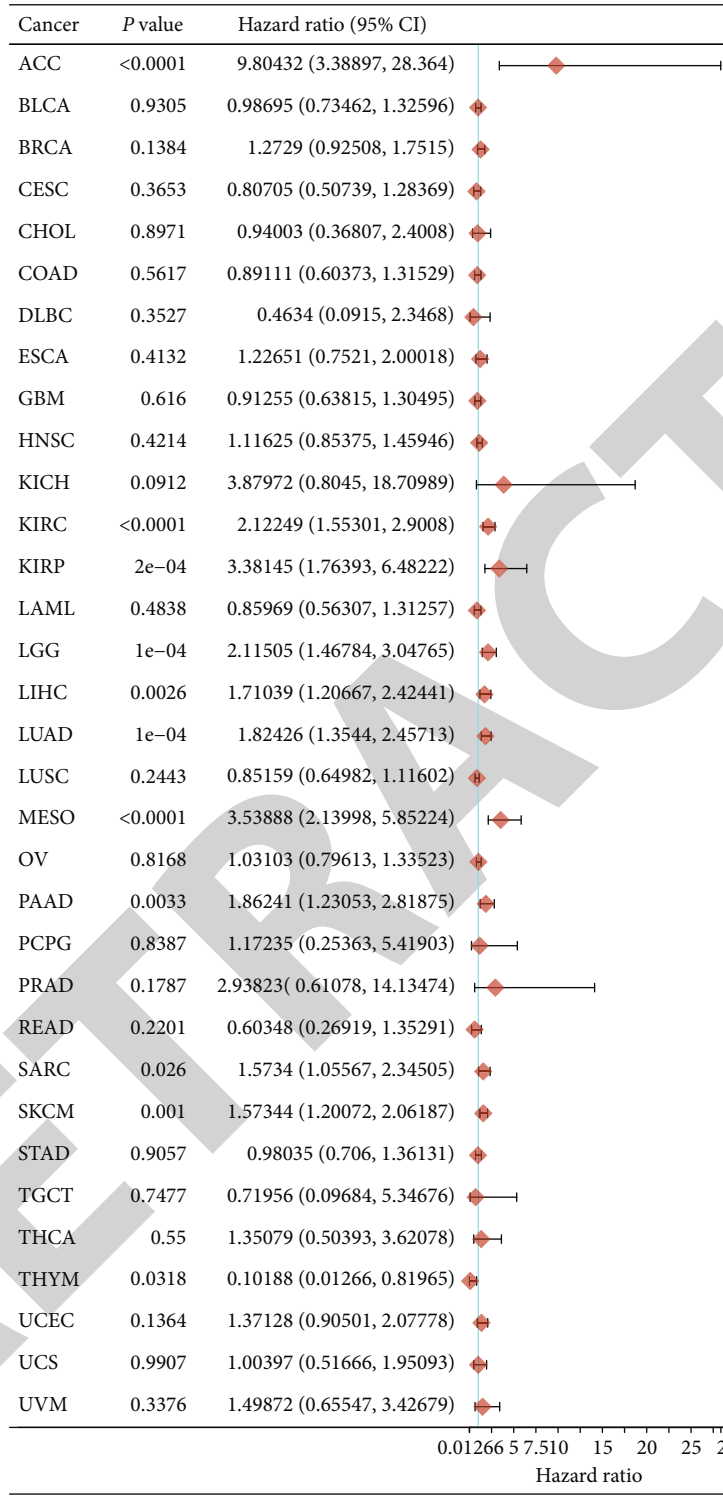
Abnormal regulation of cell cycle will lead to uncontrolled excessive proliferation of cells and promote the formation of cancer, which is of great significance in the occurrence and development of cancer. Therefore, the study of cell cycle regulation-related factors is of great significance for revealing the occurrence and development of cancer. The expression of cell division-regulating genes is required in different cell cycle phases. Previous studies have also reported the relationship between cell-cycle regulation-related genes and carcinogenesis [13–15]. With the continuous development and progress of clinical molecular biology, it has been found that cell division cycle-associated protein 3 (CDCA3) is abnormally highly expressed in non-small-cell lung cancer, gastric cancer, bladder cancer, leukemia, colon cancer, and breast cancer [16–21]. CDCA3-encoded protein triggers cell entry into mitosis and is required to properly activate cyclin-dependent kinase 1/cyclin B and cell entry into mitosis [22–24]. In addition, CDCA3 can affect cell cycle progression by affecting DNA methylation [25].

Although more and more pieces of literature report that CDCA3 plays this critical biological role in cancer progression, there is currently a lack of a study that provides a pan-cancer analysis of CDCA3 from a holistic perspective. Therefore, based on TCGA, GTEx, GEPIA, STRING, TIMER, Metascape, and other databases, this study conducted a pan-cancer analysis of CDCA3 in terms of gene expression, prognostic significance, immune correlation, tumor mutation burden, and microsatellites. We hope this study will help cancer researchers deepen their understanding of CDCA3 in pan-cancer.

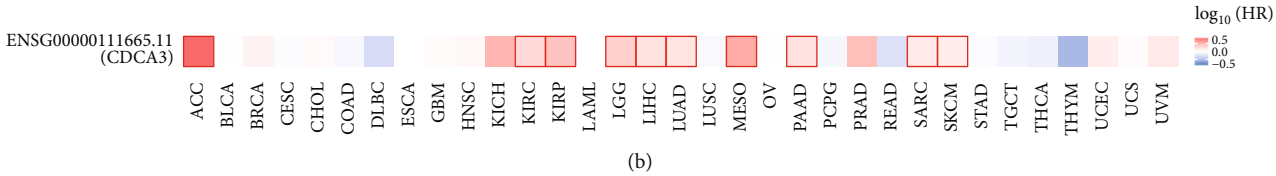
2. Materials and Methods

2.1. Data Collection and Processing. In this study, we obtained RNAseq data and corresponding clinical information for all cancer types through The Cancer Genome Atlas (TCGA) database (https://portal.gdc.com). In addition, to increase the data of normal tissue samples, we also obtained RNAseq data of more clinical samples through Genotype-Tissue Expression (GTEx) database (https://gtexportal.org/home/). We analyzed differences in CDCA3 mRNA expression between cancerous and corresponding noncancerous tissues from TCGA data. Differences in CDCA3 mRNA expression between tumors and unpaired normal tissues from TCGA and GTEx data were also analyzed. Then, we combined CDCA3 gene expression and clinical information to perform a univariate Cox regression analysis and plotted the corresponding forest plot through the "forestplot" R package to display the p value, HR, and 95% CI. Finally, to perform a reliable immune correlation assessment, we performed three different algorithms TIMER, xCell, and MCP-counter for the CDCA3 gene using the "immunedeconv" R package [26–28]. We extracted the expression information of SIGLEC15, IDO1, CD274, HAVCR2, PDCD1, CTLA4, LAG3, and PDCD1LG2 genes from the TCGA database. We then analyzed the correlation between CDCA3 gene expression and these immune checkpoint genes, and the above results were displayed as heatmaps.

2.2. Gene Expression Differential Analysis and Predictive Analysis. GEPIA is an interactive website for online analysis and mining of cancer data, designed by Zhang Zemin's Laboratory at the Peking University, mainly based on TCGA and GTEx database-related cancer data for analysis. It currently contains RNA expression profiling data for 9736 cancer and 8587 normal samples [29]. It can help medical researchers to carry out biomarker identification of related genes, expression profiling analysis of different cancer types or pathological stages, patient survival analysis, similar gene detection, correlation analysis, dimensionality reduction analysis, etc. In this study, based on the GEPIA website, we used a dichotomy to stratify cancer patients into two groups: CDCA3 high expression group and CDCA3 low expression group according to the expression of CDCA3 mRNA in cancer tissues. The association of CDCA3 expression with patient survival was analyzed using the Kaplan-Meier



(a)



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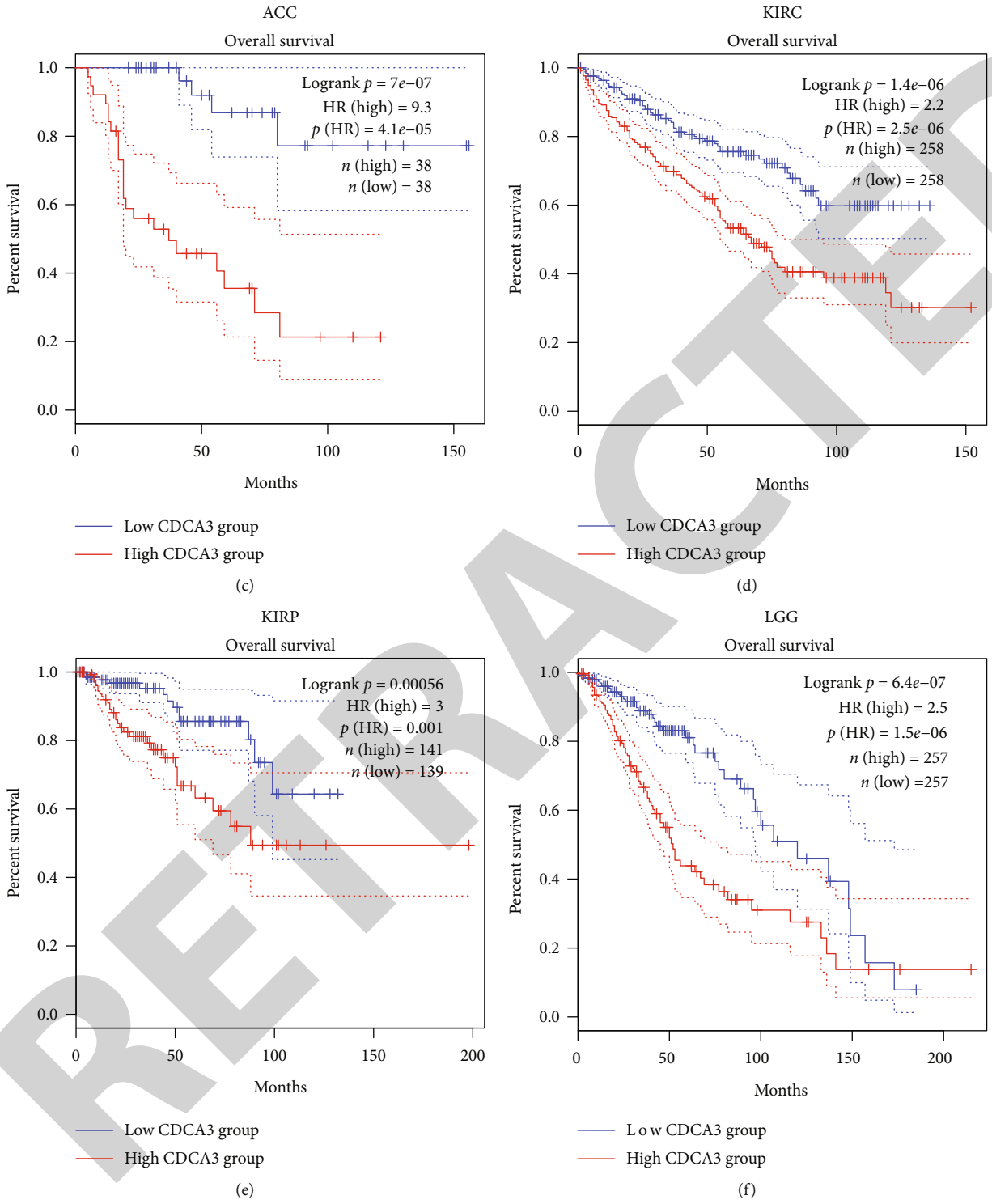

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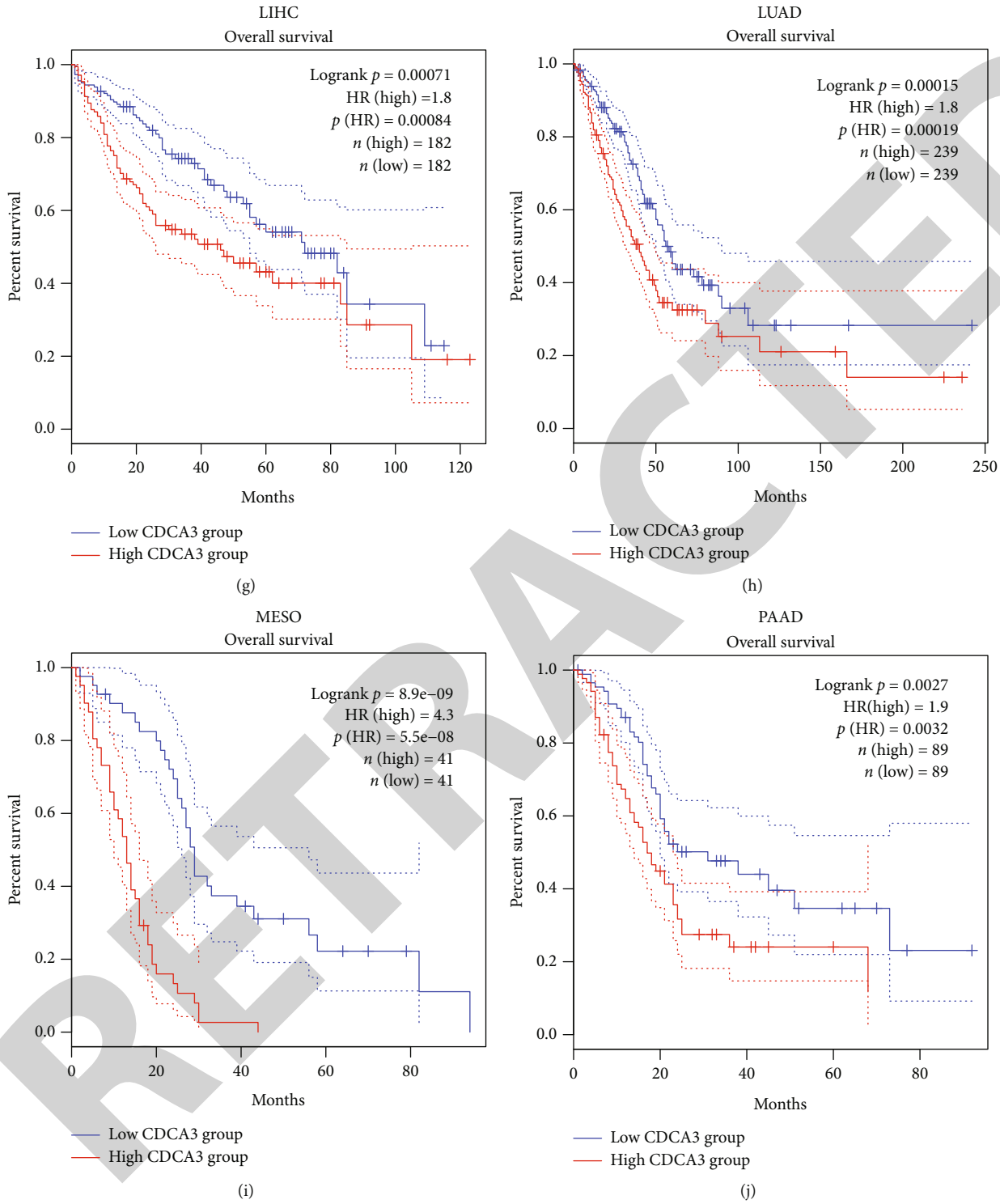

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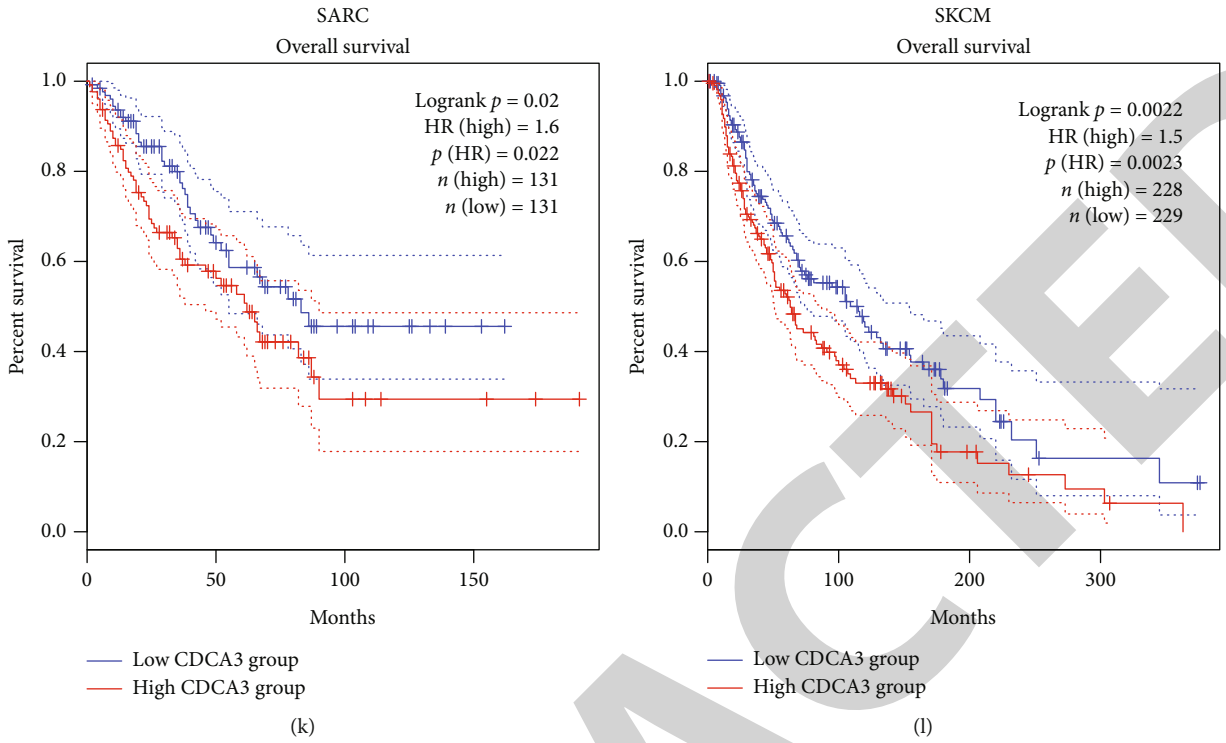


FIGURE 3: OS analysis of CDCA3 in pan-cancer. (a) The forest plot shows the univariate Cox analysis of CDCA3 gene in OS of various tumor patients, including p value, risk coefficient HR, and confidence interval. (b) Heatmap showing OS of CDCA3 gene in pan-cancer. (c–l) Kaplan-Meier curves show OS of CDCA3 gene in ACC, KIRC, KIRP, LGG, LIHC, LUAD, MESO, PAAD, SARC, and SKCM.

survival analysis. In addition, we have used a similar process in our multiple previous studies [30, 31].

2.3. Tumor Mutational Burden and Microsatellite Instability Analysis. With the development of molecular biology and next-generation sequencing technology, tumor mutational burden and microsatellite instability have become hotspots in cancer research. Therefore, we explored the correlation between tumor mutational burden, microsatellite instability, and CDCA3 gene expression. TMB is derived from Thorsson et al.'s 2018 article titled "The Immune Landscape of Cancer" [32]. MSI is derived from a 2017 article by Bonneville et al. entitled "Landscape of Microsatellite Instability Across 39 Cancer Types" [33]. Spearman's rank correlation coefficients were calculated to analyze the correlations of CDCA3 expression with the TMB and the MSI of each tumor sample.

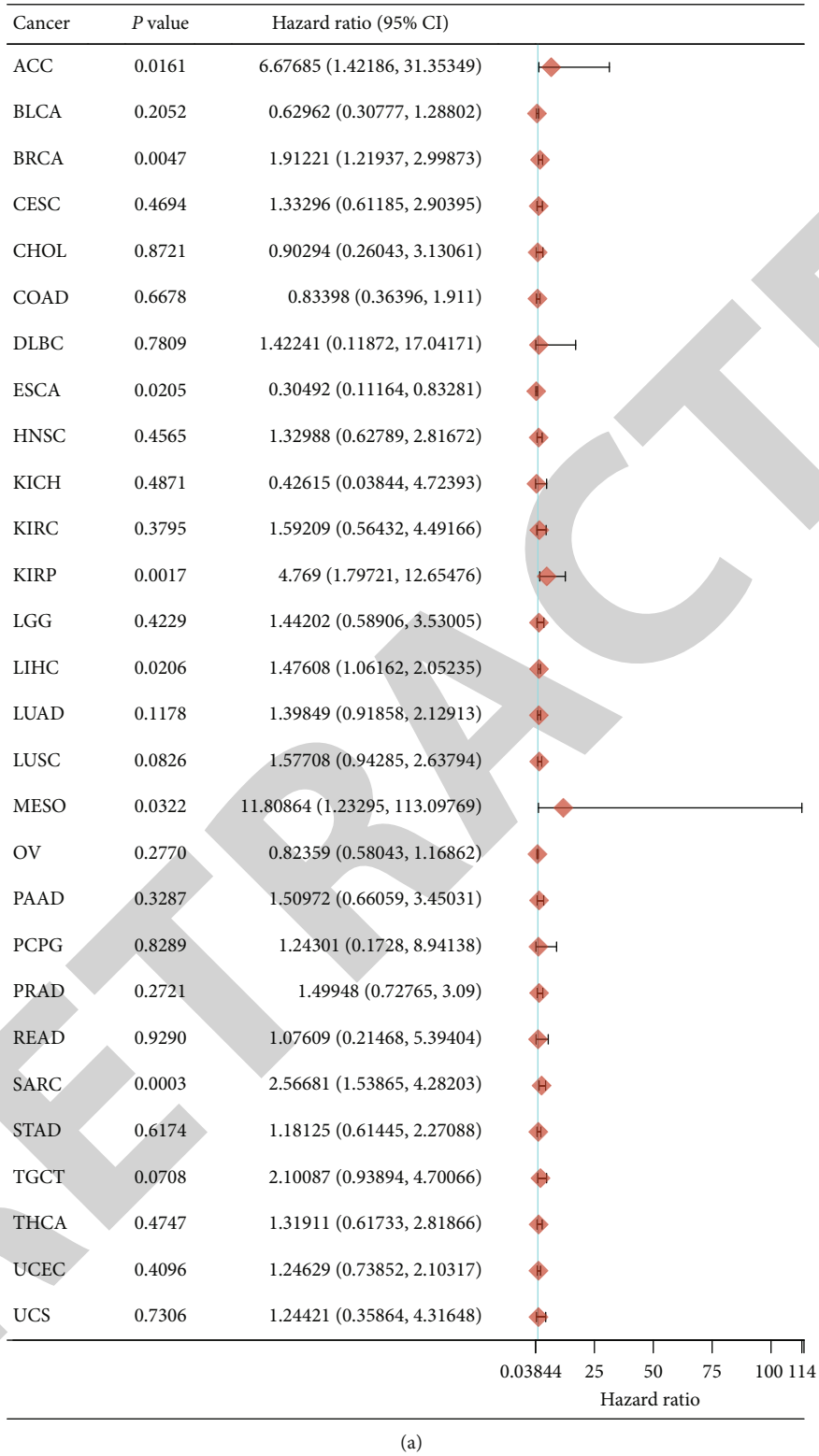
2.4. Gene-Encoded Protein Interaction Network Analysis. The STRING database is a database developed by Peer Bork's team at the European Molecular Biology Laboratory that can be used to predict protein-protein interactions (https://string-db.org/) [34, 35]. It collects protein interaction information for many species, both experimentally validated and inferred by bioinformatic methods. This study explored the top 50 genes with the strongest correlation with CDCA3 through the STRING database and mapped the corresponding PPI network. Subsequently, we performed enrichment analysis for CDCA3-related gene sets using the online tools of the Metascape website (https://metascape.org/gp/index.html#/main/step1) [36] and further beautified them using Cytoscape software [37].

2.5. Gene Set Enrichment Analysis. Gene set enrichment analysis (GSEA) is a method for enrichment analysis of target genes, which can be used to detect the correlation between target genes and known functional gene sets. This study used the GTBA database to explore the relationship between the CDCA3 gene and the HALLMARK pathway (http://guotosky.vip:13838/GTBA/), and the results of the enrichment analysis were displayed using heatmaps and bar graphs. $p < 0.05$ was defined as a statistically significant difference.

2.6. Statistical Analysis. In this study, we used R software v4.0.3 for statistical analysis, used the Wilcoxon test to compare the expression differences of CDCA3 in the two groups of samples, and analyzed the corresponding data using statistical analysis software from multiple online databases. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Transcriptional Level Analysis of CDCA3 in Pan-Cancer. To explore the expression of CDCA3 in pan-cancer, we first used the gene expression data in the TCGA database to compare the expression difference of CDCA3 in cancer and non-cancer tissues and drew the corresponding violin plots. The results showed that CDCA3 was found in cancer tissues of BLCA, BRCA, CESC, CHOL, COAD, ESCA, GBM, HNSC,



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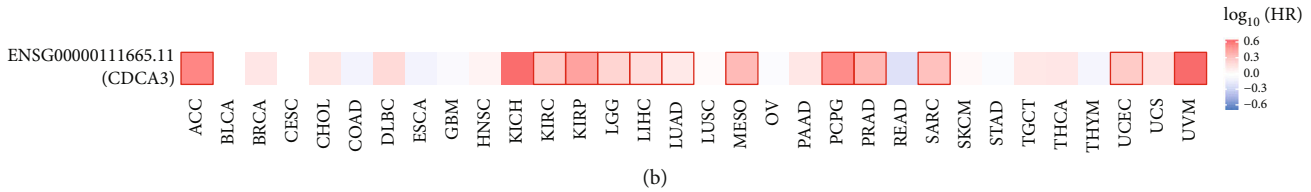

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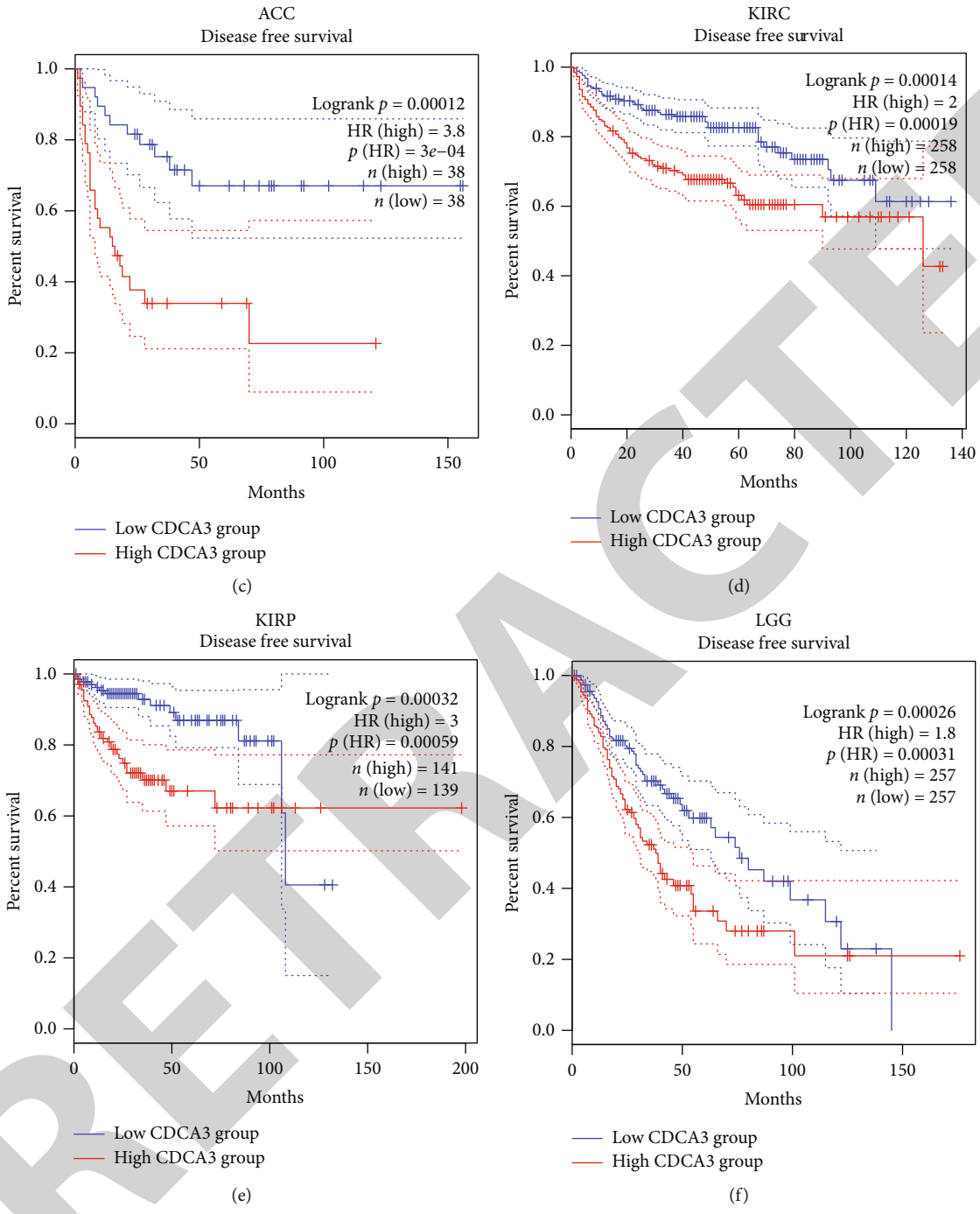

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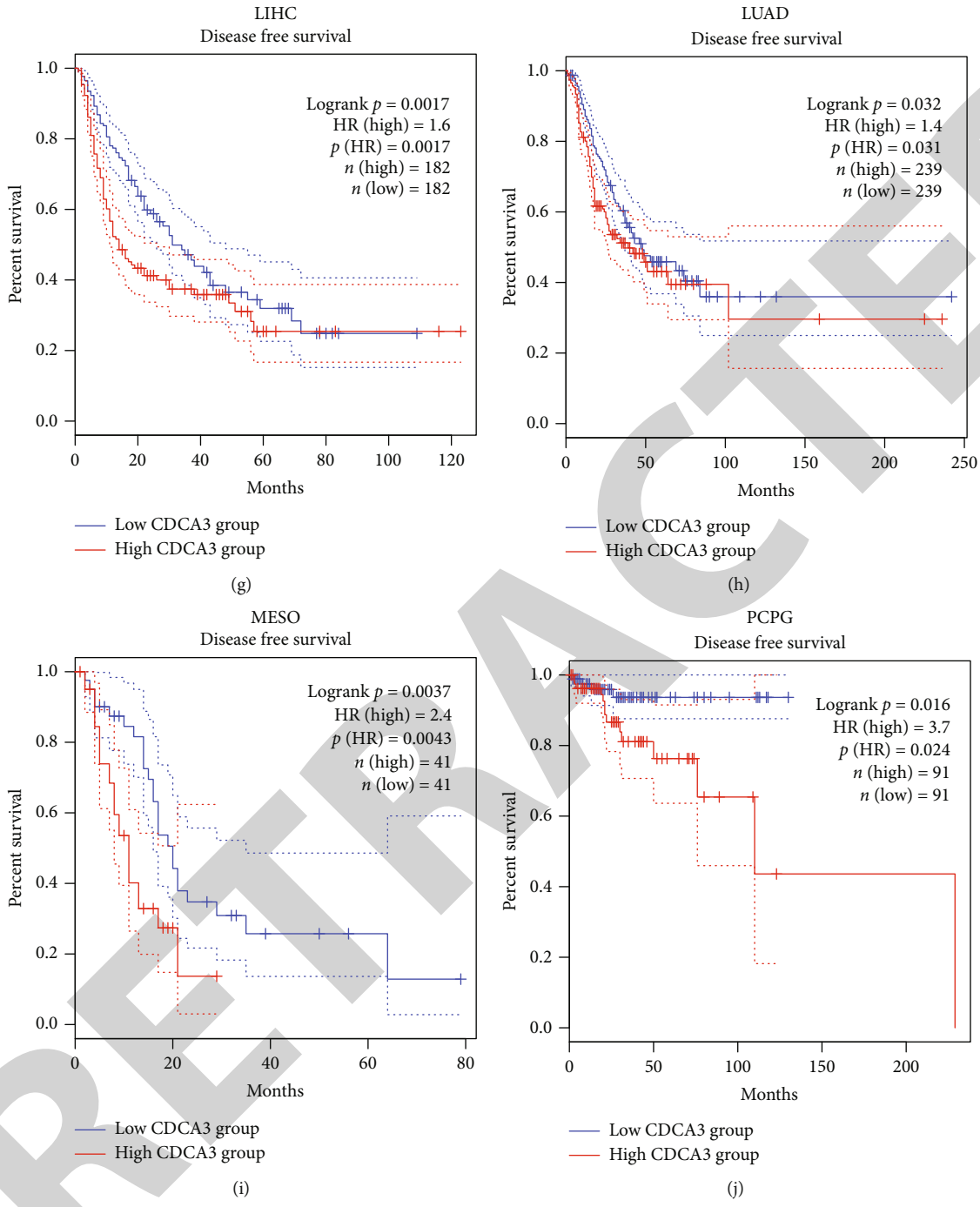

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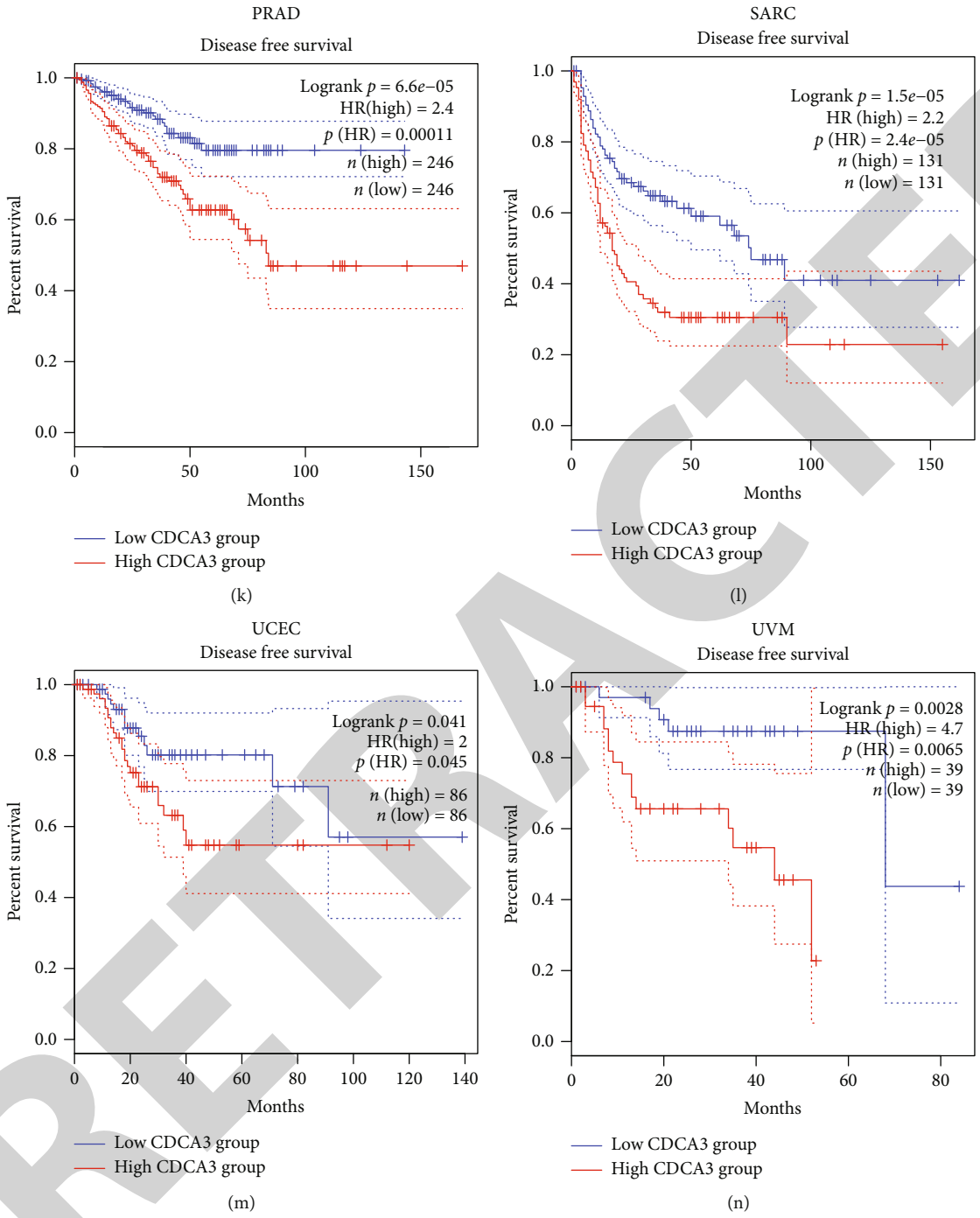
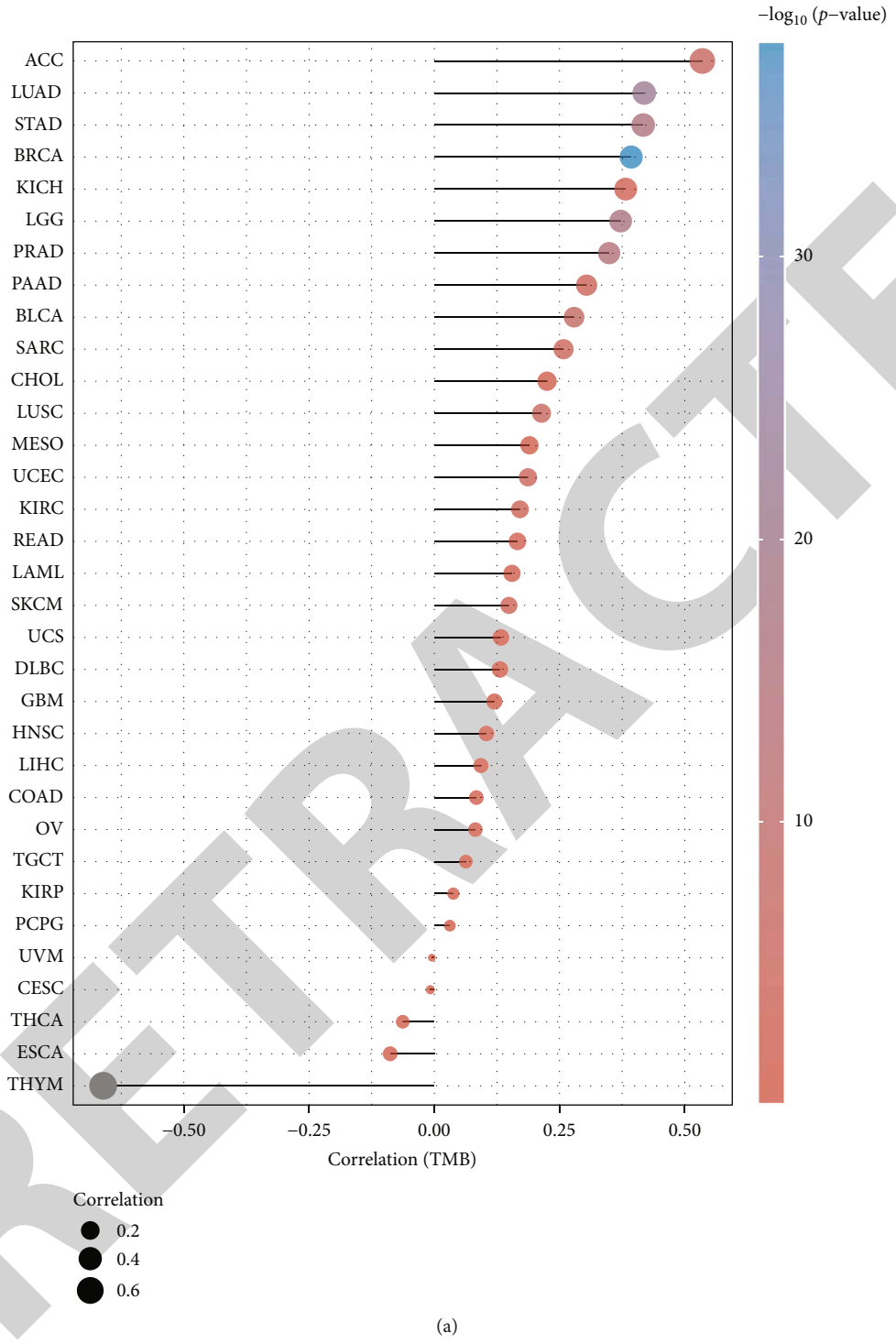


Figure 4: DFS analysis of CDCA3 in pan-cancer. (a) The forest plot shows the univariate Cox analysis of CDCA3 gene in DFS of various tumor patients, including p value, risk coefficient HR, and confidence interval. (b) Heatmap showing DFS of CDCA3 gene in pan-cancer. (c–n) Kaplan-Meier curves show DFS of CDCA3 gene in ACC, KIRC, KIRP, LGG, LIHC, LUAD, MESO, PCPG, PRAD, SARC, UCEC, and UVM.

KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, SARC, STAD, and UCEC compared to normal tissues showing significantly high expression (Figures 1(a)–1(d)). Subsequently, due to the lack of data from normal tissues in the TCGA database, we combined the GTEx database to supplement data from more normal tissues. The results showed that compared with normal tissues, CDCA3 was found in ACC, BLCA, BRCA, CESC, CHOL, COAD, DLBC, ESCA, GBM, HNSC, KIRC, KIRP, LGG, LIHC, LUAD, LUSC, OV, PAAD, READ, SARC, SKCM, STAD, TGCT, UCEC, and UCS cancer tissues showing significantly high expression (Figures 1(e)–1(h)). Overall, CDCA3 is overexpressed dramatically in most cancer types and is likely to play a similar role as an oncogene in multiple cancer types.



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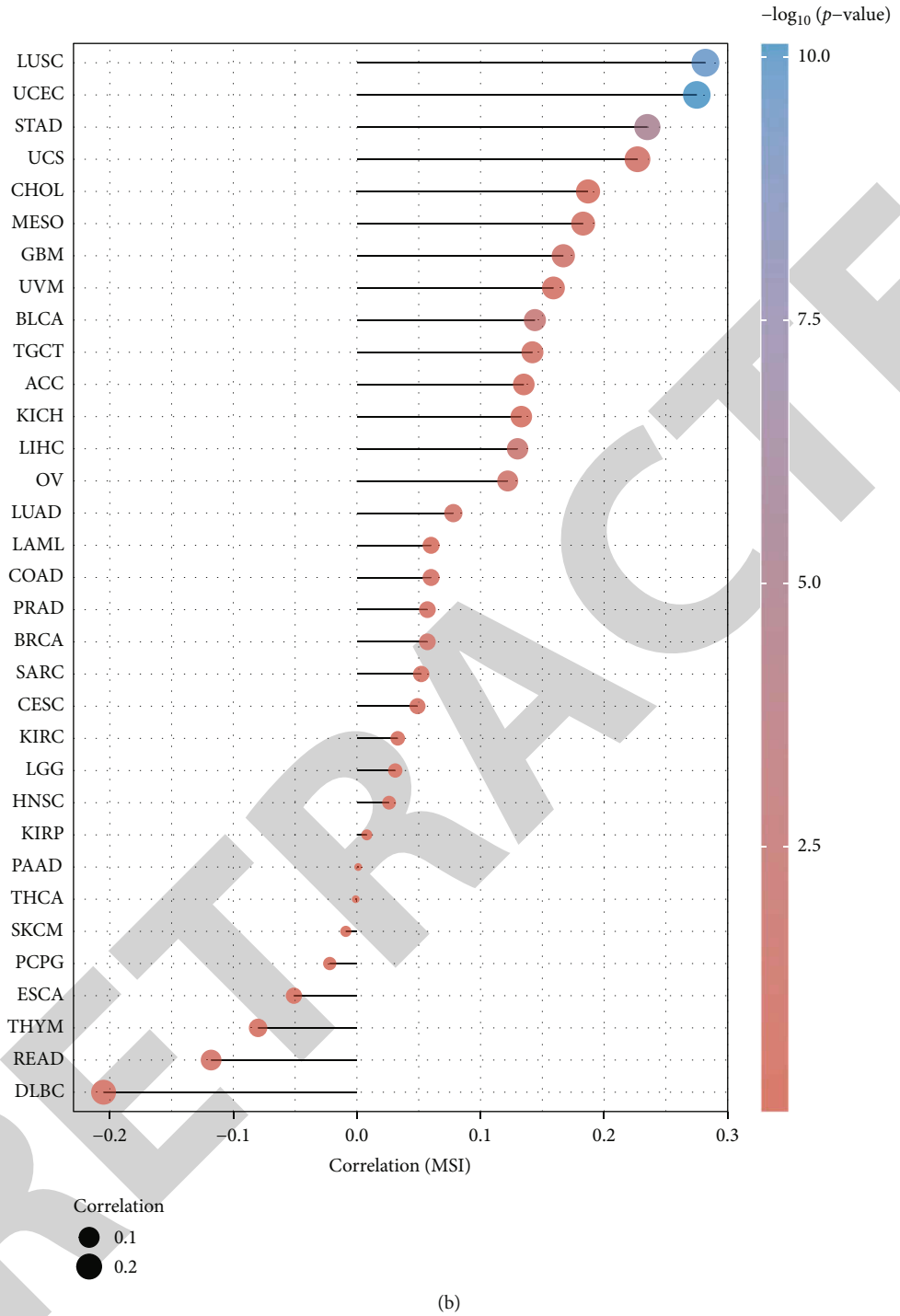
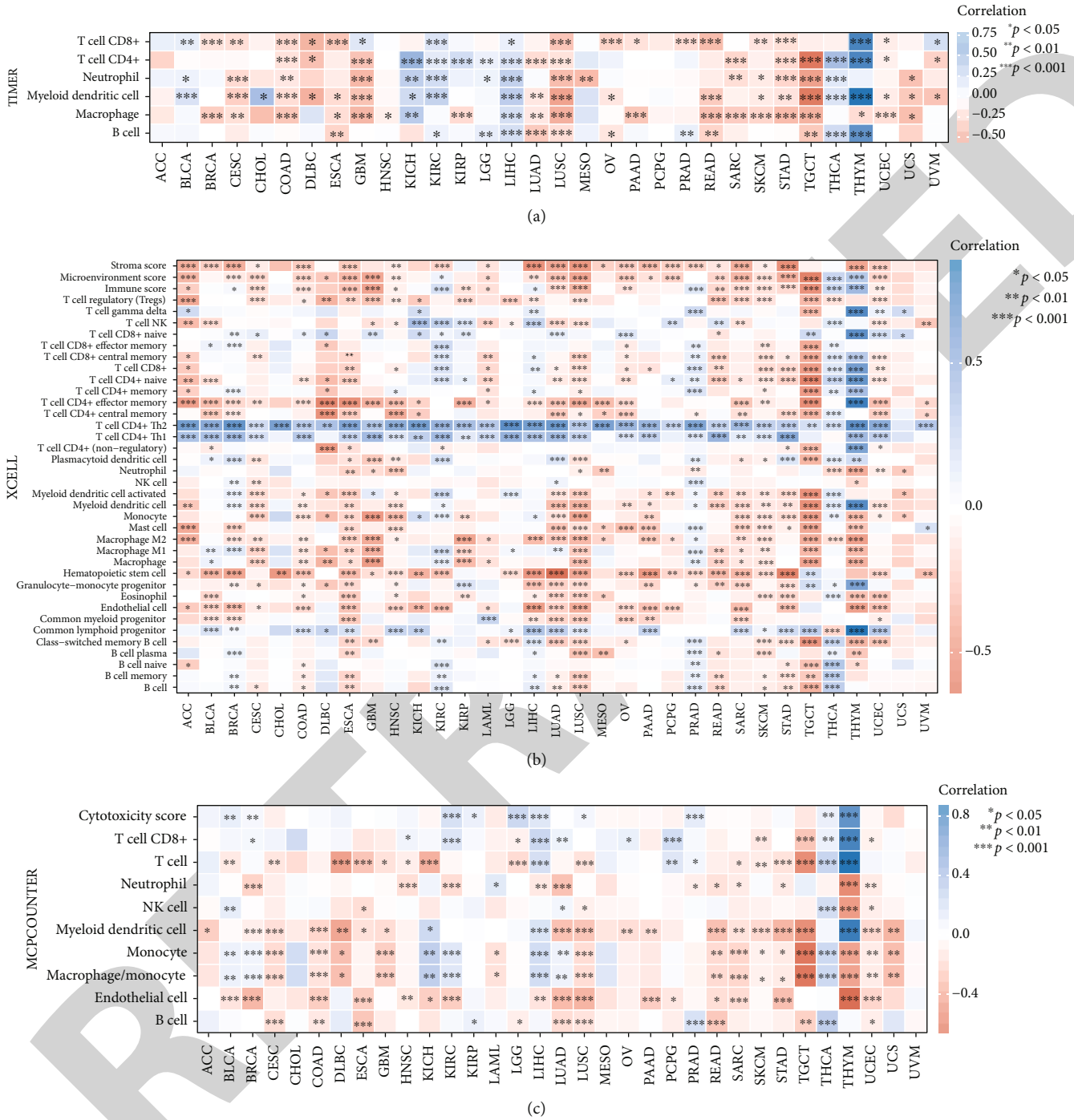


Figure 5: Mutational analysis of CDCA3 in pan-cancer. (a) Spearman correlation analysis of CDCA3 gene expression and TMB. (b) Spearman correlation analysis of CDCA3 gene expression and MSI. The size of the dots represents the size of the correlation coefficient, and the different colors represent the significance of the p value. The bluer the color, the smaller the p value.

3.2. Analysis of the Relationship between CDCA3 mRNA Levels and Different Clinicopathological Stages in Multiple Cancers. Cancer stage is a critical indicator for cancer patients. The higher the stage number, the more advanced the disease. Therefore, in this study, we investigated the expression of CDCA3 gene in different stages of various cancer types. The results showed that the expression of CDCA3 gene increased with the increase of stage in ACC, BRCA, KICH, KIRC, KIRP, LIHC, LUAD, and TGCT (Figures 2(a)–2(h)). This result suggests that CDCA3 may be positively correlated with the malignant progression of cancer.



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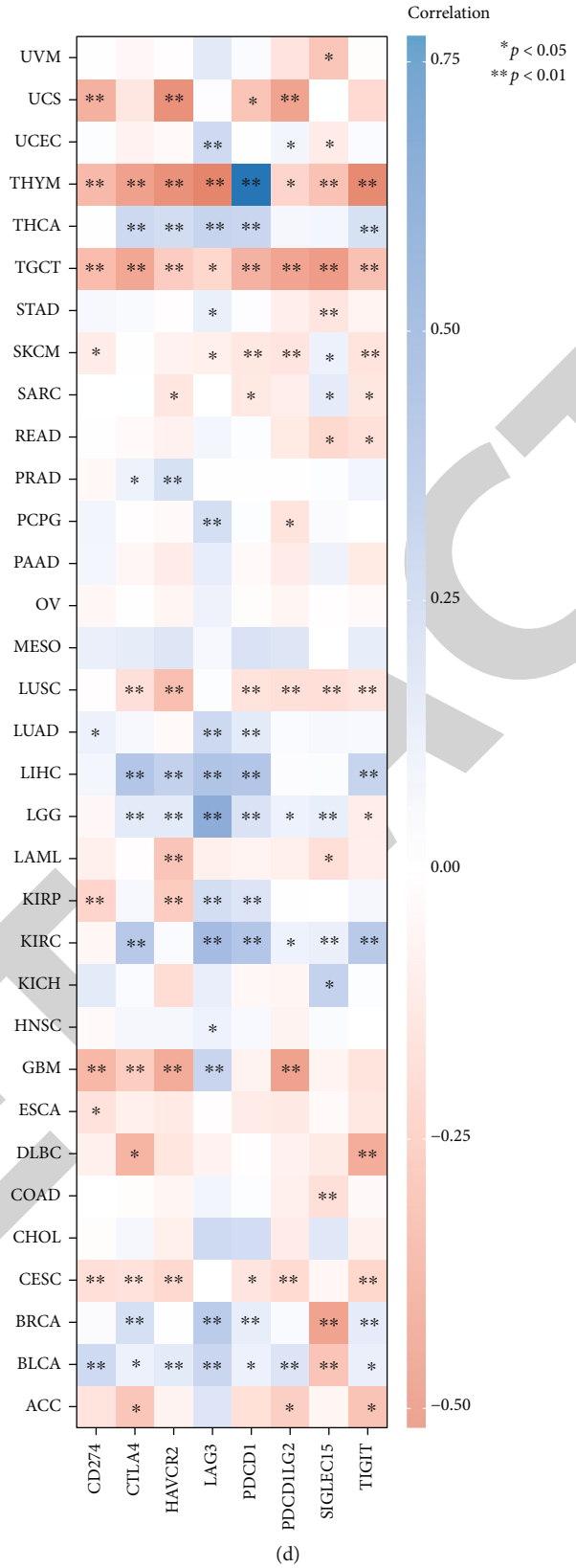
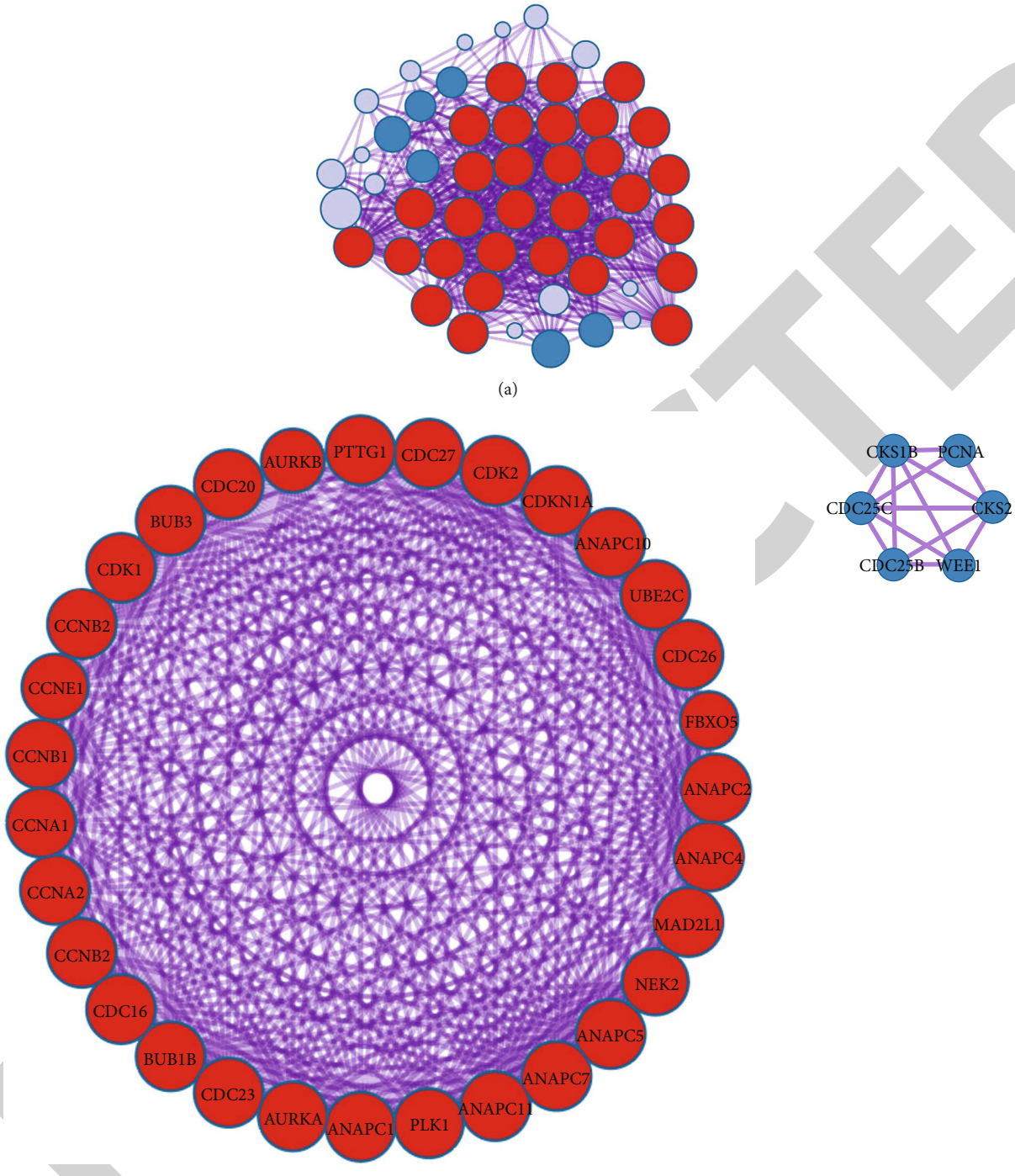


(d)

Figure 6: Immune correlation analysis of CDCA3 in pan-cancer. (a–c) Based on three different algorithms, TIMER, xCell and MCP-counter, the heatmap shows the correlation between CDCA3 expression and immune cell infiltration in pan-cancer. (d) Heatmap showing the correlation results between CDCA3 expression in pan-cancer and immune checkpoints. These immune checkpoints are SIGLEC15, IDO1, CD274, HAVCR2, PDCD1, CTLA4, LAG3, and PDCD1LG2.



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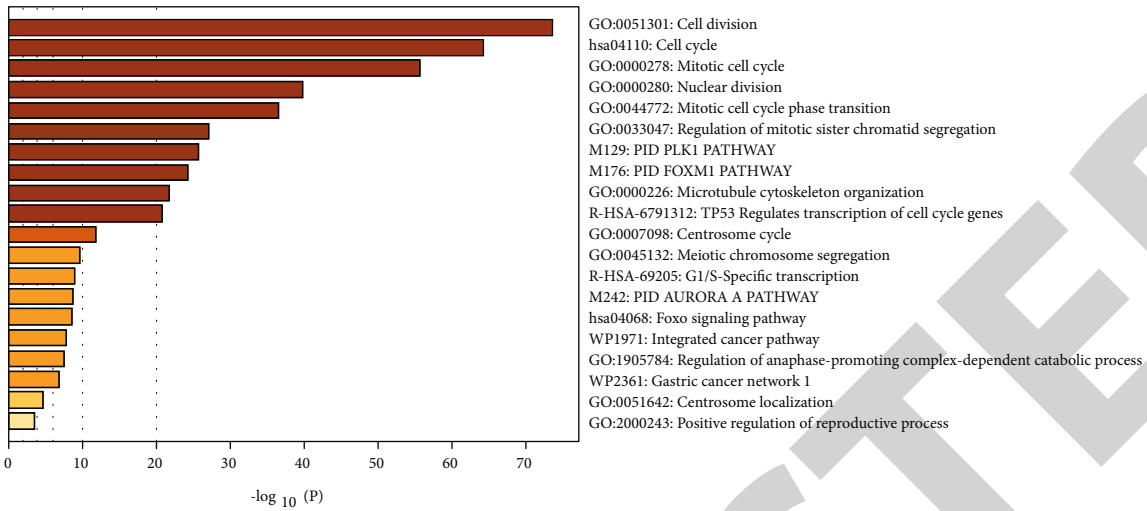

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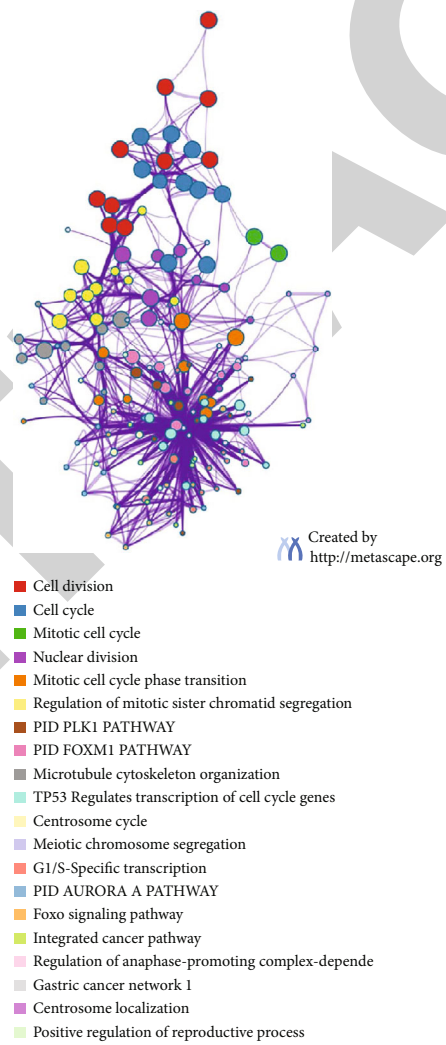

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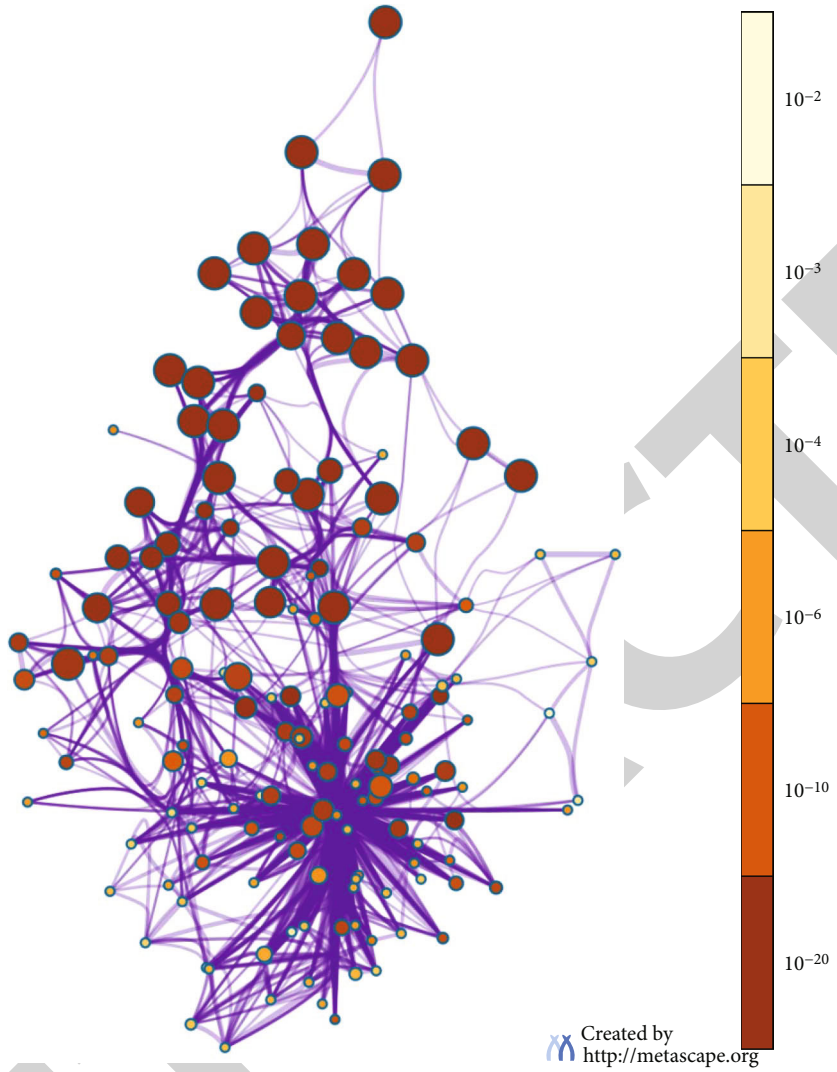

(e)

Figure 7: Enrichment analysis of CDCA3-related genes in pan-cancer. (a and b) Protein-protein interaction network and MCODE components are identified in CDCA3-related genes. (c) Bar graph of enriched terms across CDCA3-related genes, colored by p values. (d) Network plot showing enriched terms in CDCA3-related genes colored by cluster-ID. (e) Network plot showing enriched terms in CDCA3-related genes colored by p value.

3.3. Overall Survival Analysis of CDCA3 in Pan-Cancer. Overall survival (OS) was defined as the time from randomization to death from any cause. This indicator is often considered the best efficacy endpoint in oncology clinical trials. Therefore, in this study, we explored the OS of CDCA3 gene in pan-cancer. First, we obtained pan-cancer RNAseq data and corresponding clinical information from the TCGA database. We performed a univariate Cox regression analysis and displayed it using forest plots by the "forestplot" R package (Figure 3(a)). Subsequently, to test our previous results, we used the GEPIA database to explore the OS of CDCA3 gene in pan-cancer (Figure 3(b)). The results showed that high expression of CDCA3 gene was positively correlated with poor OS in ACC, KIRC, KIRP, LGG, LIHC, LUAD, MESO, PAAD, SARC, and SKCM patients (Figures 3(c)–3(l)).

3.4. Disease-Free Survival Analysis of CDCA3 in Pan-Cancer. Disease-free survival (DFS) is the time from randomization to disease recurrence or death due to disease progression. This indicator is often used as the primary endpoint of phase III clinical trials of antitumor drugs. Therefore, in this study, we explored the DFS of CDCA3 gene in pan-cancer. Similar to exploring OS in the previous step, we first performed a univariate Cox regression analysis and displayed it using a forest plot through the "forestplot" R package (Figure 4(a)). Subsequently, to test our previous results, we used the GEPIA database to explore the DFS of CDCA3 gene in pan-cancer (Figure 4(b)). The results showed that high expression of CDCA3 gene was positively correlated with poorer DFS in ACC, KIRC, KIRP, LGG, LIHC, LUAD, MESO, PCPG, PRAD, SARC, UCEC, and UVM patients (Figures 4(c)–4(n)).

(a)

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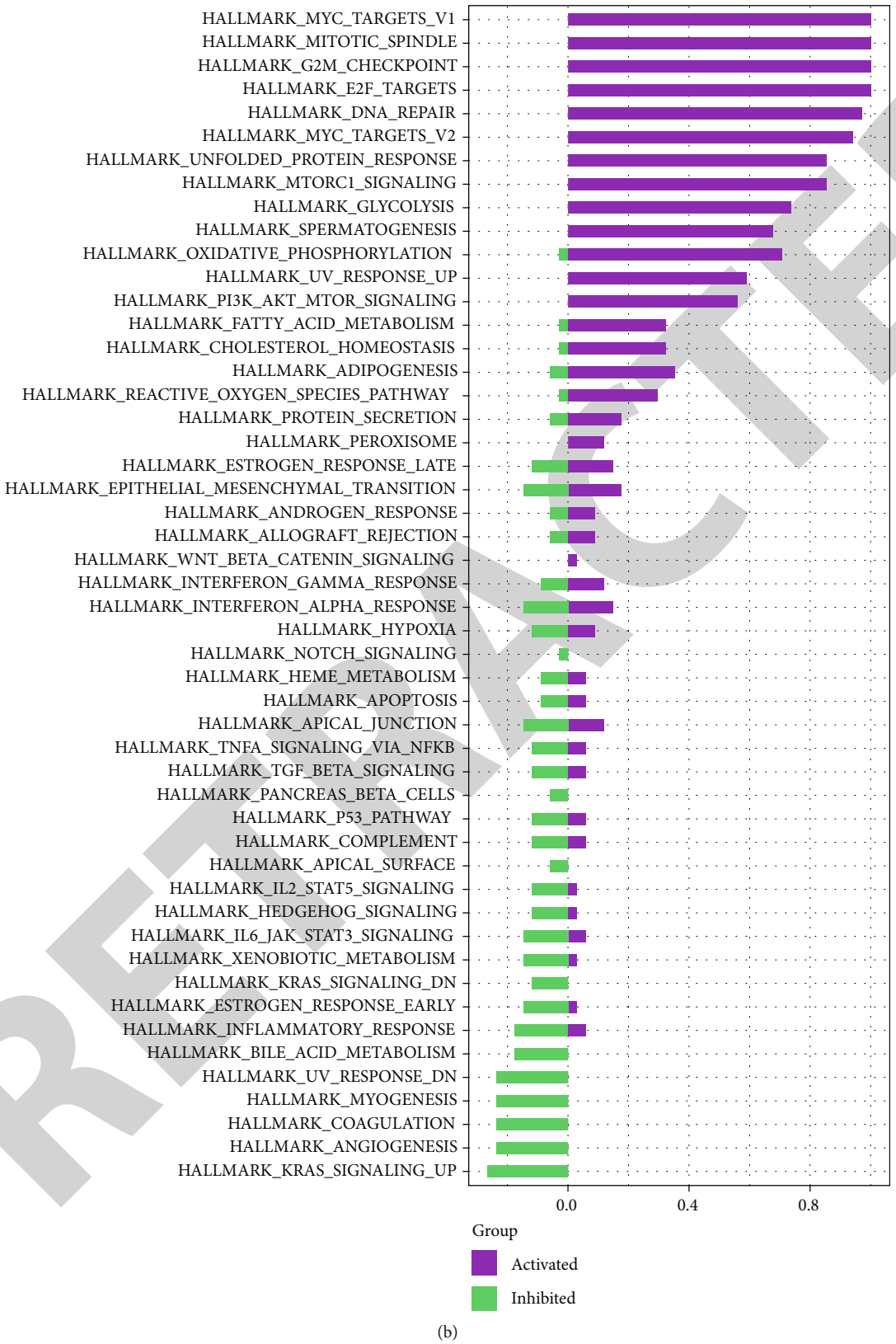

(b)

Figure 8: GSEA analysis of CDCA3 in pan-cancer. (a and b) Heatmap and bar graph showing the results of GSEA of CDCA3 gene in pan-cancer. Notably, purple represents activation, and green represents inhibition. $^{*}p < 0.05$ and $^{**}p < 0.01$.

3.5. Tumor Mutational Burden and Microsatellite Instability Analysis of CDCA3 in Pan-Cancer. TMB is highly correlated with the efficacy of PD-1/PD-L1 inhibitors, and most clinical studies using TMB as a marker have reached their endpoints with almost no failures. This allows some cancer patients to use TMB markers to predict immunotherapy's efficacy somewhat. MSI is caused by the functional defect of DNA mismatch repair in tumor tissue. The phenomenon of MSI accompanied by DNA mismatch repair deficiency is an important clinical tumor marker. Therefore, in this study, to further explore the role of CDCA3 in pan-cancer progression, we performed a Spearman correlation analysis of TMB/MSI for CDCA3 in pan-cancer. The first part of the results showed that CDCA3 was positively correlated between ACC, LUAD, STAD, BRCA, KICH, and TMB (Figure 5(a)). The second part of the results showed that CDCA3 was positively correlated between LUSC, UCEC, STAD, UCS, CHOL, and MSI (Figure 5(b)). This is helpful for a more comprehensive understanding of the biological significance of CDCA3 in pan-cancer.

3.6. Immune Correlation Analysis of CDCA3 in Pan-Cancer. To explore the correlation between CDCA3 and immune cell infiltration in pan-cancer, we used three algorithms TIMER, xCell, and MCP-counter to evaluate the correlation between CDCA3 expression in pan-cancer and immune cell infiltration in tumor tissue (Figures 6(a)–6(c)). The results showed that CDCA3 significantly correlated with various immune cell infiltrations in COAD, LUSC, STAD, and TGCT tissues. In contrast, CDCA3 is negatively associated with multiple immune cell infiltration in KIRC, LIHC, THCA, and THYM tissues. In addition, we further evaluated the correlation of CDCA3 with immune checkpoint gene expression in pan-cancer, and the results showed that CDCA3 expression was positively correlated with the expression of multiple immune checkpoint genes in THYM, TGCT, LUSC, and CESC, among which HAVCR2, PDCD1LG2, and SIGLEC15 genes were the most significant (Figure 6(d)).

3.7. Enrichment Analysis of CDCA3-Related Genes in Pan-Cancer. To perform enrichment analysis for CDCA3 genes, we performed enrichment analysis for CDCA3 and its closely related genes using STRING and Metascape databases. First, we used the STRING website to identify closely related genes interacting with CDCA3 (Figure 7(a)). To better analyze the functional mechanism between CDCA3 expression and human cancers, we performed an enrichment analysis using the Metascape database and obtained the two most important MCODE components from the analysis results. The two most important MCODE components are the regulation of mitotic cell cycle and the mitotic cell cycle process (Figure 7(b)). Next, we used the Metascape database to explore the underlying functional mechanisms of CDCA3 and its closely related genes. The top three biological effects were cell division, cell cycle, and mitotic cell cycle (Figures 7(c)–7(e)).

3.8. GSEA Analysis of CDCA3 in Pan-Cancer. Cancer researchers have increasingly used GSEA to assess the correlation between target genes and known phenotypic gene sets in recent years [30, 38, 39]. Therefore, in this study, we performed GSEA in the HALLMARK gene set targeting the CDCA3 gene in pan-cancer (Figures 8(a) and 8(b)). GSEA results indicated that CDCA3 genes were associated with abnormal activation of MYC TARGETS V2, MYC TARGETS V1, G2M CHECKPOINT, E2F TARGETS, and REACTIVE OXYGEN SPECIES PATHWAY. These data may provide a solid foundation for further studies of the CDCA3 gene and pave the way for future interventions.

4. Discussion

Despite the rapid development of molecular diagnostic and therapeutic strategies, there are currently no specific therapeutic targets for many types of cancer. Therefore, further research is urgently needed to discover more effective cancer biomarkers. Rapid cell growth and cell division are characteristic of nearly all cancer cells, and inappropriate expression of cell cycle regulatory proteins can contribute to cancer development [40, 41]. More and more studies have confirmed that dysregulated expression of CDCA3 plays a vital role in cancer progression. The clinical treatment effect of cancer patients with high expression of CDCA3 is worse, and CDCA3 may become a new potential prognostic marker and a new therapeutic target for cancer [42–45].

In this study, to gain an in-depth understanding of the differential expression of CDCA3 in pan-cancer, we first used the TCGA database to explore the mRNA expression level of CDCA3 in cancer tissues and normal tissues. There are different high expression degrees in more than ten types of cancers. However, while mining the TCGA database, we found that the sequencing results of normal tissues or paracancerous tissues included in the TCGA database are very scarce, which means that many cancer samples do not have the corresponding transcriptomes of normal tissues or paracancerous tissues, such as ACC, DLBC, LAML, LGG, MESO, OV, TGCT, and UCS. Therefore, in this study, we introduced the GTEx database, which contains more normal tissue expression information and combined it with the TCGA database to obtain more comprehensive transcriptome information. According to the mixed results of the TCGA and GTEx databases, the mRNA expression of CDCA3 was abnormally upregulated in almost all human cancers. Subsequently, we analyzed the potential prognostic value of CDCA3 in pan-cancer based on the GEPIA database. Our overall survival analysis results suggest that CDCA3 overexpression may be a predictive biomarker in multiple cancers, including ACC, KIRC, KIRP, LGG, LIHC, LUAD, MESO, PAAD, SARC, and SKCM. Compared with the corresponding normal samples, CDCA3 has different degrees of high expression in these cancer types. Patients with these cancer types in the high CDCA3 expression group had a poorer prognosis than those in the low CDCA3 expression group.

Several previous studies have shown that CDCA3 plays an essential role in the occurrence and development of cancer. Adams et al. used the GEO database, immunohistochemistry,

and western blot methods to analyze the expression of CDCA3 in tumor and normal tissues of NSCLC, depleting CDCA3 with specific siRNA against three immortalized bronchial epithelial cell lines and seven NSCLC cell lines, to determine the biological function of CDCA3 in NSCLC [17]. In this study, Adams et al. also found that the CDCA3 protein was expressed in 81.1% of lung adenocarcinoma patients, and the expression rate in lung squamous cell carcinoma was as high as 61.9%. The expression of CDCA3 in NSCLC tumor tissue is significantly higher than that in normal tissue, and increased expression of CDCA3 is associated with a worse clinical prognosis [17]. Expression of CDCA3 was also elevated in NSCLC cell lines compared to immortalized bronchial epithelial cell lines. Reducing the expression of CDCA3 significantly reduced the proliferation of NSCLC tumor cells. CDCA3 depletion can cause poor cell cycle progression in the G2/M phase, upregulation of p21, and induction of cellular senescence. In addition, Uchida et al. used qRT-PCR and western blot to analyze the expression of CDCA3 mRNA and protein in oral squamous cell carcinoma cell lines and primary tumor tissues. And they used shRNA transfection technology to analyze the function of CDCA3 in vitro [46]. The results showed that the expression of CDCA3 at mRNA and protein levels was significantly increased in all tested cell lines and primary tumor tissues compared to normal cell lines and tissues. Compared with oral squamous cell carcinoma tissues, the protein expression level of CDCA3 in oral precancerous lesions was not significantly increased. Analysis of clinical data found that the expression level of CDCA3 was positively correlated with tumor size. In addition, using shRNA transfection technology to inhibit the expression of CDCA3 can arrest the cell cycle in the G1 phase and prevent cell proliferation. Uchida et al. showed that CDCA3 overexpression frequently occurs in oral squamous cell carcinoma, which is closely related to the development of oral squamous cell carcinoma [46].

In additional studies, Phan et al. found that CDCA3 mRNA expression in breast cancer tissues was significantly higher than that in normal controls using bioinformatics analysis and was associated with the overall survival of patients [16]. CDCA3 mRNA expression was significantly upregulated in gastric cancer tissues compared with normal tissues [18, 24]. The study by Qian et al. revealed that CDCA3 mRNA expression was significantly upregulated in colorectal cancer tissues and correlated significantly with tumor size, TNM stage, and lymph node invasion [19]. Mechanistic analysis showed that CDCA3 could affect the expression of downstream molecule p21 by regulating the transcription factor E2F1, thereby affecting the G1/S transition of the cell cycle. CDCA3 can also promote the proliferation of colorectal cancer cells by activating the NF-κB/cyclin D1 pathway [25]. Qian et al. knocked out the CDCA3 gene in the colon cancer cell line SW480, significantly reducing cell proliferation [19]. Chen et al. found that HoxB3 can promote prostate cancer progression by upregulating the expression of CDCA3, and blocking this pathway may be a potential therapeutic strategy for prostate cancer [23]. The study by Bi et al. pointed out that the CDCA3-related path is expected to become a new molecular strategy for leukemia treatment [21]. Zhang et al. knocked out the CDCA3 gene in gastric cancer cells, which inhibited cell proliferation and induced G0/G1 phase arrest [18]. The expression level of CDCA3 can be regulated by transcription and protein degradation in the G1 phase [47, 48]. In addition, Hu et al. found that CDCA3 may cooperate with OY-TES-1 to participate in the proliferation, migration, invasion, and apoptosis of liver cancer cells [49]. Li et al. found that low expression of CDCA3 was associated with better overall survival in bladder cancer patients [20].

In addition, our study still has some limitations, such as the lack of clinical and laboratory data. Therefore, in the future, we will further explore the predictive value and biological role of CDCA3 in clinicopathological samples and cancer cell experiments.

5. Conclusions

Taken together, CDCA3 is a trigger for mitotic entry and is involved in regulating the initiation and termination of cellular mitosis. Whether in our study or in previous studies, CDCA3 is abnormally high expressed in various types of cancer and has a close relationship with the occurrence, development, and prognosis of cancer. CDCA3 can promote cancer cell proliferation and reduce the survival rate of cancer patients. It can be used as a prognostic indicator of cancer and is expected to become a new target for cancer therapy. Currently, the research on CDCA3 is immature, and more biological functions and mechanisms remain to be revealed.

Abbreviations

CDCA3:	Cell division cycle-associated protein 3
TCGA:	The Cancer Genome Atlas
GTEx:	Genotype-tissue expression
GEPIA:	Gene expression profiling interactive analysis
TIMER:	Tumor immune estimation resource
GSEA:	Gene set enrichment analysis
SIGLEC15:	Sialic acid binding Ig like lectin 15
IDO1:	Indoleamine 2,3-dioxygenase 1
CD274:	CD274 molecule
HAVCR2:	Hepatitis a virus cellular receptor 2
PDCD1:	Programmed cell death 1
CTLA4:	Cytotoxic T-lymphocyte associated protein 4
LAG3:	Lymphocyte activating 3
PDCD1LG2:	Programmed cell death 1 ligand 2
ACC:	Adrenocortical carcinoma
BLCA:	Bladder urothelial carcinoma
BRCA:	Breast invasive carcinoma
CESC:	Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL:	Cholangiocarcinoma
COAD:	Colon adenocarcinoma
DLBC:	Lymphoid neoplasm diffuse large B-cell lymphoma
ESCA:	Esophageal carcinoma
GBM:	Glioblastoma multiforme
HNSC:	Head and neck squamous cell carcinoma
KIRC:	Kidney renal clear cell carcinoma

KIRP: Kidney renal papillary cell carcinoma
LGG: Brain lower grade glioma
LIHC: Liver hepatocellular carcinoma
LUAD: Lung adenocarcinoma
LUSC: Lung squamous cell carcinoma
OV: Ovarian serous cystadenocarcinoma
PAAD: Pancreatic adenocarcinoma
READ: Rectum adenocarcinoma
SARC: Sarcoma
SKCM: Skin cutaneous melanoma
STAD: Stomach adenocarcinoma
TGCT: Testicular germ cell tumors
UCEC: Uterine corpus endometrial carcinoma
UCS: Uterine carcinosarcoma.

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.

Authors' Contributions

Shengchun Liu and Yingkun Xu designed the research methods and analyzed the data. Meiying Shen, Yang Peng, and Li Liu participated in data collection. Yingkun Xu, Lingfeng Tang, and Ting Yang drafted the manuscript. Dongyao Pu, Wenhao Tan, and Wenjie Zhang revised the manuscript. All authors approved the release version and agreed to be responsible for all aspects of the work.

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Retraction

Retracted: PRISM: A Novel Visual Instrument to Facilitate Self-Reflection and Learning Progress in Undergraduate Dental Education

BioMed Research International

Received 11 July 2023; Accepted 11 July 2023; Published 12 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] G. Schmalz, T. Sensky, H. Kullmann, S. Büchi, and D. Ziebolz, "PRISM: A Novel Visual Instrument to Facilitate Self-Reflection and Learning Progress in Undergraduate Dental Education," *BioMed Research International*, vol. 2022, Article ID 2009894, 12 pages, 2022.

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Research Article

PRISM: A Novel Visual Instrument to Facilitate Self-Reflection and Learning Progress in Undergraduate Dental Education

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Objectives. PRISM (Pictorial Representation of Illness and Self-Measure) is a simple visual tool that has been successfully used as a visual metaphor in medicine. In this pilot study, PRISM was used for the first time to test its potential to support self-reflection and expectations of learning in dental students. *Methods*. Dental student volunteers (25 3rd year, 10 4th year, and 10 5th year) participated. Using both quantitative and qualitative methods, PRISM interviews were compared with a numerical scale in assessing learning objectives concerning theoretical knowledge, practical skills, interest, and training need in the field of conservative dentistry. *Results*. Overall, 71% of total student group stated that they would draw personal consequences for their studies due to participating in the PRISM interviews. Compared to the numeric scales, PRISM was rated as more helpful regarding appraisal of students' theoretical knowledge ($p = 0.02$), practical skills ($p < 0.01$), training needs ($p < 0.01$), importance of dental subspecialties ($p < 0.01$), and facilitating self-reflection ($p = 0.02$). In focus groups, students commented that PRISM fostered the development of a trusting relationship with their teacher. Strengths of PRISM mentioned by the students included being able to observe and manipulate a visual summary of their individual learning needs and seeing their different learning needs in relation to one another. *Conclusion*. In this pilot study, dental students evaluated PRISM to be superior against numeric scales. Furthermore, it ameliorated the communication with teachers. The PRISM task is both simple and brief and warrants further exploration as a useful tool for self-reflection in dental education.

1. Introduction

A hallmark of all professions is the need to develop theoretical knowledge and practical skills throughout one's career. Such career-long learning is crucially dependent on developing a capacity for effective self-reflection—the professional needs to be able to identify and appraise their learning needs. In dental education, as in the training of other professions, one major aim of teachers is to assist their students to become self-directed healthcare professionals and to initiate a lifelong learning process [1]. Students are seen as self-directed and active partners in their educational environment and should develop trusting relationships with their teachers [2]. This requires continuous self-reflection, what is defined as a process where the students themselves need to get into a critical, exploratory, attentive, and interactive engagement with their own thoughts and activities [3]. Although the influence of self-reflection on academic performance remains controversial, because studies to date have found only a minor effect [4–6], it has been considered to be a core skill in dental education [7].

Four facettes of self-reflection, i.e., habitual action, understanding, reflection, and critical reflection, are explicitly mentioned; these subaspects influence learning approaches, learning goals, and academic performance [8]. The form and content of self-reflection are of practical

relevance. Different approaches are available, e.g., self-reflection combined with peer-feedback, video-watching, or expert-feedback [9, 10]. Furthermore, a recent systematic review reported on the available instruments to measure the ability of self-reflection [7]. Thereby, rubrics (or scoring guides), self-reported scales, and observed behavior were differentiated, and it has been concluded that none of these tools can be recommended as single measure [7]. Thus, based on this systematic review and to the authors' knowledge, there is no self-reflection method widely acknowledged as the 'gold standard.' Therefore, the appropriate approach for self-reflection in dental education still remains a question of theoretical and practical interest.

The present study is a 'proof of concept' investigation to determine whether a novel measure warrants further investigation as a tool to facilitate self-reflection. PRISM (Pictorial Representation of Illness and Self-Measure) is a visual instrument that has been developed in the field of medicine to assess patients' appraisal of their suffering due to illness [11] and to facilitate discussion between patient and clinician about the patient's experience of illness [12]. More recently, PRISM has been applied more widely, including in coaching. Thereby coaching and self-reflection are closely related to each other; on the one hand, coaching facilitates self-reflection [13] and on the other hand, self-assessment and developing reflective skills is a part of the coaching process [14]. Growing experience in its use indicates that PRISM functions as a visual metaphor and it is this property, which allows it to generate personally salient information [15]. Several applications beside of the original task are the usage of PRISM in context of alcohol abuse [16], acceptance of vaccinations and perceived risk of travel-related risks [17], or perceived work stress of anesthesiologists [18]. Accordingly, PRISM has the potential to be used in new fields of research and could be relevant for other contexts, including student self-evaluation of learning progress.

Up to the knowledge of the authors, there have been no publications to date describing any application of PRISM in education. The present study is aimed at assessing PRISM as a tool to facilitate self-reflection in undergraduate dental education. Both quantitative and qualitative data were collected to evaluate the strengths and limitations of the application of PRISM. It was hypothesized that PRISM would be appraised by students as a helpful tool for self-reflection. It was also anticipated that PRISM might have a positive effect on student-teacher communications.

2. Methods

2.1. Study Design. The study was cross-sectional pilot study, using both qualitative and quantitative methods and involving three groups of dental students at different stages of their training. The study protocol was reviewed and approved by the ethics committee of the medical faculty of University of Leipzig, Germany (No.: 117/20-ek). All participants were informed verbally and in writing about the study and provided their written informed consent for participation. The general study flow is shown in Figure 1.

2.2. Participants and Groups. All students who participated in the study were volunteers, and all were in the clinical years of their dental studies. Twenty-five 3rd year students were included from a group, which had completed a clinical simulation course in conservative dentistry. Ten students were included from each of the 4th and 5th years, at the end of their clinical courses in conservative dentistry and periodontology, respectively. Students resetting these courses were not permitted to participate—all participants were doing their respective courses for the first time. The study was performed between June and September 2020. To ensure safety against the background of the COVID-19 pandemic, the interviewer and student were separated by a Plexiglas pane and wore medical gloves and all instruments were disinfected at each exchange.

2.3. The PRISM Task. Initially, PRISM originates from the field of psychology/psychosomatic medicine [11, 12]. PRISM is a visual metaphor of the relationship between a subject and associated objects in a defined context [15]. A white metal board (210 × 297 mm) represents the Context, in this case "Your dental studies." A fixed yellow circle (7 cm in diameter) in the bottom right hand corner of the board, represents the Subject ("myself as a X-year dental student"). Magnetic disks, 5 cm in diameter and in different colors, represent the Objects—different aspects of dental studies like "your practical skills in periodontology" or "your theoretical knowledge of conservative dentistry" (see Figure 2). Participants are simply instructed to place each Object disk on the board to reflect their appraisal of that aspect of their studies. The main quantitative output generated by PRISM is the distance between the Subject and Object. Previous research has indicated that the closer the Object is placed to the Subject, the more salient the participant appraises the Object to be to the Subject in the defined Context [15]. Thus, putting a particular learning objective close "myself as an X-year dental student" means that the student has made good progress with that objective and regards it as a successful part of her/his learning. The crucial difference between PRISM and other quantitative measures is that its visual format coupled with the simple instructions mean that where the Object disks are placed on the board is inevitably personally salient to the individual participant. Examples of completed PRISM tasks are shown in Figures 3 and 4.

2.4. PRISM Interviews. The PRISM interviews were additional to the students' scheduled learning. Generally, all students underwent practical courses in conservative dentistry, including the treatment of patients or its simulation, respectively. These courses are regularly evaluated by questionnaires with numeric scales at the end of the term. Both, PRISM and the self-reflection questionnaire, in the current study were used in addition to the regular curriculum. All PRISM interviews were performed in the same setting by a dentist trained in the use of PRISM, who was not directly involved in the routine appraisal included in the respective course. All participants had three PRISM interviews within one week, each lasting 10-12 minutes, with exactly the same tasks in each interview. Three interviews were included to

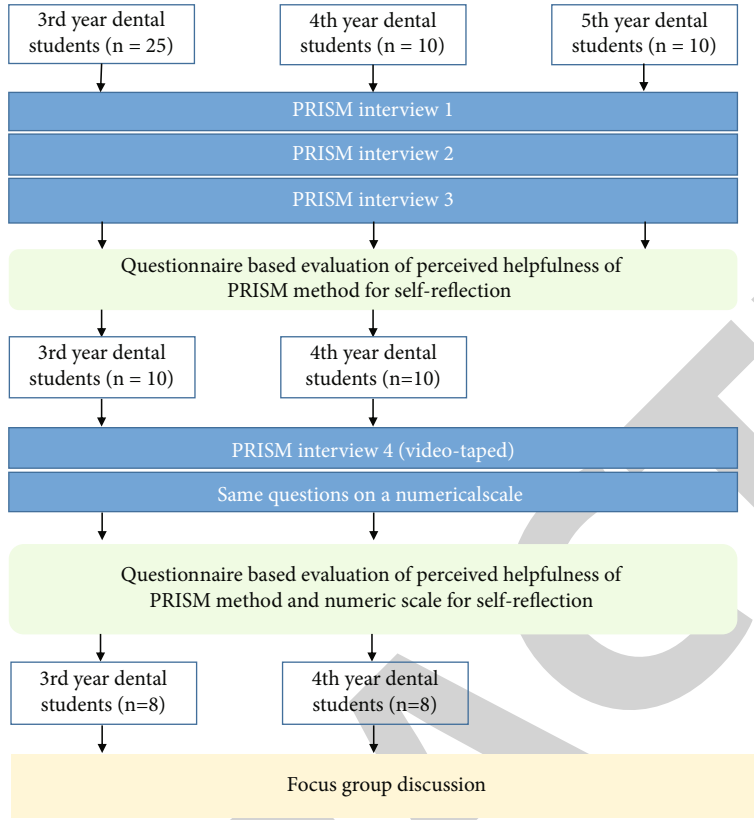


Figure 1: Study flow of interviews and evaluation steps with the respective students.

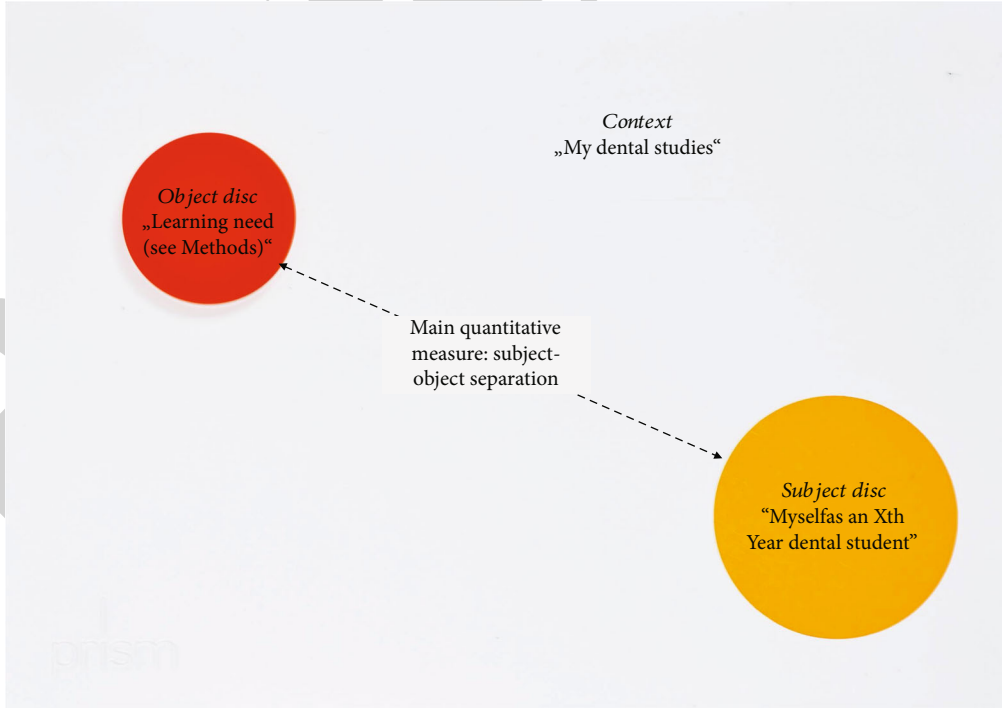
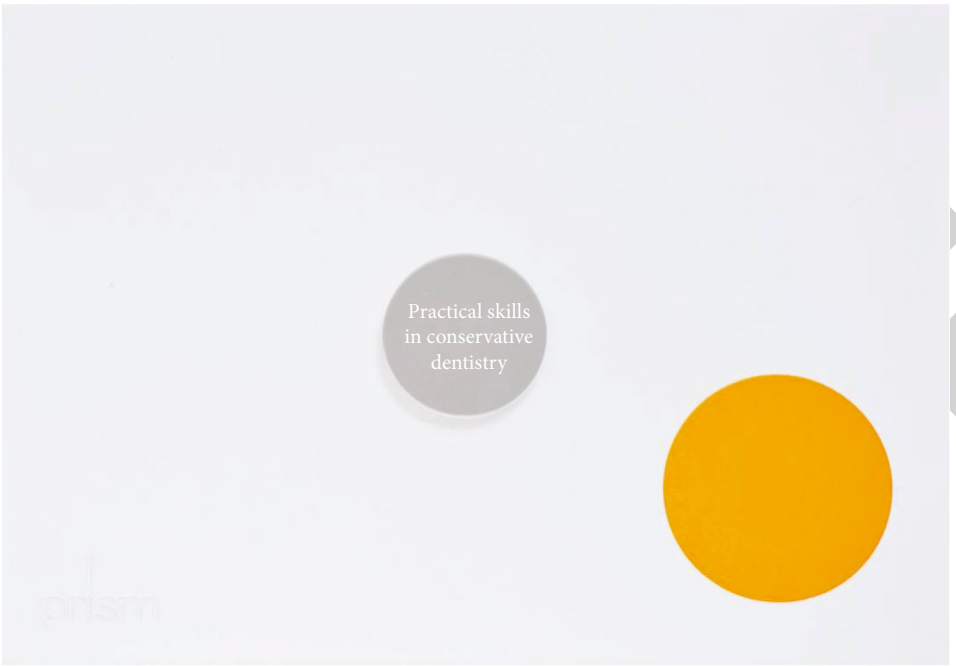


Figure 2: Principle of PRISM. The PRISM plate is the Context. The yellow Subject disc is a fixed point on the plate. The student is asked to place one or more Object disks on the plate (for example, ‘my practical skills in ….”). The distance between Subject and Object yields a quantitative measure, and can be used for self-reflection and in discussions between student and appraiser.



(a)

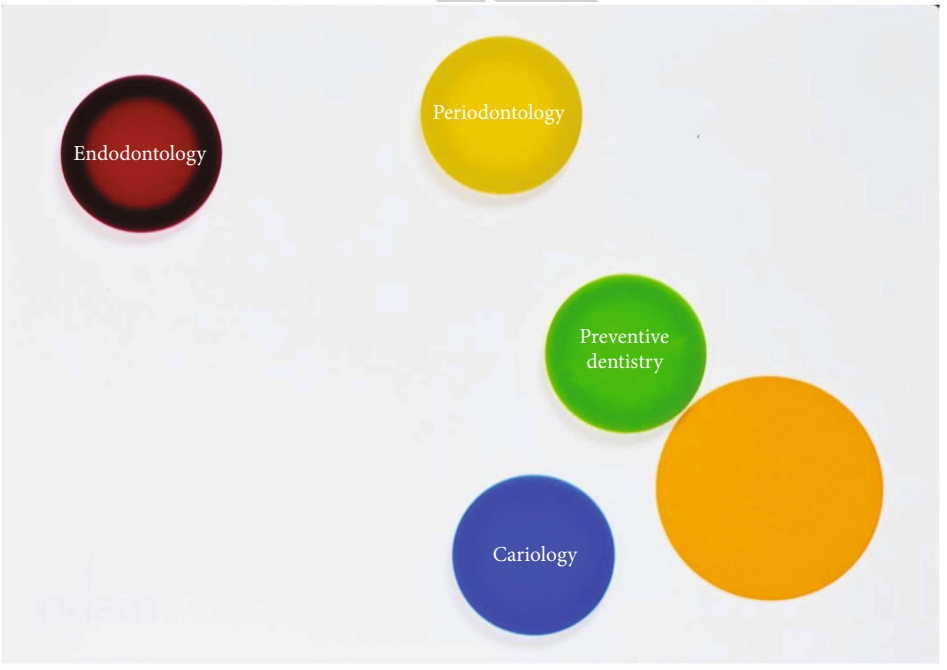


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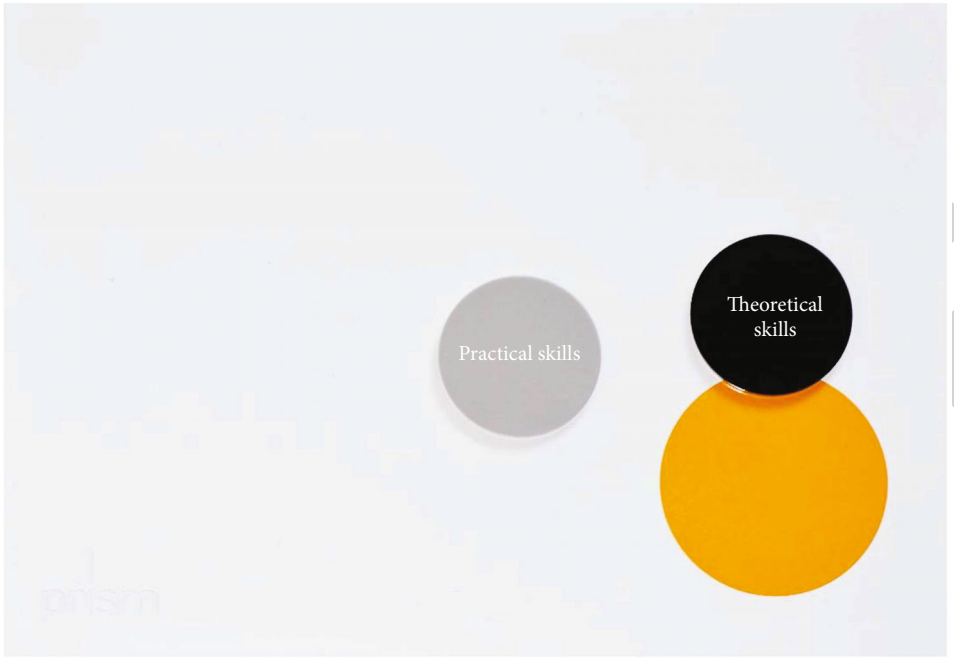
Figure 3: Continued.



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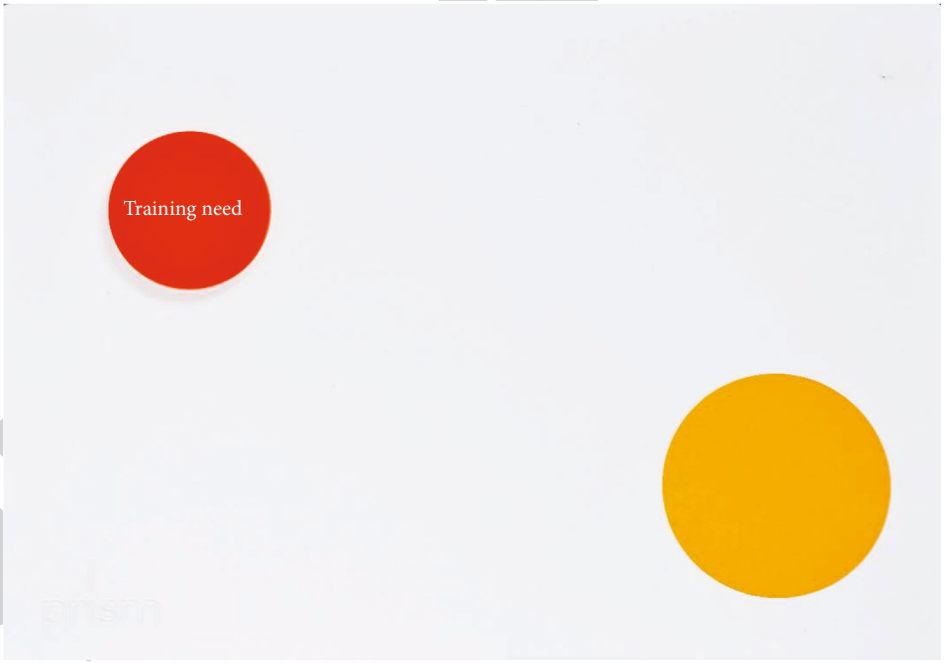
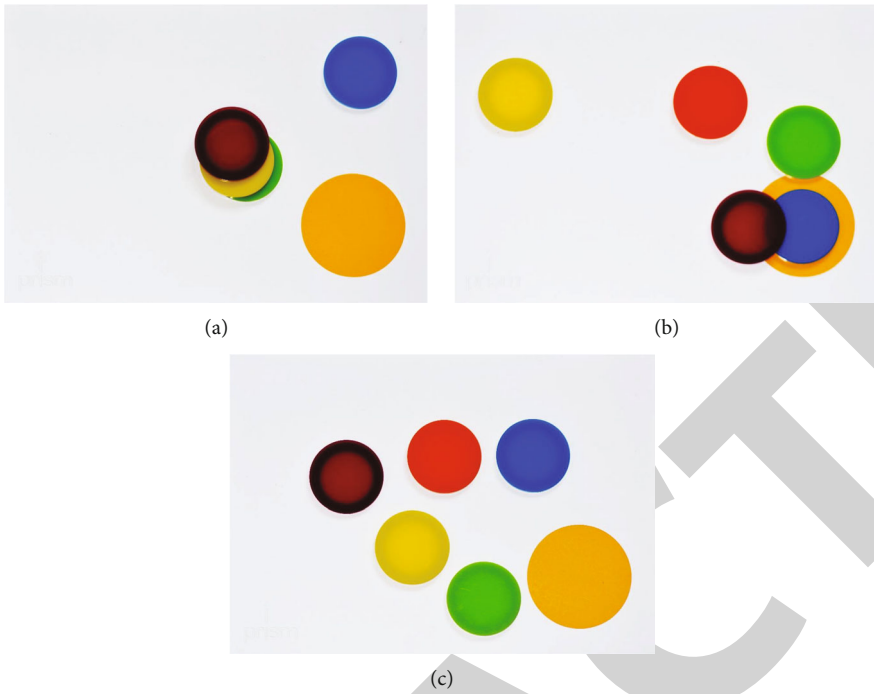


(d)

Figure 3: Examples of PRISM interview responses. (a) The results of a student for "how do you appraise your practical skills in the whole field of conservative dentistry (grey)." (b) The result of the same student for subspecialties of conservative dentistry: "how do you appraise your practical skills in periodontology (yellow), cariology and restorative dentistry (blue), endodontology (violet) and preventive dentistry (green)." Note that PRISM allows the differentiation of the subspecialties as well as giving a 'summary' measure. (c) The results of another student for "how do you appraise your practical (grey) and theoretical (black) skills in the field of conservative dentistry?." (d) The results of the same student for "how do you appraise your remaining training needs in conservative dentistry (red; the greater the distance from the Subject circle, the greater the appraised training need). While the skills and knowledge are appraised as good (c), the training need is still high (d).

assess the reproducibility of PRISM (the PRISM data will be reported separately). Moreover, multiple interviews were applied to give students the opportunity to get more experienced and accustomed with the method. At the first interview, the PRISM task was explained to all participating students and one example question given ("The white board



(a) (b) (c)

Figure 4: The individuality in answering the PRISM task is a major strength. (a) A stack of several object discs, which have nearly the same perceived importance for the student. (b) The possibility of place one disc (blue) in the center, leading to the placement of the further object disc in relation to the subject disc, but also in relation to this subject disc. (c) Another pattern of Object disks.

represents your life and the yellow fixed circle represents you. Imagine this blue disk is burger and this green disc is broccoli. Where would you put these disks to reflect how much do you like it at the moment?"). At the subsequent interviews, the PRISM task was again explained briefly. In each interview, the students were asked to place 1-5 object disks including 16 different questions on the PRISM board reflecting their theoretical knowledge, practical skills, interests, and training needs and perception of different fields in conservative dentistry. Each student was asked the same 16 questions. The topics of those questions were chosen according to validated evaluation questionnaires, which are used during the dental curriculum to evaluate the clinical courses. All potential questions were screened and discussed in the author group and finally used for the interviews. A separate validation step for the task was not performed. For example, "How do you rate your practical skills in the field of periodontology?," "How do you rate your interest in the field of endodontology?," or "How much training do you think to need in the field of cariology?" were used as questions for the PRISM task. The nearer the object was placed to the subject, the better students appraised their practical skills or the greater their interest. With the "training need" questions, the further these Object disks were from "Myself as a X-year dental student," the greater the appraised training need (a separate and specific instruction was given to the students about this). Ten of the 3rd year students and all the 4th year student participants had an additional PRISM interview six weeks after the third interview, which was videotaped. For this, 5th year students could not be included as they were in their final exams at that time. This interview was reduced to five different questions, covering theoretical knowledge, practical skills, interest, training needs, and importance of each of the five subspecialties of conservative dentistry (cariology, periodontology, endodontology, restorative dentistry, and prevention). This fourth interview included a discussion with each student about why they had placed their disks where they had on the PRISM board and how these placements might be interpreted in terms of the student's self-appraisal of successful learning and of learning needs.

2.5. Control Self-Reflection Measure. As a control, the same questions about appraisal asked using PRISM were asked on a 0-10 numerical scale after the fourth PRISM interview. The students were already accustomed to using numerical scales for evaluation, as scales are used during the dental curriculum after each student course for evaluation. These evaluation tasks for the clinical courses were the basis to develop the topics of interest in the current study. The questionnaire was composed in full accordance to the PRISM task and included exactly the same wording of questions, which were answered on the numeric scale. No separate validation step was performed.

2.6. Scales to Evaluate Use of PRISM. After the third PRISM interview, all participants were asked to rate on a scale between 0 (very low) and 10 (very high) the extent, to which they considered that the PRISM task had been helpful in their appraisal of their own competencies, including theoretical knowledge, practical skills, interest, and training needs. In other words, students rated the extent, to which PRISM

had helped them better appraise their competencies. For the 20 students who had the videotaped PRISM interview, they were all asked immediately after the PRISM interview to rate the same questions about appraisal as used in the PRISM interview on a 0-10 scale as control (see above). Afterwards, students rated on a scale between 0 (very low) and 10 (very high), to what extent they perceived an impact of PRISM and/or the numerical scales on their perception of own competencies.

2.7. Focus Group Discussion. To gain further insights into the students' perspective, two focus groups were held. Only the 20 students, who had participated in all four PRISM interviews were invited, and eight students from each of the two year groups agreed to participate. Two investigators watched the PRISM interview videotapes and the topics for group discussion were generated from these. These topics were as follows: the relationship between student and teacher and whether this is influenced by the PRISM method; the relative importance for a successful interview of the three elements—PRISM method, interviewer, and setting; whether the relationship with the interviewer built up in the PRISM interview was seen as personal or as topic-related (i.e., course-specific content explored in the PRISM task); strengths and limitations of PRISM method. First, each topic was introduced in the focus groups and examples from the video analysis were explained. Afterwards, the groups discussed each topic individually. Based on this discussion, the groups had the task to formulate main statements regarding the respective topic. These resulting summary statements or conclusions were formulated within the focus group to reflect the group consensus and to include each participant actively in the process of evaluating the method. Each summary statement has been finally rated by the whole focus group and was only fixed if all eight participants agreed, and otherwise, it was modified until a full consensus was achieved. Thus, only consensus statements, which were confirmed by all of the focus group participants, were finally formulated.

2.8. Statistical Analysis. The statistical analysis has been performed with SPSS for Windows, version 24.0 (SPSS Inc., U.S.A.). Values are presented as mean values with standard deviation or percentage, respectively. Normal distribution was tested with the Shapiro-Wilk test. Thereby, the four questions regarding competencies (theoretical knowledge, practical skills, interest, and training needs) were normal distributed ($p>0.05$), while the rest showed nonnormal distribution. Based on normal distribution, Wilcoxon-test or t -test was applied. The significance level was set at $p < 0.05$.

3. Results

3.1. Participants. In total, 45 students were included, with a mean age of 23.2 ± 3.1 years (40% male gender). Of these participants, 25 students in 3rd year (age 22.9 ± 2.9 years, 32% male), as well as 10 students in 4th (age 23.5 ± 2.9 years, 50% male) and 5th year (age 24.9 ± 2.8 years, 50% male) took part in the study. Based on the total numbers of the respective study years, 48% (25/52) of 3rd year, 22% (10/46) of 4th year, and 23% (10/44) of 5th year students participated in this study.

3.2. Evaluation of PRISM after 3 Interviews. The results of the evaluation of PRISM in the total group are shown in Table 1. Overall, 71% of total group stated that they would draw personal consequences from the PRISM interviews for their further study in dentistry. The distribution of ratings (0-4, 5, or 6-10) showed more than half of the students rated PRISM as positive (value 6-10) for all questions asked. No significant gender differences were found (Table S1).

3.3. Comparison between PRISM and Numeric Scale. PRISM was rated to be significantly more helpful than the numerical scale for the perception of students' self-reflection competencies (Table 2). Significantly, more students said that they would draw personal consequences for their learning from PRISM than from the numerical scales (80% vs. 50%, $p < 0.01$). Moreover, PRISM was rated to be a better tool for self-reflection than the numeric scale (Table 2).

3.4. Focus Group Discussion. A summary of focus group results is given in Table 3. The relationship between the student and teacher was stated as important, and PRISM was rated as supporting the building of this relationship. In evaluating the success of the interview, the students gave similar weights to the PRISM method and to the interviewer. However, the interviewer placed more importance on the PRISM method. Major strengths for the students were being able to scale their appraisals individually and to gain a visual summary of their appraisals, including being able to gain a picture of different topics in relation to one another (Table 3). The need for explanation to understand the PRISM task was identified as a limitation of PRISM. The interviewer perceived a high benefit, especially due to supported relationship building and the fact that PRISM was useful to gain a deeper understanding of the students' perspective.

4. Discussion

PRISM was originally developed to better understand the illness experience of individual patients. However, perhaps encouraged by its novelty as a visual metaphor, an increasingly wide range of applications has been reported and it has been proposed as potentially useful in coaching [15]. This led to the present study, the first reported application of this type for PRISM.

This study had modest aims, to assess the acceptability and potential utility of PRISM as a tool for appraisal in undergraduate dental education. The small sample was in keeping with the aims of the study as a preliminary investigation. However, the fact that the student participants were all volunteers could have biased their responses. Moreover, the participants were only a minority of the respective cohort and thus its representativeness is limited. Again in keeping with the modest aims of the study, no attempt was made to integrate the PRISM task into the students' teaching programme or curriculum—this would have been premature before gathering basic data on potential acceptability and

Table 1: Results of the evaluation of PRISM for the total sample. Values are rated between 0: very low and 10: very high.

	Total sample ($n = 45$)	Rated values		
		0-4	5	6-10
The assessment with PRISM 0-10 was helpful for my appraisal of…				
My theoretical knowledge	5.9 ± 2.4	22% (10)	22% (10)	56% (25)
My practical skills	5.8 ± 2.8	24% (11)	18% (8)	58% (26)
My interest	6.1 ± 2.6	24% (11)	4% (2)	71% (32)
My training needs	5.9 ± 2.5	27% (12)	13% (6)	60% (27)
Personal consequences for further study (yes/no)	71%		—	

Table 2: Comparison of the self-perceived helpfulness of PRISM and a numeric scale (0-10) in the participants of 3rd and 4th year, who underwent the video-taped PRISM interview ($n = 20$).

Topic	PRISM		Numeric scale 0-10		p value
	Mean value	Rating 6-10	Mean value	Rating 6-10	
The assessment with PRISM/numeric scale 0-10 was helpful for the appraisal of…					
My theoretical knowledge	6.8 ± 1.9	80% (16)	5.2 ± 2.2	45% (9)	**0.02**[a]**
My practical skills	6.6 ± 1.7	70% (14)	5.1 ± 2.7	45% (9)	**<0.01***
My interest	6.9 ± 2.3	70% (14)	4.5 ± 2.5	30% (6)	0.12*
My training needs	7.3 ± 2.1	85% (17)	5.6 ± 2.7	45% (9)	**<0.01***
Importance of subareas of dentistry	6.4 ± 2.7	70% (14)	4.7 ± 2.4	35% (7)	**<0.01****
Personal consequences for further study (yes/no)	80%	—	50%	—	**<0.01****
Is a good tool for self-reflection	8.5 ± 1.3	100% (20)	5.6 ± 2.5	50% (10)	**0.02****

[a]The statistics refer to the differences between means. *t-test. **Wilcoxon test.

utility. The fact that the PRISM task was repeated three or four times (to gather data in the reproducibility of its results, to be reported separately as part of the PRISM outputs) could also have influenced students' responses. The study was performed during the COVID-19 pandemic, whereby specific measures to prevent infections had to be applied. This might also limit the generalizability of the findings. A further limitation, which could not be avoided in the study design, was asking the students to use and assess the control appraisal tool (the numerical scale) after they had gained experience of PRISM—this could have biased their responses. It is known that the original PRISM task has a good test-retest reliability and interrater reliability [11, 19]. Furthermore, the PRISM method is sensitive for change over time [15]. This would be also of interest in context of education and will be addressed in a subsequent project. Generally, the PRISM task is originally understood by the vast majority of patients [11]; the questions in the current study were sometimes quite complex and therefore more challenging. Several other methodical limitations require consideration. Students were only asked, whether they would draw consequences from the PRISM task, but not which consequences would that be. Furthermore, it is difficult to state what is a "positive" result at a scale between 0 and 10 by focusing on the mean values. For this rationale, the distribution of ratings lower and higher than 5 was presented as well, whereby results of 6-10 might be considered as merit or benefit, respectively. Although the topics included in the PRISM task and self-reflection questionnaire were chosen in accordance to available and common evaluation procedures, no validation of the measures was performed. The qualitative data in the current study were presented as consensus statements, which were formulated by the participants. The topics for these statements were chosen based on video analysis of the interviews, but a validation was not performed. The authors decided to use this consensus form to allow statements reflecting the students' perspective on PRISM as a tool for dental education for the first time. Overall, this limits the usage of the applied instruments and the generalizability of the findings. Future studies should use more valid qualitative analysis methods, as the applied methodology cannot be referenced and is therefore somewhat biased.

Allowing for these limitations, the current study's results, both quantitative (Table 1) and qualitative (Table 3) indicate that the students engaged well with PRISM task and found it helpful in appraising their competencies, and superior to a numerical scale (Table 2).

The majority of the students rated PRISM as helpful in appraising their competencies and 71% endorsed that they had learned from the PRISM task something relevant to their further studies (Table 1). The students appreciated PRISM as a visual tool and one, which is 'calibrated' by each individual student, in terms of where the Object disks are placed. As a visual metaphor, the placement of each Object disk depends crucially on the individual's reflections about that Object. While it is possible to endorse a number on a 0-10 scale without giving the task much thought, this is not possible for PRISM, and this was reflected in the

Table 3: Results (consensus statements) of the focus group discussions plus interviewer's comments. The points listed in the tables reflect the consensus statements of the whole focus group.

Topic	Group I interviews in 3rd year ($n = 8$)	Group II interviews in 4th year ($n = 8$)	Interviewer's experiences
Relationship teacher–student and how PRISM can affect this	(i) Very important for success during study (ii) "If you like your teacher, you like to listen to your teacher" (iii) Personal contact of importance for relationship (iv) PRISM can serve as an appropriate basis for relationship (v) PRISM makes relationship building easier	(i) Relationship has more influence on learning than the content (ii) Respectful relationship brings perception of safety and avoids fear, in contrast fear leads to averting the field (iii) PRISM brings a personal shared level and the feeling that student's view is valued (iv) PRISM supports relationship building	(i) Very important for bond of trust in the clinical courses of dental study (ii) PRISM opened the contact and served as a good basis for forming relationship with students (iii) Students trended to open up easily by transferring the level of communication on PRISM (iv) PRISM makes relationship building easier (v) Students were not only able to summarize their learning needs but also to view them as an observer
Importance of PRISM method, interviewer, and setting for successful interview	(i) Depends on the interviewer (ii) Setting of minor relevance (iii) 49% PRISM, 49% interviewer, 2% setting	(i) Setting is important to create openness and makes relationship to interviewer easier (or more difficult) (ii) 42.5% PRISM, 42.5% interviewer, 15% setting	(i) Most importance is by PRISM method, because it facilitates the interview (ii) 65% PRISM, 30% interviewer, 5% setting
Personal or issue-related relationship due PRISM interview	(i) Both, personal and factual equally, the more PRISM interviews, the more a personal relationship is built	(i) Primarily factual because of the thematic background, the more PRISM interviews, the greater a sense of security and personal relationship	(i) More personal relationship than factual (ii) The more interviews, the more personal the relationship
Strengths of PRISM method	(i) Being able to observe and manipulate a visual summary of learning needs (ii) Individual scales for different questions (iii) Visual and haptic (iv) Individual interpretation (v) Helpful for self-evaluation and self–reflection (vi) More useful than numerical or percentage scales (vii) Visualizing the relationship between different objects (viii) Visualizing a development process for yourself	(i) Being able to observe and manipulate a visual summary of learning needs visualization of an intuitive placement of the object disk allows an individual perspective (ii) Self-reflection and direct visualization of the learning topic (iii) Individual and also nuanced (iv) Personally salient appraisal (v) Preferred to evaluation based on numerical scales	(i) Being able to observe and manipulate a visual summary of learning needs freedom to reflect student's own view on an topic, unbound by numerical values (ii) Helps the teacher to gain more understanding from the students´ perspective (iii) Haptic and visual method and use of metaphor facilitate self-reflection and –evaluation process by students and teacher
Limitations of PRISM	(i) Needs more explanation to understand the method compared to a numeric scale	(i) Needs explanation and training to understand the method (ii) More time consuming than evaluation using numeric scale	(i) Responses individual and can therefore be difficult to interpret (ii) Vulnerable to subtle influences e.g. precise wording of PRISM introduction and task (iii) More time consuming than using a numeric scale

students' responses. Both 3rd and 4th year students considered that the PRISM task and the interviewer were important, although the 4th year students gave more weight to the setting of the task. Students in 4th year had more experience of appraisals in their dental studies, while for the 3rd year students, this was their first experience of appraisal. The context of the PRISM task was therefore not new for the 4th year students; hence, they may have been more discriminating than their 3rd year colleagues. Overall, the strengths of PRISM identified by the students (Table 3) are consistent with those previously reported [15]. Thereby, the main benefit was seen in its individuality and the benefit of the concept of a metaphor. A visual metaphor allows increased flexibility in thinking and interpretation, what encourages creative thinking [20]. It has already been described that participants using such a visual metaphor are able to construct and appraise external representations of their own perspective and knowledge [21]. Additionally,

the usage of this visual metaphor enables informants thinking differently, leading to different conclusions [22]. This underlines the individuality of the PRISM task. The visual methaphorization is thereby a very special approach. Metaphors, which are visualized in this way, cannot be easily and blanked interpreted, but a specific understanding of the metaphor is needed [15]. Thereby, such a visual metaphor can only be understood in a personal context [23]. While a rubric tool, especially numeric scales are quite general and primarily focused on objectivating an evaluation for the teacher, PRISM interviews were on a personally salient way, in which the student experienced that his interests and view are relevant for the teacher.

Both the students and the interviewer noted the potential of PRISM to support the relationship between student and teacher. One of the earliest observations in using PRISM was its positive effect on communications between patients and clinicians [12]. In the present context, having the completed PRISM task as a visual summary of competencies is likely to facilitate discussion between student and teacher. Having needed to reflect on where to place each Object disk, the student can give a succinct answer to the question 'Why did you put the [Object] disk there?.' Including multiple Object disks can extend the discussion, for example to agreeing priorities.

The PRISM task is very simple, as illustrated by the Figures 2 and 3. In the past, changes have been introduced to PRISM, which make it more complicated, for example giving participants a choice of differently sized Object disks. Such changes have altered the outcome of the task [15]. This highlights the importance for PRISM, as for any other metaphor, of giving the participant the minimum information required to make a personally salient interpretation of the metaphor, but no extraneous information [23, 24]. It is crucial at the start of the task for the participant and interviewer to have a shared, explicit, and clear understanding about what are the Subject, Object, and Context of the task. In the authors' experience, it is often necessary to pilot the task to check this. For example, in the present study, defining the Subject as 'myself as a dental student' is not as precise as 'myself as an X-year dental student,' and these may yield different responses. As PRISM requires more skills and time than conventional numeric scales, potentially limiting the ability of PRISM to be promoted among students with heavy learning tasks and very little free time. On the one hand, PRISM interviews were associated with a time effort between 10 and 12 minutes, what appears an efficient time span for relationship building and reflection with the teacher. On the other hand, a software based application of PRISM is available, although this cannot include the "haptic" experience of placing an object disk. Therefore, this could be an interesting practical approach to include PRISM in education, which would require subsequent evaluation.

As already mentioned, this is the first application of PRISM method in education. Accordingly, comparable studies are not available, yet. The current study was performed in a cohort of dental students from three different years of study. In tendency, students in the earlier years of studies (3^{rd} and 4^{th} year, Table 1) experienced a higher benefit from PRISM. This is in line with the literature, showing that reflective thinking can be fostered especially in younger students [25]. Self-reflection in the early years of dental study was reported to increase the awareness and premises the context of learning environment of the students [25]. Although, statistical testing between the three groups (3^{rd}, 4^{th}, and 5^{th} year) was omitted in the current study, due to limited sample size, it might be recommendable to apply PRISM interviews in the early dental study terms.

PRISM was found to be superior against numeric scale regarding self-reflection in the current pilot study. A numeric scale (or scoring) as rubric tool for self-reflection has been evaluated in several studies [7]. A systematic review did not confirm a superiority of any instrument [7]. Different other forms or strategies of self-reflection are available. Continuous self-reflection via logbook, to help students learning from their own experiences, was found to increase student's knowledge and skills [26]. Furthermore, peer-feedback combined with self-reflection was able to increase students' performance [10]. Similarly, watching a video tape of their own patient communication was experienced to be helpful for self-reflection for dental students, which is an approach of self-observed behaviour [9]. This approach of students watching their own video implies a visualization, which can be linked to PRISM, whereby the own perspective is reflected using a visual metaphor. With regard to the different facettes of reflection [8], PRISM appears to support critical reflection of the own view. This is especially supported by the focus group finding that students reported that they needed to "position myself to my own individual perception" for the first time in their dental education.

An important study concluded that the assessment of student's perspective is of high relevance for dental education, making research projects needed, which assess this perspective by the respective feedback and perceptions of the students [27]. This approach is picked up in the PRISM method and extended on visualization of the student's perspective for the student himself. This visualization was positively emphasized in the focus group discussions and seems to be a major strength of PRISM method in dental education. Moreover, one strength of PRISM was that fostered relationship building between teacher and student and supported respectful relationship at eye level; this fulfilled the demand of Radford et al., stating that students gain from a learning environment, in which they perceive to be an essential and respected part [2]. Besides this, the interpretation of PRISM findings was experienced to be very individual. Although this can be seen as a challenge for the teacher (and possibly the student himself) to understand the students view, this can also be a chance for changing some concepts of dental education. In the few last years, individualized education has been discussed as a promising approach [28, 29]. By assessing the students' perspective by means of PRISM, training needs, and interests of the students can be helpful to individualize the teaching offers. Furthermore, the motivation of students in medical education is an issue of practical interest and strategies to positively influence students' motivation are reported [30]. Especially assessing the individual interests and training needs by the student

himself during PRISM interviews might be helpful to foster intrinsic motivation for learning in dental study. Thereby, PRISM can be seen as a tool, which helps the teacher to support or assist the student in his own process of personal advancement during study. Accordingly, it is less a teaching, but more a coaching tool, what appears a contemporary approach in education [31]. As stated in the introduction, self-reflection is mandatory for the coaching process, alongside with relationship building [13, 14], which is also supported by the PRISM task.

5. Conclusion

Undergraduate dental students perceived the use of PRISM was helpful for self-reflection and superior against a numeric scale, and the visual metaphor of students own perspective was a major strength. Within the limitations, the results of this pilot study are sufficiently encouraging to warrant further investigation of PRISM as a potentially useful tool for self-reflection and appraisal in dental education.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The data are not publically available, because of the psedonymization and data protection guidelines according to the ethics approval.

Ethical Approval

The study protocol was reviewed and approved by the ethics committee of the medical faculty of University of Leipzig, Germany (No.: 117/20-ek). All participants were informed verbally and in writing. The authors confirm that all methods were performed in accordance with the relevant guidelines and regulations and were performed in line with the Declaration of Helsinki.

Consent

All participants provided written informed consent

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

GS was head of the study, designed study, performed data curation participated in data analysis and interpretation, and wrote the manuscript. TS participated in data analysis and interpretation and drafted the manuscript. HK participated in data curation, participated in data analysis and interpretation, and reviewed the manuscript. SB and DZ were heads of the study, participated in data interpretation and analysis. and revised the manuscript. All authors gave their final approval for the manuscript. Stefan Büchi and Dirk Ziebolz contributed equally as the senior author.

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Supplementary Materials

Table S1: gender depending differences in the total cohort in results of the evaluation of PRISM for the total cohort. Values are rated between 0: very low and 10: very high. *(Supplementary Materials)*

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Retraction

Retracted: Vacuum Sealing Drainage for Primary Thoracolumbar Spondylodiscitis: A Technical Note

BioMed Research International

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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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Research Article

Vacuum Sealing Drainage for Primary Thoracolumbar Spondylodiscitis: A Technical Note

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Primary spinal infection is a challenge for neurosurgeons. Here, for the first time, we introduced the vacuum sealing drainage (VSD) sponge into the intervertebral space for the primary thoracolumbar infection treatment. This study included 6 bedridden patients with thoracolumbar spondylodiscitis without deformity formation. All 6 patients were treated with the VSD in our hospital from June 30, 2018, to August 31, 2019. All 6 cases of thoracolumbar infection achieved clinical cure at 3-month follow-up, and no surgical-related mortalities occurred in our series. One patient died of acute cerebral infarction 5 months after surgery, and the remaining 5 patients completed a 12-month follow-up without recurrence. The JOA score of all 6 cases improved significantly after VSD treatment. VSD is feasible for safe and effective treatment for primary thoracolumbar infection. The short-term follow-up effect is definite.

1. Introduction

Spinal infection is a disease with some descriptions accompanying human evolution [1, 2]. There are several types of spinal infections, and when the infection affects only the intervertebral discs, the term used to describe the condition is usually discitis. If the infection invades the endplates of the vertebral body, the infection is more correctly designated as vertebral osteomyelitis or spondylitis. However, in many cases, at the time of diagnosis, the infection has damaged both structures; therefore, this condition is often diagnosed as spondylodiscitis [3]. The literature reports that the incidence of spinal infection in the general population is 2.4/100000, and the incidence rate increases significantly with age, and the incidence of spinal infection in people over 50 years old increases to 6.5/100000, mainly due to reduced immunity [4]. At the same time, comorbidities including diabetes, uremia, urinary tract infection, pulmonary infection, and body surface infection are also important reasons for the increased incidence [5, 6].

The conservative treatment of spinal infections is challenging. Although antibiotic therapy is crucial and necessary in treating spinal infections, acquiring pathogenic microorganisms in spinal infections is more challenging than other bone infections [7]. As a result, most spinal infections are treated with antibiotics based on clinical experience alone [8]. In addition, the inadequate blood supply to the disc tissue renders antibiotic therapy ineffective [8]. Chandra et al. reported that conservative treatment of spinal infections with comorbidities is inefficient and requires surgical treatment, including neurological symptoms, lumbar instability, kyphosis, spinal abscess, infection involving more than 4 vertebrates, and infection involving the intervertebral disc [3, 9]. According to literature, conservative treatment is frequently ineffective for spinal infections, and approximately 50% of patients require surgery [10–12].

Presently, the surgical treatment of spinal infection consists mainly of the classic approach of lesion excision combined with internal fixation, which is more traumatic and cannot be tolerated by patients with a spinal infection

Table 1: Clinical information of patients.

Sequence	Gender	Age	The number of days in hospital	Infection site	BMI	Subjective global assessment (SGA)	Comorbidity	Bedridden time (months)	Prehospital pathogenic microorganisms	C-reactive protein (mg/L)	Time to return to normal (days)	Complication	Preoperative JOA	3 months after surgery JOA
1	Female	50	51	L2-4, spondylodiscitis without deformity	23.2	B	(1) Right renal abscess (2) 4 years after removal of carbuncle on lower back (3) Diabetes mellitus type 2	4	Escherichia coli	24.6	52	Stress gastritis occurred 2 months after the operation	9	24
2	Male	60	44	L4/5, spondylodiscitis without deformity	16.5	C	(1) Cervical spondylotic myelopathy complicated with incomplete paralysis (2) Diabetes mellitus type 2 (3) Hypertension (4) Stiff knees	24	Escherichia coli	94.25	40	Died from cerebral infarction 5 months after surgery	8	17
3	Female	54	35	L2-4, spondylodiscitis without deformity	16.2	C	(1) Chronic renal insufficiency (uremia stage) (2) Chronic pneumonia (3) Hypertension	3	N/A	82.4	74	N/A	7	18
4	Female	46	87	L5/S1, spondylodiscitis without deformity	18.9	C	(1) Rheumatoid arthritis (2) Anaphylactic shock (3) Cardiac insufficiency grade 4	4	N/A	112	63	Anaphylactic shock during plasma transfusion	8	20
5	Female	61	24	T8/9, spondylodiscitis without deformity	22.5	B	(1) Diabetes mellitus type 2 (2) Osteoporosis (3) Rheumatoid arthritis	3	N/A	19.5	20	N/A	12	28

Table 1: Continued.

Sequence	Gender	Age	The number of days in hospital	Infection site	BMI	Subjective global assessment (SGA)	Comorbidity	Bedridden time (months)	Prehospital pathogenic microorganisms	C-reactive protein (mg/L)	Time to return to normal (days)	Complication	Preoperative JOA	3 months after surgery JOA
6	Female	76	25	T12/L1, spondylodiscitis without deformity	25.7	B	(4) Common peroneal nerve injury	3	N/A	26.9	25	N/A	15	23

Clinical status of 6 patients. JOA: Japanese Orthopaedic Association Scores; T: thoracic vertebra; L: lumbar vertebra; S: sacral vertebrae.

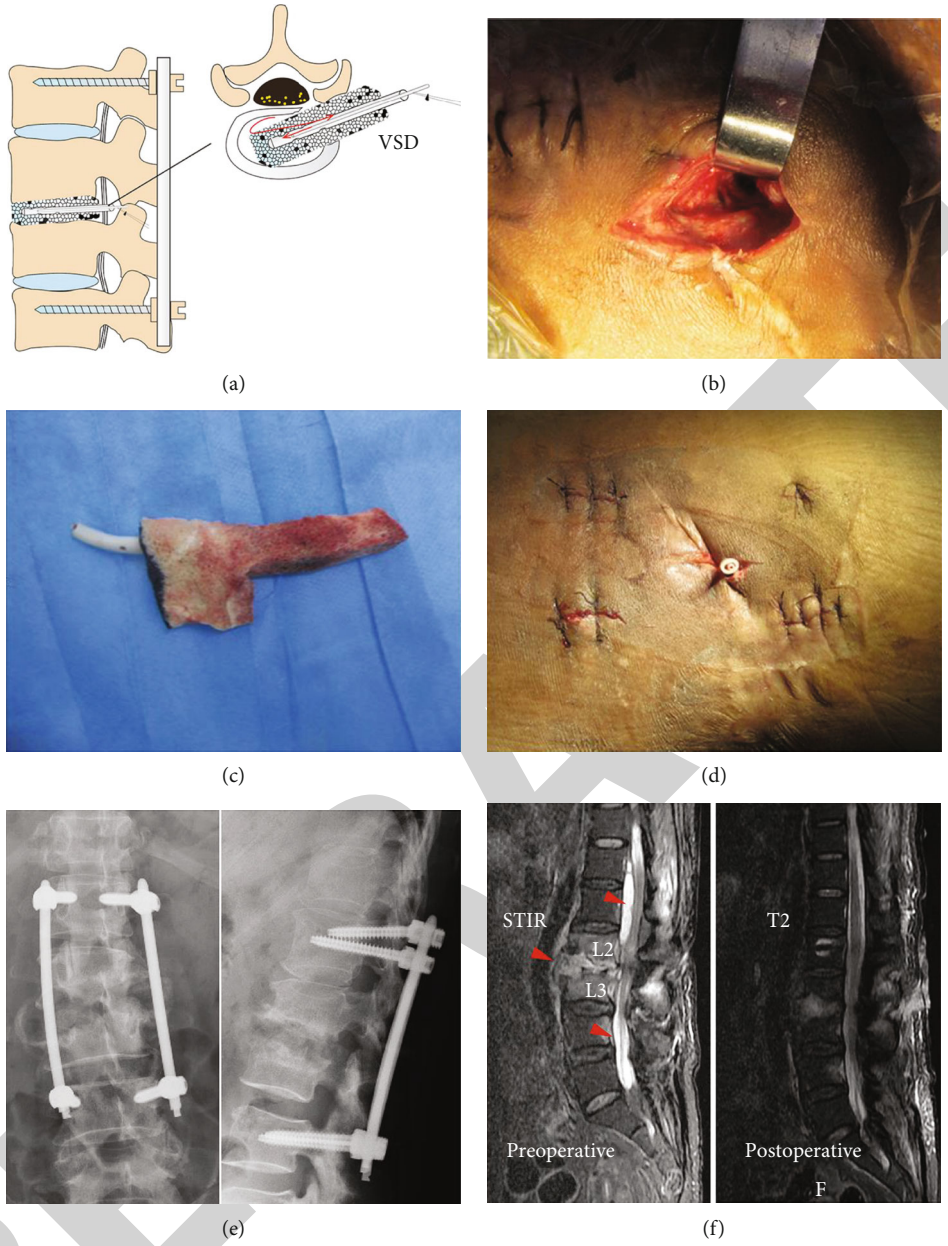


Figure 1: Percutaneous screw fixation with transforaminal debridement and vacuum sealing drainage (VSD). (a) Schematic diagram of the surgical procedure for *Operation 2*. (b) The minimally invasive incision for debridement and VSD placement. (c) VSD is used to fill the intervertebral space. (d) VSD device was implanted. (e) Percutaneous screw internal fixation at L1-L4 level. (f) MRI scans after the irrigation and drainage with VSD.

due to their physical state. Since the 1990s, it has been universally accepted that vacuum sealing drainage (VSD), also known as Negative Pressure Wound Therapy (NPWT), provides therapeutic effects for soft tissue infections, bone infections of the extremities, and chronic refractory wounds. Nonetheless, the clinical impact of VSD on spontaneous spondylodiscitis has not been investigated.

This study presents an all-new surgical paradigm for primary thoracolumbar infection patients with severe comorbidities. In this surgical paradigm, we, for the first time, apply VSD to treat primary spinal infection with intervertebral pus. The VSD treatment has proven feasible and effective for serious spondylodiscitis based on the short- and medium-term follow-up outcomes.

2. Materials and Methods

2.1. Patient Selection. The inclusion criteria were as follows: clinically diagnosed with lumbar spine infection with no spinal cord injury, with severe comorbidities, bedridden for more than three months, and accepted VSD treatment. From June 30, 2018, to August 31, 2019, 6 patients were

Table 2: Patient operation.

Sequence	Antibiotic information	Obtain pathogenic microorganisms in the hospital	Operation level	Total operation time (min)	Total bleeding (mL)
1	Cefuroxime sodium (i.v., 1.5 g, q8 h)	N/A	L1-4	317	310
2	Cefoperazone sodium and Sulbactam (i.v., 4.0 g, q12 h)	Intraoperative pus (Escherichia coli)	L4-S1	335	260
3	Cefuroxime sodium (i.v., 1.5 g, q8 h)	N/A	L1-4	294	210
4	Sulbactam (i.v., 4.0 g, q12 h)	Drainage fluid (Klebsiella pneumoniae)	L5/S1	345	235
5	Cefuroxime sodium (i.v., 1.5 g, q8 h)	N/A	T7-10	190	230
6	Cefuroxime sodium (i.v., 1.5 g, q8 h)	N/A	T11-L2	217	200

Operation status of 6 patients. T: thoracic vertebra; L: lumbar vertebra; S: sacral vertebrae.

enrolled in this study, including 1 male and 5 females, aged 57.7 ± 7.83. All 6 patients had severe comorbidities and were incapacitated with bedridden for 5.5 ± 6.17 months, including one with renal abscess, one with cervical spondylotic myelopathy and incomplete paralysis, one with renal failure, two with renal failure with rheumatoid arthritis (stage 4), and one with fibula total nerve damage. All 6 patients were diagnosed with spinal infection and received antibiotics for 2 ± 0.67 months before admission. All 6 cases had low back pain symptoms at the consultation time, and 3 cases were accompanied by fever. As for the pathogenic microorganisms, 1 case of hospital blood culture was Escherichia coli, 1 case had a history of renal abscess due to Escherichia coli infection 4 months ago, and the remaining cases were unknown. Table 1 summarizes the patient features.

2.2. Surgical Procedure. Percutaneous pedicle screws and rods were placed on healthy vertebrae spanning the level of infection under C-arm guidance. Then, part of the lateral facet joint was excised, and the superior border of the lower pedicle was exposed through the intervertebral foramina approach through the working channel. Subsequently, the lumbar annulus was dissected, and the disc infection was removed entirely. Rinse repeatedly with hydrogen peroxide, bromine, and saline solution. The VSD sponge is placed in the intervertebral disc space. The wound was sealed with negative pressure (Figure 1).

About 7 days after placing the VSD sponge, the VSD sponge was removed entirely, and the intervertebral space was scraped with a spatula and a curette and repeatedly rinsed for debridement. The formation of granulation tissue on the wound surface was closely observed. Then, place a new VSD sponge in the intervertebral space. The VSD changes are performed weekly under general anaesthesia in the operating room or under local anaesthesia at the bedside. When fresh granulation grows on the intervertebral space endplate, it is time for bone grafting.

Use a particular iliac bone extraction instrument with a minimally invasive incision, and take an appropriate amount of iliac bone according to the bone defect. After the VSD sponge was removed, the intervertebral space was scratched, and the iliac bone was implanted after irrigation. The wound was sutured and sterile bandaged.

2.3. Postoperative Management and Follow-Up. All patients were administered intravenous susceptibility (based on the findings of drug susceptibility testing) or broad-spectrum antibiotics (cefuroxime sodium, 1.5 g, q8 h) until C-reactive protein and ESR readings returned to normal levels. Then, continue intravenous or oral antibiotics for 8 weeks [13]. Postoperative computed tomography (CT) and C-reactive protein were performed to evaluate the spinal fusion and infection. Follow-up was conducted 12 months postoperatively. The normal value of C-reactive protein and the new bone formation confirmed by CT in the intervertebral space were evaluated as a clinical cure. The JOA scores were measured in all cases before and 3 months after surgery to evaluate the changes in the neurological status of patients before and after surgery.

3. Results

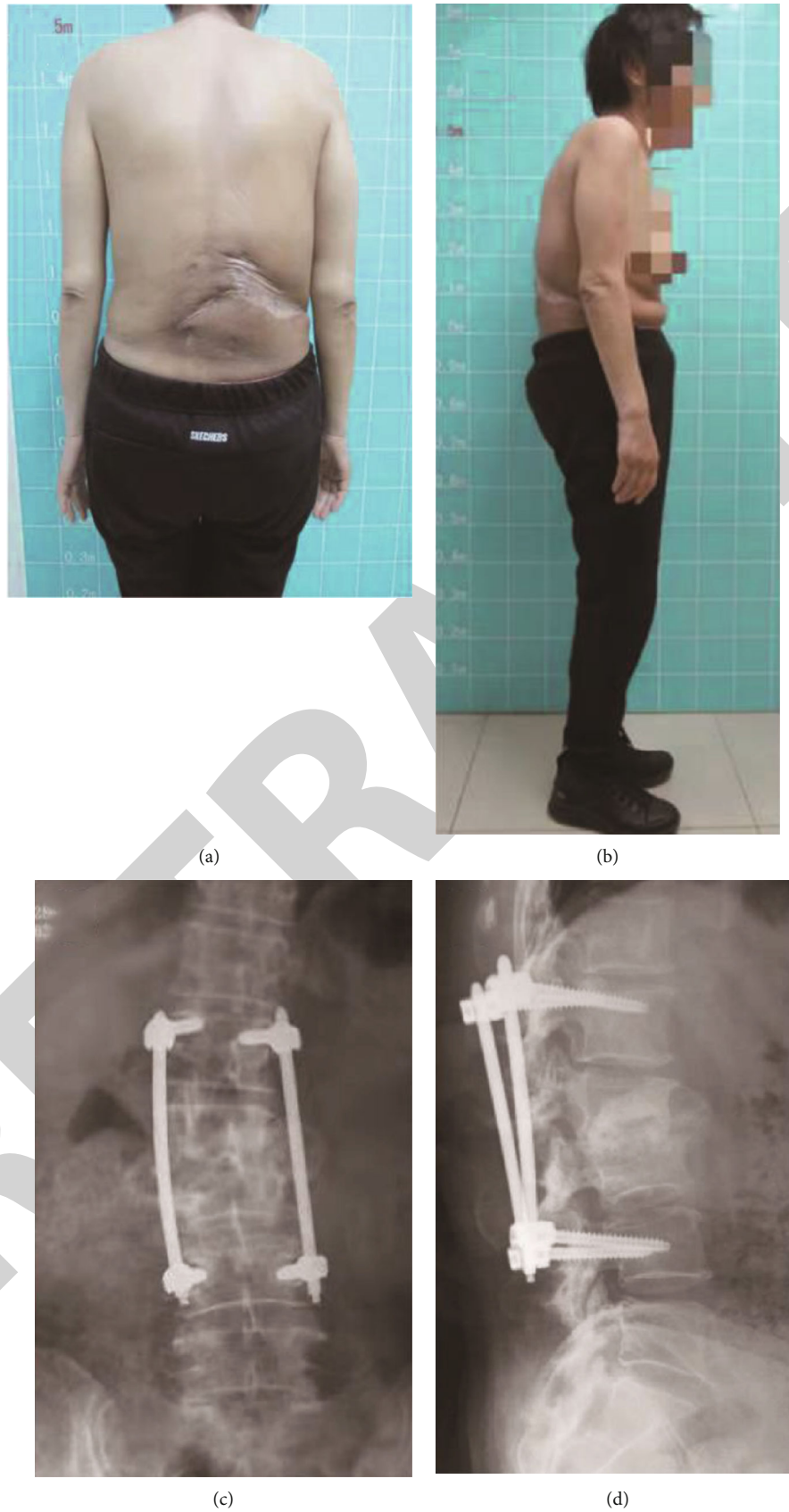
Table 2 summarizes the surgical procedure and results. This series of patients includes 1 male and 5 females. The hospital stay was 44.3 ± 16.44 days. All 6 cases of thoracolumbar infection achieved clinical cure at 3-month follow-up, and no surgical-related mortalities occurred in our series.

The total operation time was 283 ± 53 min, and the total blood loss was 240.8 ± 29.44 mL.

All 6 patients completed the 12-month follow-up except for 1 patient who died of acute cerebral infarction 5 months after surgery due to bedridden and noncompliance with antithrombotic therapy after discharge from hospital. Among the 6 patients, 1 suffered anaphylactic shock from plasma infusion during hospitalisation and recovered after rescue; 1 suffered from stress gastritis and recovered after symptomatic treatment for 6 days. Furthermore, JOA scores improved significantly in all 6 patients at 3-month follow-up, demonstrating the effectiveness of this surgical paradigm (Figure 2).

4. Discussion

The challenge of spinal infection is that it is difficult to achieve complete debridement and adequate drainage of paravertebral abscesses with traditional surgery, requiring postoperative antibiotic treatment. However, it is difficult



(a) (b) (c) (d)

Figure 2: The patient with a primary spinal infection was clinically cured after 6 months of follow-up. (a, b) Surgical site after surgery. (c, d) The L2/3 had been completely fused at the 6-month follow-up.

Table 3: The literature reports on the specific conditions of surgery for patients with spinal infections in the past 10 years, including operating time, blood loss, and complications.

Reference	Age (years)	Number of cases	Postoperative ESR (mm/h)	Operation name	Operation time	Bleeding volume (mL)	Complication	Follow-up time
Fu et al. [22]	59.9 ± 12.1	31	50.8 ± 29.3 days back to normal	Anterior decompression and internal fixation	N/A	585 ± 428	1 case died from renal failure and fungal infection; 4 cases of unplanned second surgery	More than 2 years
Fu et al. [22]	56.5 ± 14.4	37	38.4 ± 21.6 days back to normal	Foraminal focus debridement and drainage	N/A	<50	5 cases underwent debridement and internal fixation again	More than 2 years
Qian et al. [24]	43.8 ± 11.5	37	The average value of 3 months decreased to normal	Thoracolumbar lesion removal and bone grafting and internal fixation	223.5 ± 41.7 (minutes)	812.6 ± 309.2	2 cases of lung infection; 4 cases of incision infection	Reach the clinical cure standard after 12 months
Qian et al. [24]	45.3 ± 12.6	37	The 3-month average dropped to 36	Thoracic and lumbar spine internal fixation with simple posterior approach	87.4 ± 18.9 (minutes)	104.7 ± 25.0	N/A	Reach the clinical cure standard after 12 months
Lai et al. [25]	42.3 ± 9.8	32	1-month average 28.5	Debridement and internal fixation	105.7 ± 16.3 (minutes)	206.5 ± 39.2	N/A	Average 12 months
Jin and Wang [26]	39.07 ± 18.30	54	Decreased to normal in 24 weeks	Single-segment fixation for debridement	4.05 ± 0.59 (hours)	750.3 ± 51.35	N/A	58.09 ± 17.01 months
Jin and Wang [26]	41.98 ± 15.20	52	Decreased to normal in 24 weeks	Debridement and short-segment fixation	6.13 ± 0.81 (hours)	1150.6 ± 60.23	N/A	58.09 ± 17.01 months
Shen et al. [27]	42.3 ± 10.1	30	3 months after operation 11.5 ± 3.3	Simple posterior debridement and internal fixation	140.2 ± 20.4 (minutes)	641.2 ± 148.2	3 cases of cerebrospinal fluid leakage; 2 cases of superficial infection	36.5 ± 9.2
Shen et al. [27]	38.5 ± 12.1	30	3 months after operation 10.8 ± 1.3	Anterior and posterior combined lesion removal and internal fixation	248.4 ± 50.2 (minutes)	850.2 ± 200.5	6 cases of cerebrospinal fluid leakage; 5 cases of superficial infection	34.6 ± 10.2
Chen et al. [28]	65.6 ± 9.73	41	3 months after operation 33.46 ± 27.51	Single-space intervertebral foraminoscope to clean up the lesion	N/A	N/A	1 case of kyphosis	Average 42.46 months
Zeng et al. [29]	31.7	56	N/A	Anterior debridement and single rod internal fixation	203.66 ± 43.12 (minutes)	530.45 ± 121.63	2 cases of recurrence; 1 case of injury to the pleura; 1 case of drug-induced hepatitis; 8 cases of broken nails	Average 37.5 months

for antibiotics to reach sequestrum and bloodless tissues due to the inadequate blood supply. Notably, the intervertebral disc, a structure frequently linked with spinal infections, is supplied by endplate arterioles in adolescence but develops avascular in age [8]. Low blood antibiotic levels in dead, pus-filled, and avascular tissues result in the formation of drug-resistant bacteria and bacterial biofilms, which are essential for the recurrence of postoperative infections [14]. Literature indicates that the recurrence rate will be significantly reduced if all infected lesions are entirely eliminated [14, 15]. Evidence shows that complete debridement substantially reduces the rate of infection recurrence. However, due to the specificity of the spine structure, extensive debridement of extremity bone infections is contraindicated. Although VSD has been reported in the literature for other sites and spinal SSI infections, in this study, for the first time, we applied VSD to the treatment of primary spinal infections with intervertebral pus. By removing exudate, necrotic tissue, and bacteria using VSD, a microenvironment favorable to bacterial development is destroyed [16]. Additionally, VSD increases the formation of granulation tissue, which is highly antimicrobial and good for wound healing [17]. Simultaneously, VSD fills the postdebridement void and avoids hematoma development, facilitating autologous iliac bone grafting.

Although spine surgeons have a general consensus about the surgical indications for spinal infections, not all infected patients are tolerant of conventional surgical treatments. First, elderly patients with comorbidities have a much higher incidence of severe postoperative complications than general patients [18, 19]. On the other hand, most patients with spinal infections require debridement, spinal internal fixation, and conventional surgery with autologous iliac bone grafting. The extended operation time and significant blood loss of this traditional surgery will significantly reduce systemic immunity, which is not conducive to postoperative recovery and infection control. This surgical approach usually results in higher complication and recurrence rates. We summarize the traditional surgical modalities reported in the literature in Table 3. The results showed that minimally invasive implantation of VSDs significantly reduces operative time, blood loss, and complications. Therefore, minimally invasive VSD is a feasible approach for patients with clear surgical indications but severe comorbidities who cannot afford surgery [20].

Antibiotic treatment is required for all spinal infections. However, identifying pathogenic microorganisms is necessary to determine the most effective antibiotic. After repeated collection of blood, intraoperative tissue, abscess, and postoperative pathogen drainage, it was challenging to get pathogenic microorganisms from 4 patients in this series. These negative results may be caused by prehospital antibiotic administration or blood and specimen collection methods [21]. It has been claimed that metagenomics is utilised to promptly and accurately discover harmful microbes, although this use must be proven in clinics.

The benefits of VSD for patients with poor surgical tolerance are as follows. First, the intervertebral space installation of the VSD sponge is minimally invasive. This method is less invasive, causes less bleeding, and is suitable for patients with severe comorbidities [22, 23]. Second, this is a staged paradigm of precise individualised treatment, which provides a buffer opportunity for patients with severe comorbidities and determines whether further surgical treatment is required based on the treatment effect. Compared with the conventional surgery in Table 3, this new surgical paradigm significantly reduced the total blood loss and resulted in a faster postoperative recovery without increasing the total operative time [22, 24–29].

In conclusion, the VSD is safe and effectively treats spinal infections with severe comorbidities. Short- and medium-term follow-up demonstrated its efficacy. To our knowledge, this is the first time that VSD has been applied to treating the primary spinal infection with intervertebral pus. In long-term follow-up, complications and recurrence need to be further studied. Furthermore, this surgical paradigm requires further prospective controlled studies.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

All protocols involving human subjects were approved by the Ethics Committee of the 960th Hospital of PLA (approval. no. KYLL201843).

Consent

All patients were asked to sign an informed consent statement for publication.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

HX and ZQ contributed substantially to data acquisition, analysis, and interpretation. ZQ was responsible for the conception and design of the study and the drafting and writing of this manuscript. YY and WQ were surgical assistants. All authors had read and approved the final manuscript. All authors confirm the authenticity of all the raw data.

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Retraction

Retracted: Review on the Effect of Exercise Training on Immune Function

BioMed Research International

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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] F. Du and C. Wu, "Review on the Effect of Exercise Training on Immune Function," *BioMed Research International*, vol. 2022, Article ID 9933387, 6 pages, 2022.

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Review Article

Review on the Effect of Exercise Training on Immune Function

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Exercise training is not only a necessary means to improve the level of exercise, but also an important means to improve the body's immunity. Different time, intensity, items, and forms of exercise training have different effects on the body's immune function. As a double-edged sword to improve the body's immune function, exercise training is a different reaction mechanism of different immune cells after exercise training. This paper combined with foreign scholars' studies on the immune function of the body of literature from different exercise intensity, different time, different sports, different movement forms, and different external environment such as angle of view for athletes body's immune cells and humoral immunity summarized the various indexes such as combing, in order to help academia, medicine, and sports. It provides enlightenment to the contemporary public on how to participate in sports training more healthily.

1. Introduction

As for the well-known viruses, "smallpox," "SARS," and "novel coronavirus" in recent years, the stronger the immunity of the body, the lower the incidence rate of virus infection. Contemporarily, people pay more attention to improving the immunity of the body. As the main means to improve and enhance the body's immunity, exercise training can effectively resist the risk of virus infection. Combined with the needs of society and the public, this paper classifies and summarizes previous studies and summarizes the effects of sports training on immune cells and humoral immunity in different time, intensity, project, and special environment, in order to provide reference for academic, medical, and sports circles.

2. The Effects of the Intensity of Exercise Training and Different Exercise on Immune Cells

2.1. Function of Immune Cells. Lymphocytes play a central role in the immune process of the body, and they can also secrete a variety of cytokines which can not only act on the immune cells themselves but also act on the nervous system and endocrine system to complete the immune function [1]. Macrophages are the core components of early physiological response after bone injury and late bone remodeling. Monocytes and macrophages are considered to play an important role in skeletal muscle repair and remodeling, mainly because they can promote the potential of angiogenesis, the secretion of growth factors, and the clearance of tissue fragments [2]. Dendritic cells are important outposts of the immune system and are responsible for presenting antigens to T cells. Dendritic cells are at the forefront of maintaining intestinal integrity, and they are professional antigen-presenting cells, including various subsets which are resident cells or migratory cells in lymphoid and nonlymphoid organs [3]. NK cells are the core members of the innate immune system, and they have the functions of early recognition and elimination of virus infection and tumor cells. At the same time, they are also the bridge between innate immunity and acquired immunity [4]. Neutrophils are the largest number of white blood cells in the blood. They are an important part of the body's nonspecific immune function and directly participate in the first "defense line" of the body's immune system [5]. Hematopoietic stem cells are mainly stored in the hematopoietic microenvironment of bone marrow and are the original cells of all immune cells.

They are mainly responsible for inputting normal hematopoietic stem cells into the body of patients. They can enhance human hematopoietic and immune functions and effectively alleviate malignant blood diseases, genetic diseases, severe immunodeficiency, and other diseases [6].

2.1.1. Effects of Different Intensity of Exercise Training on Immune Cells. When different intensity stimulation is used in sports training, the number of immune cells and immune function of the body will change, including the monitoring, self-stabilization, and defense of immune cells. Similarly, exercise training for different events has a different impact on the immune response of immune cells.

High-intensity exercise training has an adverse effect on most epidemic cells, especially the damage of long-term high-intensity exercise training to cells is very obvious, while the effect of short-term high-intensity exercise training on NK cells is more obvious. Regular moderate intensity exercise training can improve the body's immunity. In addition, long-term nonexercise will inhibit the function of immune cells.

2.1.2. Effect of High-Intensity Exercise Training on Immune Cells. Foreign scholars have found that the intensity of exercise training affects the oxidation/antioxidant balance of lymphocytes and neutrophils, but only high-intensity exercise training will induce lymphocyte oxidative damage, which will cause oxidative damage to indicators such as erythrocytes and lymphocytes, but will not cause oxidative damage to neutrophils [7], which may be due to the decrease of catalase and glutathione peroxidase activities in neutrophils, glutathione peroxidase activity in lymphocytes, and the myeloperoxidase in neutrophils and the increase of catalase protein level in neutrophils. Shaw et al. found that resting peripheral blood type 2 and regulatory T-cells produced the anti-inflammatory cytokines interleukin 4 and interleukin 10, respectively, during high-intensity exercise training [8]. In addition, decreased secretory immunoglobulin A in elite athletes after high-intensity training leads to the alteration of mucosal immunity, which impairs the athlete's intracellular defense against pathogens and increases the incidence and risk of symptoms of upper respiratory tract symptoms [9]. In addition, the ratios of granulocytes/lymphocytes and lymphocyte/monocyte were shown to be sensitive to changes of fatigue [10]. Therefore, it can be used as an indicator of the body's cellular immunity and to evaluate the physiological state of its training state.

2.1.3. Effects of Long-Term High-Intensity Exercise Training on Immune Cells. Long-term high-intensity training affects the function of innate immune cells, reduces the ability of immune cells to cope with acute exercise, and increases the risk of infection [11]. Long-term high-intensity exercise can also damage the function of macrophages which result in a reduction in macrophages and a decrease in phagocytic ability. The authors found, although a large amount of amino acid supplementation after exercise training, the degree of damage to macrophages could not be improved [12]. And Shephard and Shek [13] believed that NK cells recovered within 24 hours under long-term exercise training, and long-term high -intensity training would have adverse effects on immune surveillance and health of the body. In addition, Iwasaki and Medzhitov believed that a single prolonged exercise would impair the functions of T cells, NK cells, and neutrophils, alter the balance of type I and type II cytokines, and attenuate the immune response to primary and recall antigens in vivo.

2.1.4. Effects of Short-Term High-Intensity Exercise Training on Immune Cells. There is a positive correlation between exercise and NK cell count and cytotoxic activity, and a short exercise affects the number and function of NK cells, but it does not affect the cytotoxicity of NK cells. Millard et al. [14] believed that short-term high-intensity exercise training may increase the number of NK cells but can reduce the toxicity of the cells, probably because NK cells rapidly redistribute between blood and tissues after acute exercise which causes the preferential redeployment of NK cell subsets with a well-differentiated phenotype and enhances cytotoxicity against HLA-expressing target cells. While a single exercise session induces the increase of leukocytosis and redistribution of effector cells between the blood compartment and lymphoid and peripheral tissues, this response is mediated by the increase of hemodynamics and the release of catecholamines and glucocorticoid following activation of the sympathetic nervous system.

2.1.5. Effects of Moderate-Intensity Exercise Training on Immune Cells. Simpson et al.'s research shows that the improvement of immunity is due to regular moderate-intensity exercise. And regular moderate-intensity exercise has been shown to benefit cardiovascular health and reduce overall disease mortality. Regular short-term up to 45 minutes of moderate-intensity exercise is beneficial for immune defense [15]. Moderate-intensity exercise attenuates muscle ring finger 1-mediated atrophy of limb and respiratory muscles and improves limb muscle force production in mice with acute lung injury. Modulation of systemic neutrophil chemokine responses was by exercise training to restrict neutrophil influx into alveolar space. And early activity therapy attenuates muscle wasting and limits ongoing alveolar neutropenia by modulating systemic neutrophil chemokines in lung-injured mice and humans [16].

2.1.6. Effects of Inactivity on Immune Cells. Prolonged bed rest significantly affects immune cell populations and cytokine concentrations. During spaceflight and simulated weightlessness (bed rest), immune function is suppressed, the number of granulocytes, natural killer, T cells, hematopoietic stem cells, and CD45RA and CD25 expressing T cells is increased, and the number of monocytes is significantly decreased. Exercise has different effects on the concentration of lymphocytes and B cells, but only regular exercise can enhance the immune function of human body functions [17].

2.2. The Effect of Training in Different Sports on Immune Cells. The number of T lymphocytes does not change after intensive exercise training by professionally trained athletes in cycling events, but exercise training or competition in

cycling events can cause an increase in the number of myeloid cells in B cells, dendritic cells, and neutrophils. The number of T lymphocytes does not change after intensive exercise training by professionally trained athletes in cycling events, but exercise training or competition in cycling events can cause myeloperoxidase in B cells, dendritic cells, and neutrophils. There was an increase in the number of cells. Compared with cyclists, the immune cells of professional distance runners are more adversely affected, but there is no difference between the risk of respiratory tract infection and innate immune cells after long-term adaptation. The changes of immune cells are different in professional and amateur distance runners during the competition. In addition, swimming and running have different effects on the body's T cells. In swimming, men and women have different effects on cells. It reduced cytotoxicity of NK cells in volleyball pregame training.

2.2.1. Effects of Cycling Training on Immune Cells. After completing a 20-minute continuous cycle cycling race at 80% VO2max, B cells increased by an average of 60% during exercise, with the largest increase in immature cells, followed by memory cells, and then naive cells [18]. Similarly, total dendritic cells increased by 150% during 80% VO2max exercise, plasmacytoid dendritic cells mobilized to a greater extent than myeloid dendritic cells, and plasmacytoid dendritic cells were preferentially mobilized during exercise, and exercise enhances immune surveillance by preferentially mobilizing effector cells [18]. After the cycle stage of professional cycling, myeloperoxidase in neutrophils increased, hemolysis and lymphopenia caused by exercise were negatively correlated with cell markers of oxidative stress [19]. The amount of ITN-Y produced by stimulated T lymphocytes at rest did not change in endurance trained male cyclists after a 6-day intensive training period. In endurance-trained male cyclists, the amount of ITN-Y produced at rest by stimulated T lymphocytes did not change after the intensive training period at a 6-day intensive training period. Neither acute nor chronic exercise training resulted in changes in circulating percentage or interleukin (IL)-4(+) (type 2) T lymphocyte counts [20].

2.2.2. The Effects of Marathon Training on Immune Cells. Well-trained long-distance runners had significantly more muscle damage compared to the cyclists, and 3 days of functional overuse may result in significantly more muscle damage, soreness, and inflammation responses in runners, but upper respiratory symptoms and the decrease in innate immune after exercise have no difference. Linear increases in white blood cells, monocytes, and lymphocytes prior to initiation in ultraendurance runners in a multiphase ultramarathon; they increase before phase 3 and decrease thereafter. There was a significant increase in granulocytes followed by a decline to baseline until stage 3. Hemoglobin and hematocrit showed linear decline and had no changes in red blood cells and platelets throughout the multiphase ultramarathon [21]. Amateur middle-distance runners had significantly lower lymphocyte and eosinophil values prior to the start of the half-marathon than prerun values, while for mean red blood cell volume, platelets, mean platelet volume, white blood cells, neutrophils, and monocytes significantly decreased and then increased [22]. But the lymphocytes have increased in ultraendurance marathon runners before the marathon, while the number of lymphocytes decreased before the amateur half-marathon runners.

2.2.3. The Effects of Swimming Sports on Immune Cells. Increased numbers of T cells in the blood after strenuous running and decreased numbers of lymphopenia after swimming exercise and the accumulation of T cells in the lungs and Peyer's patches may enhance immune alertness in these compartments, which are the body's main defensive barrier [23]. Oxidative damage in neutrophils and induction of antioxidant defense in lymphocytes, both neutrophil and lymphocyte responses to exercise are slightly weaker in women than in men .

2.2.4. The Effects of Volleyball Exercise Training on Immune Cells. A-month preseason retraining (5 hours a day, 6 days a week) in college volleyball players significantly increased counts of CD56bright NK and CD56dim T cells (a subset with lower cytotoxicity) and decreased overall NK cell cytotoxicity from pretraining to posttraining, but the interleukin-6, interferon-gamma, and tumor necrosis factor-alpha levels did not change, and extensive training reduces total NK cell cytotoxicity as well as lysis units per NK cell [24].

2.2.5. The Effect of Training on Immune Cells of Chinese Traditional Lianqi Sports. The cytotoxicity of natural killer cells increased by 60% immediately after lianqi training and returned to the basic level within 2 hours after training. The number of natural killer cell subsets did not change after lianqi training, and lianqi training had acute effects on natural killer cell activity [25].

3. Effects of Exercise Training in Special Environment on Immune Cells

3.1. Effects of Exercise Training in Cold or Hot Conditions on Immune Cells. Two 45-minute runs at 75-80% VO2max in cold, hot and humid conditions, white blood cell, neutrophil, and basophil counts increased significantly after exercise in both environments and more noticeable in hot environments. The activity of antioxidant enzymes and carbonyl index in lymphocytes and neutrophils were significantly increased or decreased, respectively, in a high temperature environment, and the lymphocyte expressions of catalase, H, and superoxide dismutase increased in hot conditions only after exercise [26]. The numbers of leukocytosis significantly increased immediately after intense actual firefighting exercises and firefighting activities and persisted after recovery. Most notably, plasma levels of ACTH and cortisol significantly elevated, and the number and percentage of lymphocytes significantly decreased, but the cortisol level still remained elevation after 90 minutes of recovery [27]. Leukocytes, neutrophils, lymphocytes, monocytes, platelets, mean platelet volume, interleukins, and cardiac troponin increased after a day of heavy training [28]. Exercise with protective clothing exacerbates the body's heat

storage when compared with that in high temperatures, and because exercise alters the immune response and produces psychological and environmental stress on firefighters. In addition, fire instructors exposed to fires are 10 times more than firefighters, and physiological stress is also many times higher and 16 times more likely to experience symptoms of ill health [29].

3.2. Effects of Exercise Training at High Altitude on Immune Cells of the Body. Athletes, military personnel, firefighters, climbers, and astronauts need to train in extreme environments such as heat, cold, and high-altitude microgravity. Physical exercise in hot and thermoneutral conditions increases circulating stress hormones, catecholamines, and cytokines, with a concomitant increase in circulating white blood cells [30]. CD3(+) T lymphocytes significantly reduced during acute and chronic exposure to high altitude, the decline in T cells was entirely due to the decrease in CD4(+) T cells, and B lymphocytes were not affected by high-altitude exposure; natural killer cells significantly increased during acute and chronic exposure to high altitude, and the numbers of NK cell increased, but NK cytotoxic activity was not affected by high-altitude exposure [31]. Only in high altitude, even moderate exercise training also can activate the potential cytotoxic function of circulating granulocytes, but vigorous physical exercise strongly inhibits this activation, which prevents inflammatory damage and also activates the potential toxic function of circulating granulocytes [32].

4. The Influence of Psychological Index Changes on Immune Cells

Loss of T lymphocytes can negatively impact emotional health and cognition [33], and in a psychoneuroimmunological perspective, the immune system plays a role in the link between exercise and emotional health [34]. Study suggests that acute aerobic exercise may promote subjective emotional recovery from subsequent stressors and enhance emotional flexibility [35]. Chronic stress (lasting weeks/months/years) can suppress/dysregulated immune function, but acute stress (lasting minutes to hours) can have immune-enhancing effects. Dhabharet [36] found that short-term stress enhances the transporting, maturation, and function of dendritic cells, neutrophils, macrophages, and lymphocytes, which have been shown to enhance innate and adaptive immunity; chronic stress induces chronic increases of proinflammatory factors and inhibits the number, transport, and function of immune protective cells to suppress innate and adaptive immune responses by altering type 1 and type 2 cytokine balance.

4.1. Effects of Exercise Training after Sleep Interruption on Immune Cells. Nocturnal sleep disruption was associated with increased concentrations of total lymphocytes and CD3 (-)/CD56 (+) NK cells, mobilizing cytotoxic lymphocyte subsets (NK cells (including CD8 (+) T cells) $\gamma\,\delta$ T cells) have a greater response to exercise after sleep interruption at night, and the enhancement is more obvious 1 hour after exercise, and short-term changes in sleep structure will "activate" the immune system and lead to a slight enhancement of lymphocyte transport by acute dynamic exercise [37]. People who sleep less than six hours at a night are four times more likely to be diagnosed with an upper respiratory infection, which prevent more training. Since sleep restriction is considered an essential element of military training, future studies should examine interventions to reduce all negative effects on immunity and host defense [38]. Moreover, sleep interruption at night and exercise training with sleep time less than 6 hours per night will have an adverse impact on the production of immune cells and affect the kinetic energy of immune cells.

4.2. Effects of Different Periods of Exercise Training on Immune Cells. Foreign scholars studied the effect of repeated exercise in a day on the number of circulating leukocytes and NK cell activity. The results showed that the counts of leukocytes and neutrophils increased significantly both in the morning and afternoon after the exercise training. The change of lymphocyte count after exercise in the afternoon was more obvious, and the activity of NK cells was also significantly higher than that in the morning, indicating the interaction between exercise and diurnal effect. Two endurance exercises in one day had a "superposition effect" on the total number of leukocytes and neutrophils but did not affect the change of NK cell activity [39]. The number of NK cells in high-intensity training participants increased significantly during training in the morning and afternoon, the number of NK cells in high-intensity training participants decreased in the morning, but it was still significantly higher than the baseline level at 60 and 90 minutes after training in the morning; in the afternoon, the number of NK cells in high-intensity training participants decreased below the baseline level at 60 and 90 minutes after training, and the change of NK activity was mainly affected by day and night [40].

4.3. Effects of Supplements on Immune Cells after Exercise Training. Lactococcus lactis is a unique lactic acid bacteria, which can activate the plasma cell like dendritic cells and it can reduce the incidence rate and symptoms of upper respiratory tract infection by supplementing Lactococcus lactis to activate dendritic cells and reduce the fatigue accumulation of athletes during continuous high-intensity exercise. In addition, the intake of plasma will not affect muscle damage [41]. Wang et al. believed that taking Zhenqi Fuzheng Capsule can inhibit the decline of athletes' immune function caused by high-intensity training and accelerate the recovery of the body's immune function. It is widely believed that supplementing carbon compounds during long-term exercise can weaken the body's immune and endocrine response, but carbohydrate supplements will not affect the decline of body immunity after long-term exercise [42].

5. Conclusion

Each cell has its own unique immune function and has different effects on the body. Carrying out its own tasks, individuals form a complex and diverse strong immune system

to maintain our health. Whether the general public or athletes or firefighters, they need a strong immune system to cooperate organically. There are different intensities of exercise training, such as long time high-intensity exercise on innate immune cells, and the body is adverse impact on health; in the usual sports training to avoid the process of long duration and high-intensity exercise, moderate intensity and regular exercise training to improve the body's immune function has good effect compared with the other strength of sports training, and not for a long time to exercise the body's immune function will be suppressed. Different sports training such as marathon, swimming, volleyball, and cycling have different change mechanisms on the immune cells of the body. Chinese traditional qi training has a certain influence on the immune function of the body. In the exercise training under the special environment of cold, hot, and high altitude, the adverse effect of hot environment on body immunity is greater than that of cold environment. The changes of psychological indicators, the number, and function of immune cells are different after sleep interruption and different periods of exercise training. Supplements after exercise training have a positive effect on the body's immune function. Through the above use of literature and materials to sort out, in order to bring help to the academic, medical, and sports circles, to the contemporary public on how to participate in sports training in a healthier way.

Data Availability

The experimental 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 to report regarding the present study.

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Retraction

Retracted: Effects of Vibration Training on Weight Loss and Heart Rate Variability in the Obese Female College Students

BioMed Research International

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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] W. Deng, "Effects of Vibration Training on Weight Loss and Heart Rate Variability in the Obese Female College Students," *BioMed Research International*, vol. 2022, Article ID 1041688, 7 pages, 2022.

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Research Article

Effects of Vibration Training on Weight Loss and Heart Rate Variability in the Obese Female College Students

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Objective. The present study examined the effects of a 12-week whole-body vibration training (WBVT) regimen on heart rate variability (HRV) and body composition in the obese female college students. *Methods*. Participants were assigned to either the WBVT ($n = 17$) or obese control group ($n = 19$). The students in the WBVT group conducted a 12-week (5 times per week and 30 min per time) exercise protocols (30 to 40 Hz of frequency and 4 mm of amplitude), and the obese control group did not perform regular physical training during 12 weeks of study. Then, body composition (body weight, BMI, body fat, body fat percentage; trunk fat mass, muscle mass, MM) and HRV (time domain and frequency domain index) were measured in all subjects before and after WBVT intervention. *Results*. (1) After 12-week WBVT intervention, body fat mass, trunk fat mass, and body fat percentage significantly decreased and muscle mass increased in the WBVT group ($P < 0.01$, respectively); there was no significant change in body weight and BMI ($P > 0.05$, respectively). (2) After 12-week WBVT intervention, LFn, LF/HF, and HR significantly decreased ($P < 0.05$, $P < 0.01$), R-R interval and RMSSD significantly increased ($P < 0.01$, respectively), and there was no significant difference in HFn ($P > 0.05$). Nevertheless, there was no significant change before and after the test in body composition and HRV in the obese control group ($P > 0.05$, respectively). (3) After 12-week WBVT intervention, compared with the obese control group, body fat mass, body fat percentage, trunk fat mass, and LF/HF significantly decreased ($P < 0.05$, $P < 0.01$), muscle mass, and RMSSD increased ($P < 0.05$) in the WBVT group; but there were no significant difference in other indicators ($P > 0.05$) between the obese control group and WBVT group. (4) The reduction of body fat percentage before and after the WBVT intervention are positively correlated with the reduction in the LFn and LF/HF ($r = 0.542$, $r = 0.504$; $P < 0.05$, respectively) and negatively correlated with the increase in the RMSSD ($r = -0.514$, $P < 0.05$), and the reduction of trunk fat mass are positively correlated with the reduction in the LF/HF ($r = 0.540$, $P < 0.05$). *Conclusion*. The results indicate that WBVT improves HRV and body composition in obese female college students, and the reduction in body fat percentage and trunk fat mass are associated with a shift in cardiac autonomic regulation towards vagal dominance and improve sympathetic-vagus balance after WBVT intervention. In conclusion, WBVT may be a feasible treatment to improve cardiac autonomic function and body composition.

1. Introduction

Obesity is a global and increasingly serious problem, and it is also one of the main public health problems. The survey report on the physique and health of Chinese college students show that the overweight and obesity rate of college students is increasing year by year, and the rate of obesity and overweight in the female college students is higher than that of boys. Studies by Yumuk et al. have found that obesity is a risk factor for many chronic diseases such as diabetes, hypertension, dyslipidemia, and cardiovascular disease [1], and many studies have confirmed that obese patients are often accompanied by autonomic dysfunction, manifested as sympathetic dominance in sympathetic-vagal balance, and sympathetic activation can cause insulin resistance and increase food intake which aggravate obesity, while the secretion of proinflammatory factors (TNF-α and IL-6) from adipose tissue of obese patients is considered a possible mediator of sympathetic activation. Therefore, the interaction between sympathetic overactivation and obesity plays a key role in the pathogenesis of cardiovascular disease in obese patients [2]. Heart rate variability (HRV) is one of

the most commonly used quantitative indicators to judge autonomic activity [3]. Studies suggested that reductions in HRV and vagal activity were associated with low muscle mass and high fat in overweight individuals which increased the risk of adverse cardiovascular events [4]. Most studies showed that traditional exercise, such as aerobic exercise and resistance training might improve vagal activity and were helpful to reduce the risk of cardiovascular disease and sudden cardiac death [5]. However, most obese patients have sedentary habits and poor exercise tolerance due to physical constraints, musculoskeletal discomfort, and lacking of self-motivation, which may prevent them from participating and adhering to traditional physical activity.

Whole-body vibration training (WBVT) is a kind of movement mode of static or dynamic movement on the vibration platform and has been used as an alternative strength training method to improve muscle mass loss in diverse populations including obese patients [6]. And studies on overweight and obese individuals have found that WBVT combined with dietary control can accelerate the reduction of visceral fat mass [7]. However, the study of Wong et al. [8] found that 8 weeks of WBVT training could significantly reduce the rate of LnLF/LnHF, systolic blood pressure, and diastolic blood pressure in obese postmenopausal women, which suggested that WBVT can improve cardiac autonomic regulation by balancing the sympathetic-vagus nerve. However, there is less literature research whether the improvement of cardiac autonomic regulation in obese patients by WBVT is related to the improvement of body composition in obese patients. Therefore, in order to provide a theoretical basis for WBVT intervention in obesity, the present study investigated the effects of 12-week WBVT intervention on body composition (body weight, BMI, body fat mass, body fat percentage, trunk fat mass, and muscle mass) and HRV (time and frequency domain indicators) of obese female college students.

2. Objects and Methods

2.1. Research Objects. According to the results of college students' physical fitness test in 2020 by the School of Guangxi Medical University, 39 obese female college students with body mass index (BMI) $\geq 30\,kg/m^2$ were selected and randomly divided into two groups, the obese group ($n = 20$) and the WBVT group ($n = 19$). The inclusion criteria are as follows: all subjects are simply obese without any regular exercise or diet plan for 6 months before the experiment, without spinal, muscle, and cardiovascular diseases. All subjects were informed the purpose of the experiment and voluntarily participated in WBVT. Then, informed consent forms were filled out by the subjects before the WBVT intervention and explained in detail about the purpose of the study, process, benefits, and possible inconveniences to the all subjects. In addition, 3 participants withdrew from the study due to personal reasons (there were 2 patients in the obese control group and 1 patient in WBVT group). As shown in Table 1, there were no significant differences in age, height, weight, and BMI between the two groups before WBVT intervention by independent samples t-test analysis ($P > 0.05$).

2.2. Methods

2.2.1. WBVT Program. From March to July in 2020, female college students in the WBVT group underwent 12-week whole-body vibration training by using the Power Plate pro5 vibrator (5 times/week, 30 min/time), the frequency is between 30 and 40 Hz, and the amplitude is 4 mm. The training process is guided and supervised by specialized experimental staff, including 5 minutes of warm-up and 5 minutes of relaxation. All subjects complete 4 movements in sequence which include knee flexion, half squat, calf raise, deep squat, and high leg raise. Each movement is completed 5 groups, each group is 10-12 times, and the interval between groups is 30 s.

2.2.2. Body Composition Measurement. Body Composition Analyzer (Tsinghua Tongfang) was used to measure body composition before and after WBVT intervention. The specific method is as follows: the number, date of birth, and height of the subjects were fed into the computer before the test. Then, the subjects took off their socks, stood on the feet, and hold the electrode handle. During the test, the subjects must keep a fixed posture and the test data were automatically entered into the computer and stored.

Test indicators and derived indicators include the following: body weight (kg), BMI (kg/m^2), body fat mass (kg), body fat percentage (%), trunk fat mass (kg), and muscle mass (kg).

2.2.3. HRV Evaluation. Before and after the experiment, the subjects wore the Polar Team2 (Finland), and the height, weight, date of birth, and other information of subjects were input into the computer, then collect the heart rate of subjects for 10 minutes when the subjects rest for 5 minutes in the supine position with eyes closed (10 subjects for each test). Finally, time domain and frequency domain index of HRV were calculated by Kubios HRV software version 3.1 (Kuopio, Finland).

The following spectral HRV parameters were obtained for analysis: Time domain indicators include heart rate (HR, beats/min), RR interval (ms), and RMSSD (square root of the squared difference between adjacent RR intervals and the mean, ms). Frequency-domain indicators of HRV include total power (TP, 0.00-0.40 Hz), low-frequency power (LF, 0.04-0.15 Hz; sympathetic activity indicator), and high-frequency power (HF, 0.15-0.40 Hz; vagal activity level indicator). Since HF and LF are affected by TP, their values are normalized and then compared. LFn (the normalized low-frequency power) = LF/TP $*$ 100%; HFn (the normalized high -frequency power) = HF/TP $*$ 100%; the LF/HF ratio is used as the index of sympathetic-vagal balance. The final statistical parameters include LFn, HFn, and LF/HF ratio.

2.3. Statistical Analysis. All experimental data are expressed as (mean ± standard deviation), and SPSS19.0 statistical software was used for statistical analysis of the data. Paired t-test was used to compare within-group difference before and

Table 1: Basic information of subjects $\bar{X} \pm ç$.

Group	(n)	Age (year)	Height (cm)	Body weight (kg)	BMI
Obese control group	19	19.02 ± 1.08	1.60 ± 0.58	80.37 ± 2.59	31.19 ± 0.83
WBVT group	17	19.36 ± 1.43	1.59 ± 0.92	80.88 ± 1.99	31.82 ± 1.03
P		0.468	0.349	0.513	0.051

Table 2: Results of HRV in time domain and frequency domain before and after the WBVT intervention ($\bar{X} \pm ç$).

HRV	Group	Before experiment	After experiment	t value Before vs. after	P value Before vs. after
HR (beat/min)	Obese control group	73.79 ± 4.47	73.63 ± 5.07	0.262	0.797
	WBVT group	72.88 ± 3.99	$70.94 \pm 4.26^{\#\#}$	7.778	≦0.001
R-R interval (ms)	Obese control group	815.99 ± 50.12	818.48 ± 55.48	-0.377	0.710
	WBVT group	825.59 ± 45.46	$848.69 \pm 51.68^{\#\#}$	-7.321	≦0.001
RMSSD (ms)	Obese control group	36.37 ± 3.55	37.10 ± 4.03	-1.085	0.292
	WBVT group	36.88 ± 3.84	$40.71 \pm 4.77^{\#\#\Delta}$	-11.066	≦0.001
LFn	Obese control group	30.95 ± 8.60	32.09 ± 8.40	-1.790	0.090
	WBVT group	31.42 ± 9.76	$29.34 \pm 8.97^{\#}$	2.281	0.037
HFn	Obese control group	26.63 ± 7.64	26.33 ± 7.43	0.710	0.487
	WBVT group	26.09 ± 7.44	26.84 ± 8.59	-1.156	0.265
LF/HF	Obese control group	1.17 ± 0.05	1.21 ± 0.06	-1.899	0.074
	WBVT group	1.21 ± 0.11	$1.12 \pm 0.12^{\#\#\Delta}$	4.848	≦0.001

Note: $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, comparison before and after the experiment; $^{\Delta}P < 0.01$, comparison between the obese control group and WBVT group.

after experiment. Independent samples t-test was used to analyze the differences of body composition and HRV parameters between two groups (obese control group and WBVT group) before and after WBVT intervention. The correlation between HRV parameter changes and body composition changes before and after WBVT intervention were analyzed by Pearson correlation, with $P < 0.05$ indicating that the difference was statistically significant.

3. Results

3.1. The Effects of WBVT Intervention on HRV in the Obese Female College Students. As shown in Table 2, after 12 weeks WBVT intervention, compared with before the intervention, the HR significantly decreased, and the R-R interval and RMSSD significantly increased ($P < 0.01$, respectively) in the WBVT group. The LFn and the ratio of LF/HF significantly decreased ($P < 0.05$, $P < 0.01$), while there was no significant difference in HFn before and after WBVT intervention ($P > 0.05$). There was no significant difference in the above indicators in the obese control group before and after the experiment (all $P > 0.05$).

The independent sample t-test showed that there was no significant difference in time domain and frequency domain indicators of HRV between the two groups before WBVT intervention (all $P > 0.05$). After WBVT intervention, compared with the obese control group, the RMSSD significantly increased ($t = -2.457$, $P = 0.019$), LF/HF significantly decreased ($P = 0.012$) in the WBVT group; however, there was no significant difference in HR, R-R interval, LFn, and HFn between the two groups ($t = 1.712$, $P = 0.096$; $t = -1.684$, $P = 0.101$; $t = 0.948$, $P = 0.350$; and $t = -0.194$, $P = 0.848$).

3.2. The Effects of WBVT Intervention on Body Composition in the Obese Female College Students. As shown in Table 3, after 12 weeks WBVT intervention, compared with before the intervention, the body fat mass, body fat percentage, and trunk fat mass in the WBVT group significantly decreased ($P < 0.01$), the muscle mass significantly increased ($P < 0.01$) in the WBVT group; there was no significant difference in body weight and BMI before and after the WBVT intervention ($P > 0.05$); and there was no significant difference in the above indicators in the obese control group before and after the experiment ($P > 0.05$).

The independent sample t-test showed that there was no significant difference in the body composition between the two groups before WBVT intervention (all $P > 0.05$). After the WBVT intervention, compared with the obese control group, the body fat mass, body fat percentage, and trunk fat mass significantly reduced ($t = 3.992$, $P \leqq 0.001$; $t = 4.223$, $P \leqq 0.001$; and $t = 4.674$, $P \leqq 0.001$), muscle mass significantly increased ($t = -2.050$, $P = 0.048$) of the obese female college students in the WBVT group; however, there was no significant difference in body weight and BMI between the two groups after WBVT intervention ($t = -0.581$, $P = 0.565$; $t = -1.886$, $P = 0.068$).

Table 3: Results of body composition before and after the WBVT intervention ($\bar{X} \pm \varsigma$).

Body composition	Group	Before experiment	After experiment	t value Before vs. after	P value Before vs. after
Body weight (kg)	Obese control group	80.36 ± 2.58	79.84 ± 2.01	1.882	0.076
	WBVT group	80.88 ± 1.99	80.24 ± 2.05	1.782	0.094
BMI (kg/m^2)	Obese control group	31.19 ± 0.83	30.99 ± 0.82	1.822	0.085
	WBVT group	31.82 ± 1.03	31.57 ± 0.99	1.794	0.092
Body fat mass (kg)	Obese control group	33.79 ± 2.15	33.63 ± 2.19	0.497	0.625
	WBVT group	33.89 ± 1.27	$31.33 \pm 1.08^{\#\#\Delta\Delta}$	12.672	≦0.001
Body fat percentage (%)	Obese control group	42.06 ± 2.66	42.14 ± 2.85	-0.210	0.836
	WBVT group	41.98 ± 1.63	$39.09 \pm 1.28^{\#\#\Delta\Delta}$	9.535	≦0.001
Muscle mass (kg)	Obese control group	42.52 ± 2.03	42.29 ± 2.00	1.205	0.244
	WBVT group	42.25 ± 2.21	$43.77 \pm 2.31^{\#\#\Delta}$	-11.766	≦0.001
Trunk fat mass (kg)	Obese control group	12.86 ± 1.08	12.74 ± 0.81	0.969	0.346
	WBVT group	12.52 ± 0.83	$11.35 \pm 0.97^{\#\#\Delta\Delta}$	12.521	≦0.001

Note: $^{\#\#}P < 0.01$, compared before and after the experiment; $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.01$, compared with the obese control group and the WBVT group.

Table 4: Correlation coefficients (r) of alternations between heart rate variability and body composition after a 12-week WBVT intervention ($\bar{X} \pm \varsigma$).

HRV		Δ body weight (kg)	Δ BMI (kg/m^2)	Δ body fat mass (kg)	Δ trunk fat mass (kg)	Δ muscle mass (kg)	Δbody fat percentage
ΔHFn	r	-0.418	-0.170	-0.157	-0.073	0.403	-0.007
	P	0.095	0.515	0.547	0.780	0.109	0.978
ΔLFn	r	-0.457	-0.446	0.387	0.023	-0.147	0.542
	P	0.065	0.072	0.125	0.999	0.574	0.025*
ΔLF/HF	r	-0.099	-0.094	-0.148	0.540	0.379	0.504
	P	0.706	0.720	0.570	0.038*	0.133	0.048*
ΔHR (beat/min)	r	-0.055	-0.056	-0.378	-0.246	-0.299	0.210
	P	0.834	0.831	0.135	0.341	0.244	0.419
ΔR-R interval (ms)	r	-0.031	-0.030	0.396	0.218	0.304	0.320
	P	0.906	0.910	0.116	0.400	0.236	0.210
ΔRMSSD (ms)	r	0.178	0.188	0.113	-0.013	0.217	-0.514
	P	0.496	0.469	0.667	0.961	0.402	0.041*

3.3. Correlation Analysis between HRV Parameter Changes and Body Composition Changes after WBVT Intervention. As shown in Table 4, Pearson correlation analysis showed that after 12 weeks of WBVT intervention, there was no significant correlation between the decrease in body weight, BMI, body fat mass, and the alternations of HRV all indicators (all $P > 0.05$). The decrease in body fat percentage significantly positively correlated with the alterations in LFn and LF/HF ratio ($r = 0.542$, $r = 0.504$; $P < 0.05$) and significantly negatively correlated with the increase in RMSSD ($r = -0.514$, $P < 0.05$), while the decrease of trunk fat mass was only significantly associated with reductions in the LF/HF ratio ($r = 0.540$, $P < 0.05$).

4. Discussion

4.1. The Effects of WBVT Training on Body Composition in Obese Female College Students. WBVT can be regarded as a light resistance movement mode, which automatically adapts to the repeated and rapid vibration of vibration platform based on the body. Some people believe that regular WBV training has a positive impact on body composition and strength. Milanese et al. [9] performed 10-week WBVT intervention (twice/week, 14 min/each time, vibration frequency is 40-60 Hz, amplitude is 2.0-5.0 mm) in obese women (BMI: 35.1 ± 3.55 kg/m^2), the results showed that WBVT could significantly reduce BMI, trunk fat mass, and

waist-to-hip ratio in obese female college students but had no significant effect on body weight, body fat percentage, and body fat; however, in a study about the young nonobese women, Milanese et al. [10] found that the body fat mass of the subjects significantly reduced, and the muscle mass significantly increased, while the body weight did not change after 8 weeks vibration training. And some researchers have found that WBVT has a greater potential for reducing visceral adipose tissue than combine aerobic and resistance training programs [7]. The results of this study found, after 12-week WBVT intervention, the body fat mass, trunk fat mass, and body fat percentage significantly decreased, and the muscle mass significantly increased, but there was no significant change in body weight and BMI in the WBVT group when compared with the obese control group. Some scholars have found that 6-12 weeks of WBVT intervention has no significant effect on body composition in the overweight and obese postmenopausal women [11, 12], and different results may be related to the amount of WBVT training and different subjects. Nowadays, the exact mechanism by which WBVT increases muscle mass and decreases fat mass remains unclear. Clinical studies have shown that 10 weeks of WBVT training can increase the cross-sectional area of thigh muscles in elderly women [13], and it has been previously reported that WBVT may increase the levels of serum testosterone and growth hormone [14]. Furthermore, studies in rats have shown that long-term WBVT stimulates lipolysis [15]. Therefore, in this study, the improvement of body composition of obese female college students by WBVT training may be related to the induction of anabolic hormone secretion and the increase of metabolic demand and energy consumption, which result in the increase of muscle mass and the decrease of fat mass in obese college students. However, the body weight and BMI of obese female college students who received WBVT training did not significant change in this study, which might be related to WBVT training reducing body fat mass and increasing muscle mass. The specific mechanism needs further study.

4.2. The Effect of WBVT Training on HRV of Obese Female College Students and Its Relationship with Changes in Body Composition. The cardiac autonomic nervous system is an important system that regulates the cardiovascular system and energy expenditure, and it is associated with involuntary physiological processes such as digestion, hormone regulation, blood pressure, and heart rate [16], and HRV has been recognized as a noninvasive method for assessing cardiac autonomic function, and it can indirectly reflect the tension and balance of the sympathetic-vagal nerve. Triggiani et al. [2] found that HRV in obese women (23.74 ± 3.40 years old, BMI: 30.1 ± 5.4) showed a downward trend, suggesting that sympathovagal imbalance may increase the risk of cardiovascular disease. However, studies have suggested that autonomic control of heart rate impaired is associated with an increased risk of cardiovascular disease, and improvement of HRV is an independent protective factor against sudden death [17]. Most studies have shown that WBVT as an effective training modality has been widely used in improving cardiac autonomic function in different populations, including obese patients. Figueroa et al. [18] found that 6 weeks of WBVT (static and dynamic half-squat training, 3 times/week, 25-30 Hz, amplitude 1-2 mm) could significantly reduce the nLF (low-frequency power) and LFnu/HFnu ratio of obese women (21 ± 2 years; BMI: $29.9 \pm 0.8\,\text{kg}\cdot\text{m}^{-2}$), which suggested that WBVT can improve sympathovagal balance and reduce cardiovascular risk in overweight/obese women. The same results were obtained in the current study. After 12 weeks of WBVT intervention, the frequency domain indicators (LFn and LF/HF) in the obese female college students decreased, and HFn did not significantly change, which was basically consistent with the previous research results. There are few reports in the literature about the effect of WBVT on time-domain indicators of HRV in obese women, and the results are different. Figueroa et al. [18] found that obese women had significantly lower resting HR underwent WBVT intervention. In addition, Licurci et al. [19] found that WBVT could significantly increase the SDNN, RMSSD, pNN50, and the R-R interval in the elderly, and HR decreased. The results suggest that WBVT can significantly improve HRV and may help to reduce the risk of heart disease in older adults. However, the study by Wong et al. [20] found that 8 weeks of WBVT (1-5 groups per training session) had no effect on rest HR in postmenopausal obese women. Therefore, it can be concluded that whether WBVT leads to changes in resting HR or R-R interval to be related to the amount of WBVT training and the different subjects. Similarly, previous studies have shown that low-intensity exercise intervention have no effect on resting HR or R-R interval in older adults [21]. In this study, we observed a significant decrease in HR and a significant increase in R-R interval and RMSSD in obese female college students after 12 weeks of WBVT. However, compared with the obese control group, there was no significant difference in HR and R-R interval of obese female college students in the WBVT group which showed that long-term WBVT may partly protect the heart of obese female college students by increasing the excitability of the vagus nerve, decreasing the heart rate, and promoting the balance of sympathetic and parasympathetic nerves.

Although the effect of body composition on heart rate variability has been extensively studied, the relationship between body composition and beneficial alterations in cardiac autonomic function is unclear. Meta-analysis found that there was no significant correlation between weight loss and changes in HRV parameters [22]; another study found that sustained endurance training of moderate intensity had no effect on resting heart rate in obese women without fat loss [23]. In addition, it has been previously reported there is an association between the intra-abdominal fat increasing and sympathetic nerve activity increasing in Canadian adolescents [24]. And Soares-Miranda et al. [25] found that the ratio of LF/HF in obese children was significantly positively relevant to abdominal fat, but not with body fat mass, suggesting that abdominal fat may be an important factor in evaluating the effect of obesity on autonomic function. However, Soares-Miranda et al. [26] found that the decrease in the ratio of Ln LF/Ln HF was positively

correlated with the body fat percentage, and the subjects with the more the percentage of body fat decreasing, the more obvious the of sympathetic nerve activity decreasing, which is more helpful to improve the sympathetic vagal balance of obese postmenopausal women. The results of this study are basically consistent with previous studies. After 12 weeks of WBVT intervention, the decrease in body weight, BMI, and body fat mass was not significantly correlated with HRV all indicators. The decrease in body fat percentage was significantly positively correlated with the alterations in LFn and LF/HF ratio and was significantly negatively correlated with the increase in RMSSD, while the decrease of trunk fat mass was only significantly associated with reductions in the LF/Ln HF ratio. There are few relevant literatures on the relationship between muscle mass and HRV. Baek et al. [27] found that the LF/HF ratio of 1150 workers (43.55 ± 11.45 years old) with overweight muscle was significantly higher than that of subjects with overweight and low muscle mass which indicated that reduced muscle mass may have a negative impact on the regulation of cardiac autonomic function. However, Freitas et al. [28] found that the RR interval, SDNN, RMSSD, and pNN50 significantly reduced in elderly patients with sarcopenia (≥60 years), which suggested that older adults with sarcopenia exhibit lower parasympathetic modulation and might lead to poor cardioprotection. Different results were obtained in the current study, it was found that the changes of muscle mass in obese female college students before and after WBVT intervention were not significantly correlated with the alterations of HRV all indicators by the correlation analysis. This difference may be related to the different subjects in the studies, and whether it is also affected by other factors needs to be confirmed by further research.

5. Summary

The current study showed that 12 weeks of WBVT training improves body composition and heart rate variability in obese female college students, and correlation analysis showed that the decrease of trunk fat and body fat percentage were related to the transition of cardiac autonomic regulation to vagal innervation after WBVT training, thereby improving sympathovagal balance. Therefore, it can be considered that WBVT may be an effective method to improve cardiac autonomic function and body composition in obese female college students.

Data Availability

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

Conflicts of Interest

The author declares that they have no conflicts of interest to report regarding the present study.

Acknowledgments

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Retraction

Retracted: N-myc Downstream-Regulated Gene 1 (NDRG1) Regulates Vascular Endothelial Growth Factor A (VEGFA) and Malignancies in Glioblastoma Multiforme (GBM)

BioMed Research International

Received 3 October 2023; Accepted 3 October 2023; Published 4 October 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. Zhang, Q. Chen, Y. Li, H. Chen, Q. Jiang, and Q. Hu, "N-myc Downstream-Regulated Gene 1 (NDRG1) Regulates Vascular Endothelial Growth Factor A (VEGFA) and Malignancies in Glioblastoma Multiforme (GBM)," *BioMed Research International*, vol. 2022, Article ID 3233004, 9 pages, 2022.

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Research Article

N-myc Downstream-Regulated Gene 1 (NDRG1) Regulates Vascular Endothelial Growth Factor A (VEGFA) and Malignancies in Glioblastoma Multiforme (GBM)

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Background. NDRG1 has been reported to exhibit relatively low expression levels in glioma tissues compared with adjacent brain tissues. Additionally, NDRG1 is reported to be a tumor suppressor with the potential to suppress the proliferation, invasion, and migration of cancer cells. However, its exact roles in GBM are still unknown. *Methods*. Gene Expression Profiling Interactive Analysis (GEPIA) was employed to evaluate the expression level of NDRG1 in GBM. After the introduction of NDRG1, proliferation, analyses of colony formation, migration, and invasion capacities were performed. A luciferase reporter assay was performed to detect the effect of NDRG1 on the vascular endothelial growth factor A (VEGFA) promoter. *Results*. In this study, data from GBM and healthy individuals were retrospectively collected by employing GBM, and VEGFA was found to be differentially expressed in GBM tissues compared with adjacent brain tissues. Furthermore, NDRG1 expression is positively correlated with VEGFA expression, but not expression of the other two VEGF isoforms, VEGFB and VEGFC. In the glioma cell lines U87MG and U118, overexpression of NDRG1 significantly upregulated VEGFA. By performing a dual-luciferase reporter assay, it was observed that overexpressed NDRG1 transcriptionally activated VEGFA. Expectedly, overexpression of NDRG1 decreased cell viability by blocking cell cycle phases at G1 phase. Additionally, overexpression of NDRG1 inhibited invasion, colony formation, and tumor formation in soft agar. Remarkably, VEGFA silencing or blockade of VEGF receptor 2 (VEGFR2) further inhibited malignant behaviors in soft agar, including proliferation, invasion, colony formation, and tumor formation. *Conclusions*. NDRG1-induced VEGFA exerts protective effects in GBM via the VEGFA/VEGFR2 pathway. Therefore, targeting both NDRG1 and VEGFA may represent a novel therapy for the treatment of GBM.

1. Introduction

GBM, formerly known as pleomorphic glioblastoma, also called glioblastoma, is the most common primary malignant brain tumor [1]. It is caused by malignant transformation of astrocytomas and is the most malignant type of astrocytoma [2]. Its incidence is approximately 3.19/100,000 per year, and the prognosis is extremely poor. Its five-year survival rate is approximately 4-5%, and the two-year survival rate in clinical trials is only 26-33%.

N-myc downstream-regulated gene 1 (NDRG1) is a tumor suppressor gene with the potential to inhibit the proliferation,

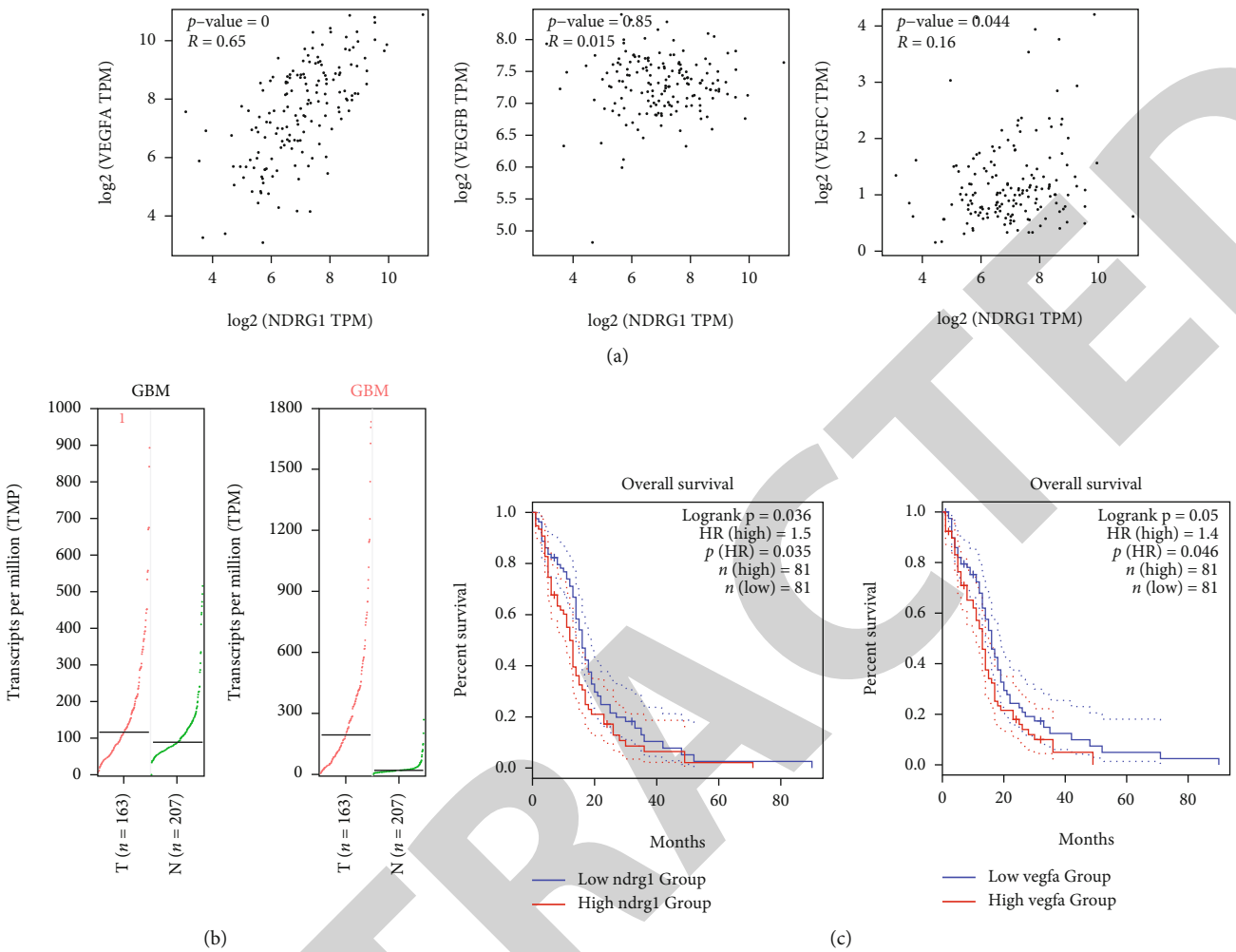

Figure 1: Comparison and correlation of NDRG1 with VEGFA, B, and C in GBM tissues. (a) The correlation between NDRG1 and VEGFA, B, and C were compared in GBM tissues. (b) NDRG1 and VEGFA mRNA expressions obtained from the Gene Expression Profiling Interactive Analysis database in GBM tissues (tumor $n = 163$ and adjacent tissues $n = 207$). (c) The prognostic value of NDRG1 and VEGFA in GBM tissues were obtained from GEPIA.

invasion, and migration of tumor cells. The expression of NDRG1 is positively correlated with the survival rate of patients with GBM; thus, it is considered a tumor suppressor gene in GBM. According to a report analyzing the tumor tissue specimens of GBM patients, it has been found that the overall survival (OS) of patients with high NDRG1 expression is significantly longer than that of those with low NDRG1 expression, and the NDRG1-positive cell rate is positively correlated with prolonged survival in GBM patients [3]. Yang Y et al. studied polymorphisms of the NDRG1 gene in 1,061 participants, including 558 patients with glioma and 503 healthy individuals, and determined a relationship between polymorphisms and the risk of glioma [4]. In addition, an experiment using human glioma cell lines revealed that overexpression of NDRG1 inhibits cell proliferation and invasion in a subcutaneous tumor mouse model and suppresses tumor occurrence [5]. Based on these findings, NDRG1 has been considered to be a powerful tumor suppressor in GBM and gliomas.

At present, the therapeutic efficacy for gliomas is poor, especially GBM. The recent experimental report of VEGF- or VEGF receptor- (VEGFR-) targeted therapy combined with chemotherapy in patients with malignant gliomas demonstrates that its antitumor effect and acceptable safety have reached an unprecedented level. More specifically, bevacizumab (BV) combined with irinotecan presents a 10-fold improvement in radiological response and a significant improvement in progression-free survival (PFS) and OS in patients with recurrent GBM [6, 7]. Therefore, a major current focus of neurooncology is to further develop antiangiogenic strategies.

NDRG1 plays an important role in VEGFA-induced angiogenesis. It has been shown that NDRG1 deficiency significantly attenuates VEGFA-induced angiogenesis, and NDRG1 is closely correlated with plcγ1, suggesting that NDRG1-mediated plcγ1 activation may be a reliable therapeutic target for VEGFA-mediated vascular diseases, including cancers [8].

Based on this previous research, we hypothesized that NDRG1 could exert crucial regulatory roles in GBM. The aim of this study was to investigate the potential regulatory role of NDRG1 on malignant behaviors and the downstream VEGFA/VEGFR2 axis in GBM.

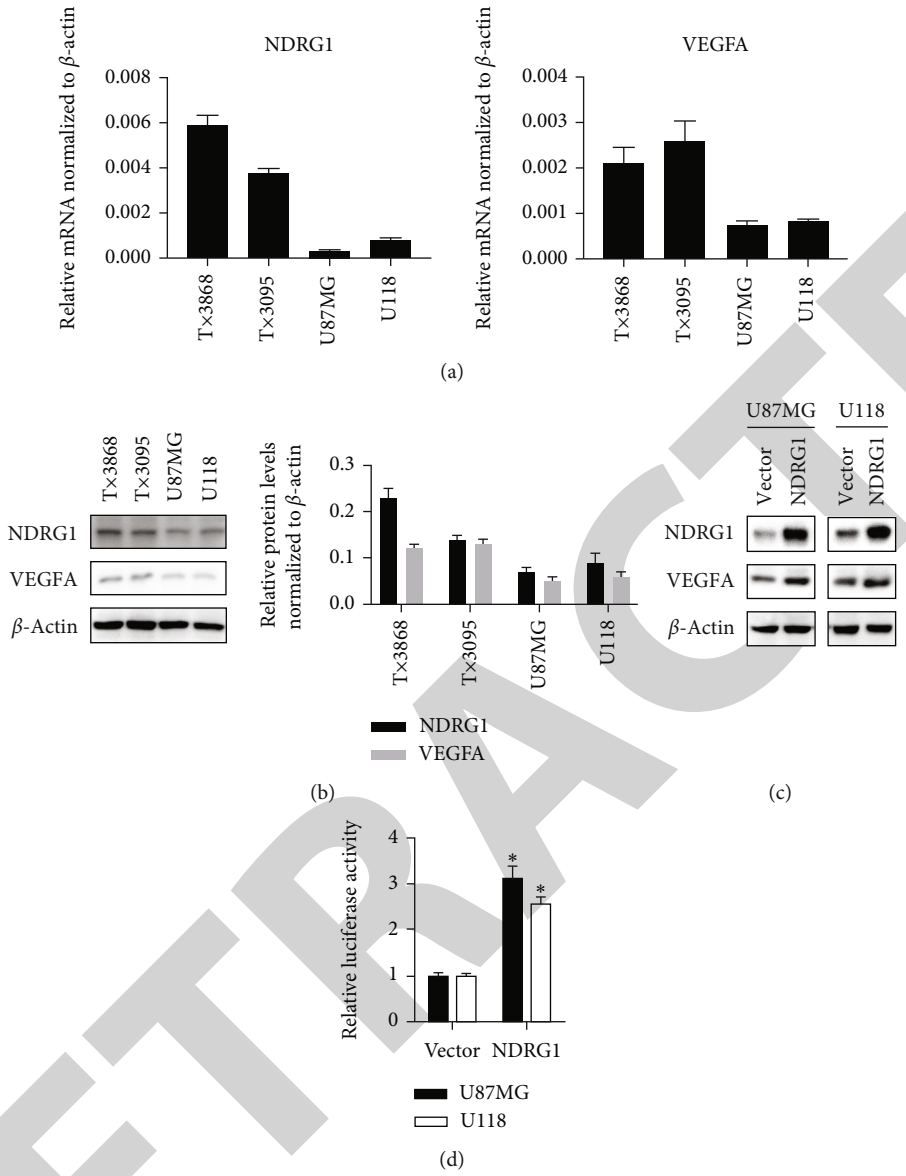

Figure 2: Detection of NDRG1 and VEGFA in glioma cell lines. (a) The mRNA levels of NDRG1 and VEGFA in Tx3868, Tx3095, U87MG, and U118 were detected by performing RT-qPCR. (b) Western blot was performed to detect NDRG1 and VEGFA protein in Tx3868, Tx3095, U87MG, and U118 cells. (c) After overexpression of NDRG1 in U87MG or U118 cells, efficient introduction of NDRG1 was detected by western blot. $^{*}P < 0.05$ vs. vector group.

2. Material and Methods

2.1. Publicly Available Datasets and Resources. The transcription data of the NDRG1 was collected from Gene Expression Profiling Interactive Analysis (http://gepia.cancer-pku.cn/index.html) [9]. The Cancer Genome Atlas (TCGA) (https://portal.gdc.cancer.gov/) was employed to collect NDRG1 RNA-seq data and related clinical information [10].

2.2. RNA Extraction and Quantitative Reverse Transcription-PCR Analysis (RT-qPCR). Total RNA was isolated using an animal tissue/cell total RNA isolation kit (Cat. No.: RP003, DocSense, Chengdu, China) according to the manufacturer's instructions. Complementary DNA (cDNA) was obtained from 0.5 μg of total RNA using ReverTra Ace qPCR RT Master Mix (Toyobo) according to the manufacturer's instructions. Quantitative PCR was performed using SYBR Green qPCR Master Mix (Life Technologies, USA). Briefly, qPCR was conducted in a final volume of 20 μL, including 10 μL qPCR Mix, 4 μL primers (3.75 μmol/L and 2 μL each of both forward and reverse primers), 0.5 μL cDNA templates, and 5.5 μL distilled water. The primers are described as follows: NDRG1 5′-CTCCTGCAAGAGTTTGATGTCC-3′ and 5′-TCATGCCGATGTCATGGTAGG-3′ and VEGFA 5′-AGGG CAGAATCATCACGAAGT-3′ and 5′-AGGGTCTCGAT TGGATGGCA-3′. The running procedure is described as follows: initial denaturation at 95°C for 1 min, 40 amplification cycles of real-time fluorescence measurement and denaturation

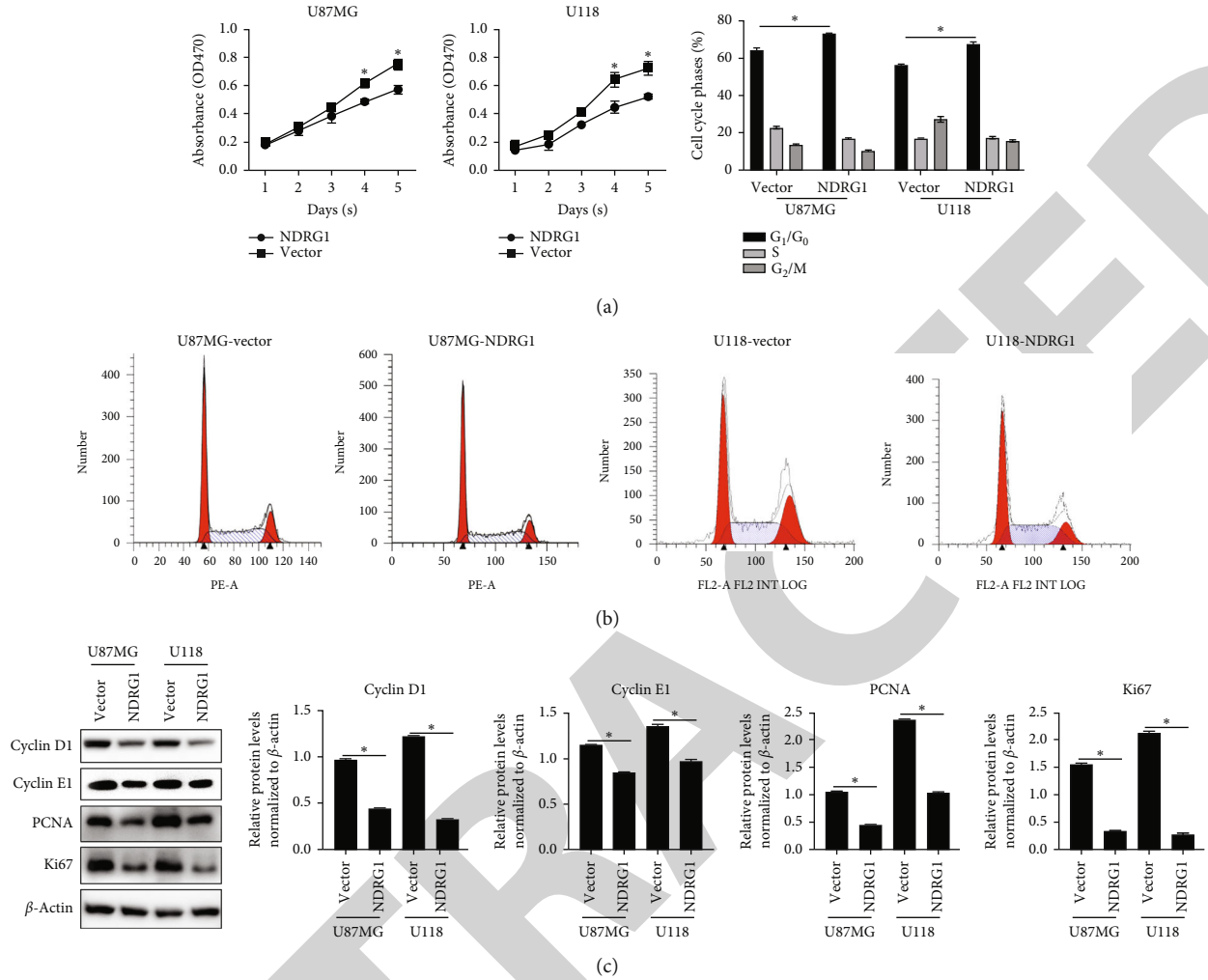

Figure 3: The effects of NDRG1 on cell proliferation. (a) NDRG1-overexpressed and vector-transfected cells were detected by performing CCK-8 assay from day 1 to 5. $^*P < 0.05$ vs. vector group. (b) Cell cycle phases were detected by performing PI staining followed by flow cytometry. $^*P < 0.05$ vs. vector group. (c) Cell proliferation-related proteins including cyclin D1, cyclin E, PCNA, and ki-67 were detected by performing western blot. $^*P < 0.05$ vs. vector group.

at 94°C for 30 s, annealing at 55°C for 30 s, and elongation at 72°C for 30 s.

2.3. Lentiviral Infection and RNA Interference (RNAi). Lentiviral particles carrying the NDRG1 vector (Ubi-MCS-3FLAG-CBh-gcGFP-IRES-puromycin-NDRG1) were constructed by GeneChem (Shanghai, China). Harvested virus was then used to infect cells. Stable clones were selected using puromycin and confirmed using Western blot. Short-hairpin RNA (shRNA) oligonucleotides targeting VEGFA were purchased from ORIGENE (Cat. No.: TL308426V, Guangzhou, China).

2.4. Dual-Luciferase Reporter Assay. The promoter regions of wild-type and mutant *VEGF-A* genes were cloned into the pGL4 basic luciferase reporter vector (Thermo Fisher Scientific, MA, USA) as described previously [11]. All vectors were verified by sequencing. The cells were seeded in 6-well plate and transfected with *VEGF-A* promoter luciferase reporter gene (0.5 μg). 48-hour later, cell lysates were collected, and the dual-luciferase reporter assay kit (E2920, Promega, USA) was used to analyze the firefly and *Renilla* luciferase activity. The ratio of firefly-to-*Renilla* luciferase activity was used as a standardization index for the luciferase activity of each group.

2.5. Cell Viability Assay. For each 96-well plate, 5×10^3 cells were seeded, and the viability was determined using a Cell Counting Kit-8 assay (CCK-8; Dojindo, Kumamoto, Japan) every 24 h for 4 consecutive days. Briefly, culture medium was replaced with 100 μL original medium containing 10 μL CCK-8 solution, and absorbance was measured on a microplate reader (Bio-Rad) at 450 nm. Five replicates of each treatment were used, and experiments were performed in triplicate.

2.6. Cell Cycle Distribution. Cells were pelleted and washed by precold PBS for 3 times. 1×10^6 cells were collected and fixed using 1 mL of 75% ice-cold ethyl alcohol, stored overnight at 4°C for 16 h, and washed by PBS for 2 times.

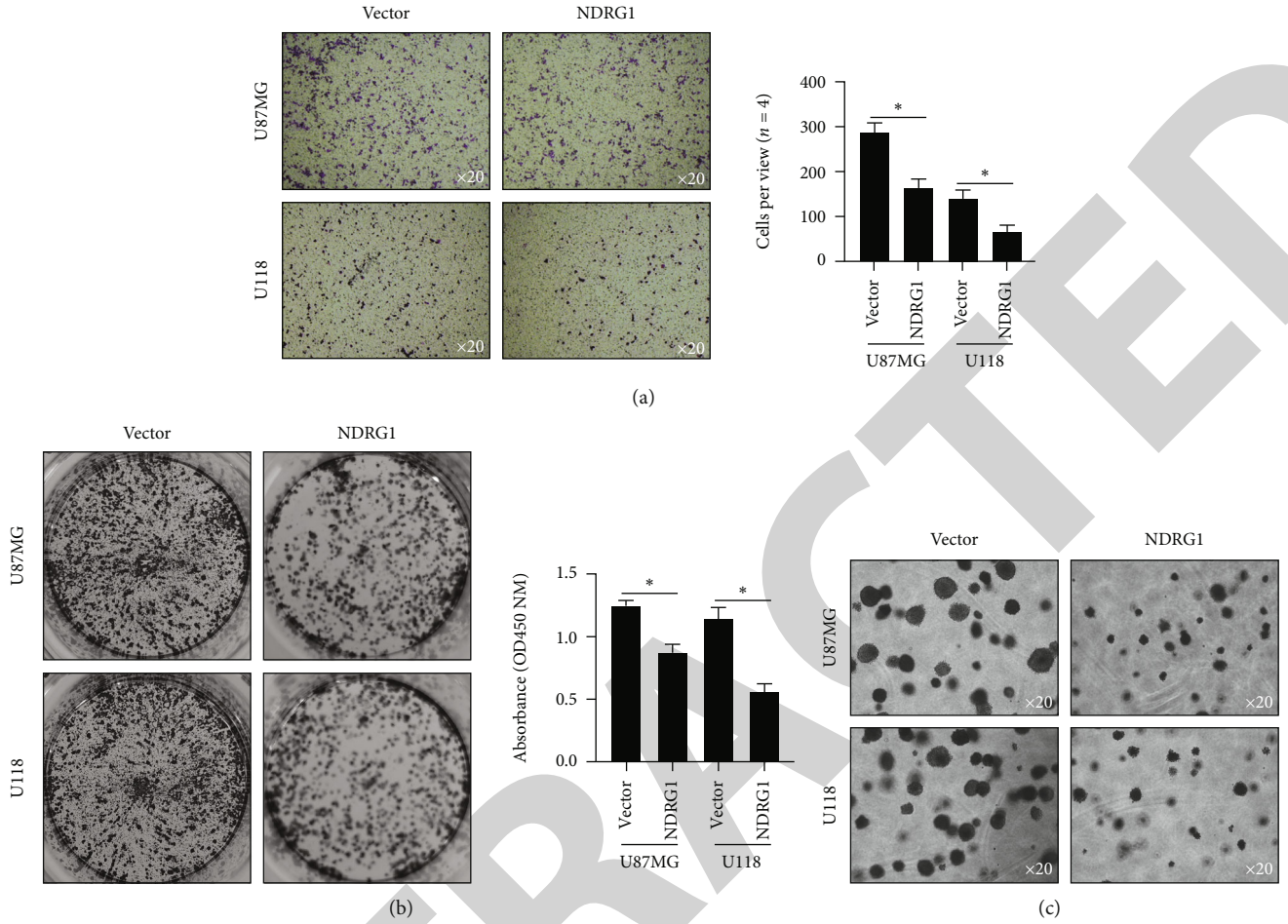

Figure 4: The effects of NDRG1 on malignant behaviors. The effects of overexpressed NDRG1 on invasion (a), colony formation (b), and tumor formation on soft agar (c) were measured. $^*P < 0.05$ vs. vector group.

100 μL RNase A and 400 μL propidium iodide (PI) (Sigma-Aldrich Chemical Company, St Louis, MO, USA) were added in the dark and incubated for 30 min at room temperature. After 30 min incubation at 4°C, it was measured using the FACS LSRII flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA).

2.7. Colony Formation Assay. 5×10^3 cells were plated in 6-well plates and cultured for 14 days. After that, colonies were washed three times with PBS and fixed with 4% paraformaldehyde at room temperature for 10 min. Then, fixed colonies were stained with 0.5% crystal violet for 10 min at room temperature. Cell colonies with diameters >1.5 mm were counted. The experiment was performed in triplicate.

2.8. Transwell Assay. The cells were suspended with 0.25% Trypsin and washed with ice-cold PBS for three times. 1×10^4 cells were seeded on the top chamber of inserts containing 8 μM pore polycarbonate filters (Corning Incorporated, Corning, NY, USA), precoated with Matrigel membrane (BD Biosciences, Franklin Lakes, NJ, USA). Experiments were performed in triplicate. After 48 h, the cells on the upper membrane were removed and the invaded cells were fixed with 4% paraformaldehyde at room temperature for 10 min; then, fixed cells were stained with crystal violet (Beyotime Institute of Biotechnology, Beijing, China) and counted under a microscope (magnification, ×100).

2.9. Western Blot Analysis. To analyze protein levels, cultured cells were lysed using SoniConvert® Tissue Cell Convertor (DocSense, Chengdu, China) according to manufacturer's instruction. Briefly, 1×10^6 cells were suspended using animal tissue/cells/bacteria total protein isolation kit (Cat. No.: PP003, DocSense). Protein concentrations were quantified using the Bio-Rad Protein Assay (Bio-Rad Laboratories). Equivalent quantities of lysate protein (20 μg/lane) were electrophoresed using an Any kD™ Mini-PROTEAN® TGX™ Precast Protein Gel for sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to an Immuno-Blot® PVDF Membrane (Bio-Rad Laboratories). Transferred membrane was blocked with 10% skim milk powder in Tris-buffered saline for 1 h. The blots were then incubated overnight at 4°C with primary antibodies as follows: anti-NDRG1 (Cat. No.: ab124689), anti-VEGFA (Cat. No.: ab52917), anti-Cyclin D1 (Cat. No.: ab16663), anti-Cyclin E1 (Cat. No.: ab33911), anti-PCNA (Cat. No.: ab29), and anti-Ki67 (Cat. No.: 15580) at

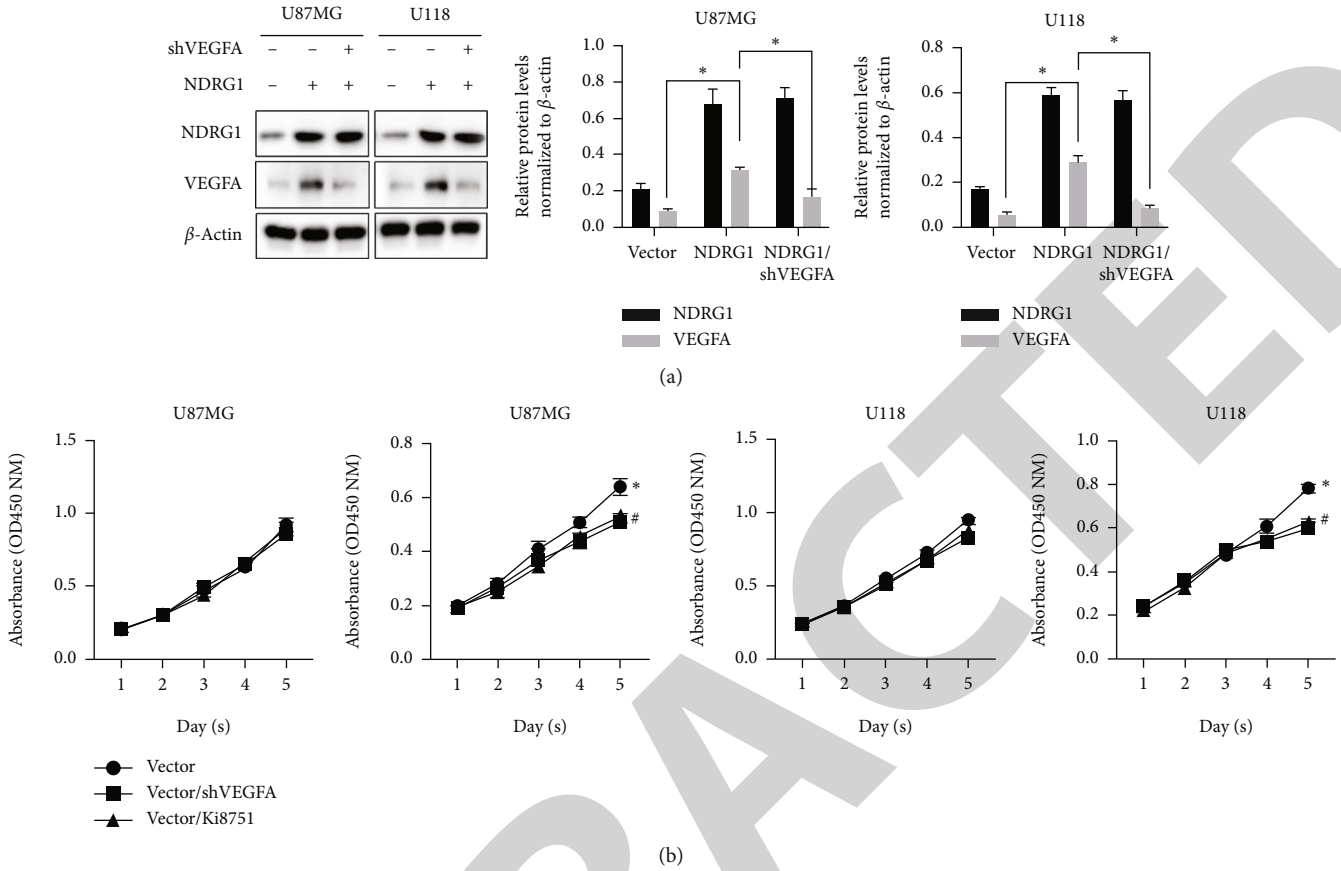

Figure 5: Inhibition of VEGFA/VEGFR2 pathway promotes the inhibitory effects of overexpressed NDRG1 on cell proliferation. (a) Efficient knockdown of VEGFA by LV-shVEGFA was confirmed by western blot. $^{*}P < 0.05$ vs. vector group. (b) Cell viability from day 1 to 5 was performed after VEFGA knockdown or inhibition by adding Ki8751. $^{*}P < 0.05$ vs. vector group; $^{\#}P < 0.05$, vector/shVEGFA group.

dilution of 1 : 1000. Then, membrane was incubated with anti-rabbit immunoglobulin IgG peroxidase-labeled secondary antibody at dilution of 1 : 2000. All antibodies were bought from Abcam. Immune complexes were visualized using enhanced chemiluminescence plus Western blotting detection reagents (GE Healthcare Life Sciences).

2.10. Statistical Analysis. All experimental results are expressed as the mean ± standard error of the mean (SEM). For experiments involving only two groups, the data were analyzed using a *t* test. Multiple comparisons were assessed using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, Inc.). Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Expression of NDRG1 Is Significantly Correlated with VEGFA in GBM Tissues. By employing Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/), we found that in GBM tissues (163 tumor tissues and 207 adjacent tissues), transcription of NDRG1 is positively correlated with VEGFA, but not VEGFB or VEGFC, which are two main isotypes of VEGF (Figure 1(a)). To understand the expression pattern of NDRG1 and VEGFA in GBM tumor, we further employed GEPIA and found that VEGFA is significantly upregulated in tumor tissues, but not NDRG1 (Figure 1(b)). As for overall survival (OS), patients in the NDRG1-low group and VEGFA-low group had a significantly better prognosis (Figure 1(c)). NDRG1 is realized as a tumor suppressor gene in GBM [R1] and contributes to better prognosis in patients, which is controversial to these results.

3.2. NDRG1 Transcriptionally Activates VEGFA in GBM Cell Lines. To confirm the correlation of NDRG1 with VEGFA in GBM cell lines, the expression levels of NDRG1 and VEGFA were measured in glioma cell lines Tx3868, Tx3095, U87MG, and U118. As it is illustrated in Figures 2(a) and 2(b), in U87MG and U118 cells, both NDRG1 and VEGFA presented a relative lower mRNA and protein levels. U87MG and U118 were picked for further analysis of NDRG1's role due to their relative low level of NDRG1. By performing western blot, efficient introduction of NDRG1 in both U87MG and U118 was confirmed (Figure 2(c)). Furthermore, the luciferase activity of the VEGFA reporter was activated in NDRG1-overexpressed U87MG and U118 cells (Figure 2(d)).

3.3. Overexpression of NDRG1 Inhibits Malignancies of GBM Cells. NDRG1 is considered as a tumor suppressor gene, including in gliomas and glioblastomas [5, 12]. Controversially,

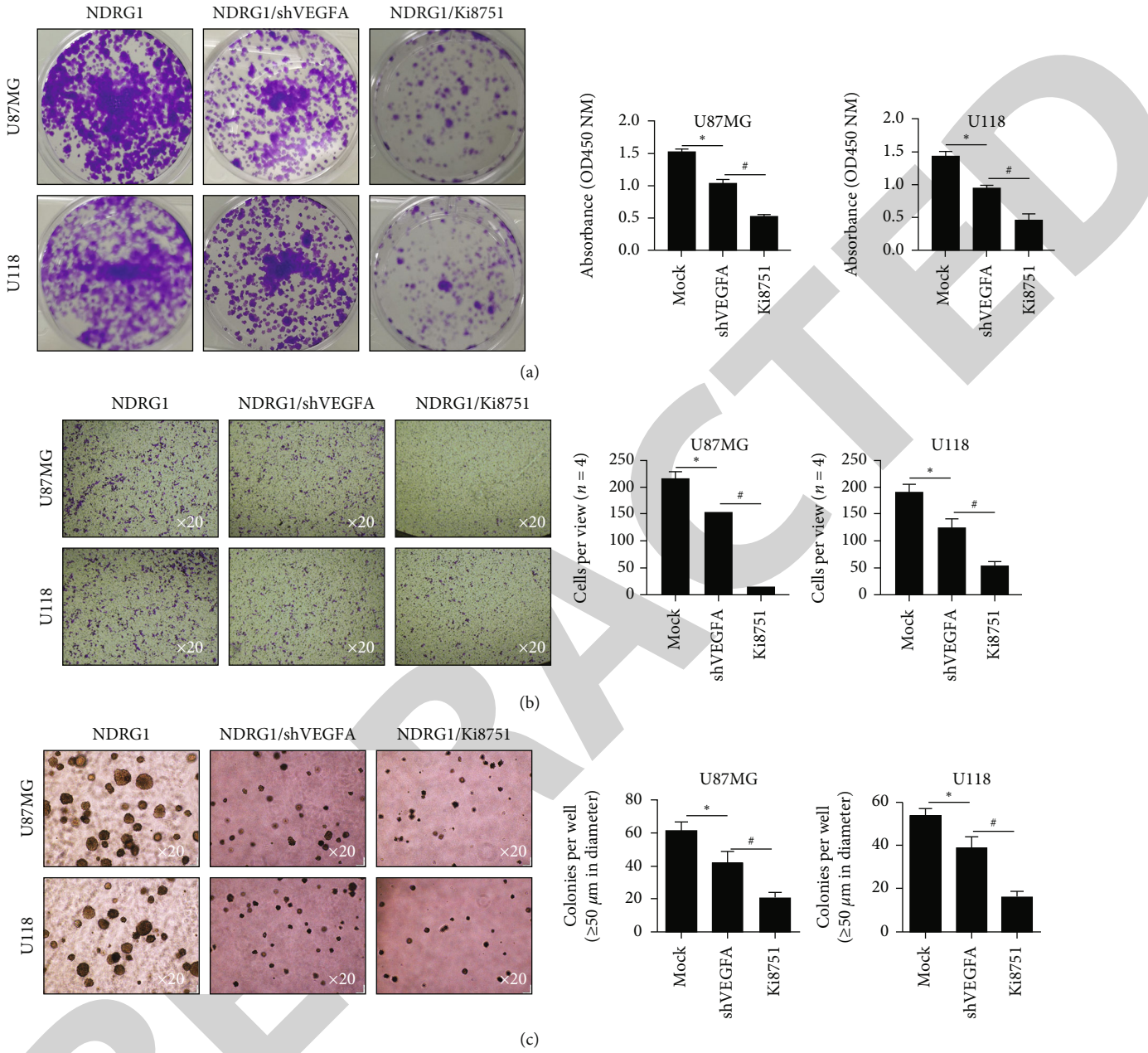

Figure 6: Inhibition of VEGFA/VEGFR2 pathway promotes the inhibitory effects of overexpressed NDRG1 on malignant behaviors. After VEGFA knockdown or inhibition of VEGFR2, malignant behaviors, including invasion (a), colony formation (b), and tumor formation in soft agar (c), were performed. $^{*}P < 0.05$ vs. vector group; $^{\#}P < 0.05$, vector/shVEGFA group.

VEGFA is acting promoting roles in various kinds of tumors [13], which promotes us to further confirm whether overexpressed NDRG1 promotes malignancies in GBM. By evaluating the effects of NDRG1 on cell viability in U87MG and U118 cells, CCK-8 assay was performed and results illustrated that overexpressed NDRG1 inhibited cell viability significantly at day 4 and 5 ($p < 0.05$) (Figure 3(a)). Expectedly, overexpressed NDRG1 blocked cell cycle progression at G_1/G_0 phase significantly ($p < 0.05$) (Figure 3(b)). Furthermore, by detecting cell cycle-related regulator, we found that overexpressed NDRG1 decreased cyclin D1, cyclin E, PCNA, and ki-67 significantly ($p < 0.05$) (Figure 3(c)).

Then, we also detected other malignant behaviors, including invasion, colony formation, and tumor formation in soft agar. Expectedly, overexpression of NDRG1 significantly decreased all these behaviors (Figures 4(a)–4(c)).

3.4. Blockage of VEGFA/VEGFR2 Pathway Promotes Inhibitory Effects of Overexpressed NDRG1. We first confirmed efficient VEGFA knockdown after infection of LV-shVEGFA (Figure 5(a)) and then evaluate the effects of VEGFA knockdown or inhibition of VEGFR2 via adding Ki8751. By performing CCK-8 assay, it is observed that in NDRG1-overepressed cells, VEGFA knockdown or addition

of Ki8751 significantly inhibited cell viability (Figure 5(b)). In vector-transfected cells, VEGFA knockdown or addition of Ki8751 slightly affected cell viability, potentially due to low endogenous VEGFA level (Figure 5(b)). Surprisingly, no obvious difference on cell cycle phases was observed after VEGFA knockdown of VEGFR2 inhibition in U87MG and U118 cells without NDRG1 overexpression, possibly due to low endogenous level of VEGFA (data not shown).

We then also detected the effects of VEGFA knockdown or addition of Ki8751 on invasion, colony formation, and tumor formation. Consistent with previous finding, inhibition of VEGFA/VEGFAR2 pathway further decreased all these behaviors (Figures 6(a)–6(c)).

4. Discussion

The presented results indicate that expression of NDRG1 exerts suppressive roles in GBM, including U87MG and U118 cells. Overexpression of NDRG1 transcriptionally activates VEGFA, but not VEGFB or VEGFC. Although overexpressed NDRG1 inhibited malignant behavior of GBM, including cell proliferation, colony formation, migration, and invasion, blockage of VEGFR2 inhibited all these behaviors even further, indicating that NDRG1-induced VEGFA may contribute to promoting angiogenesis and malignant behaviors in a VEGFA/VEFAR2 axis-dependent manner. Accordingly, we hypothesize that NDRG1 contributes to suppressing malignant behaviors in GBM. Moreover, blockade of the VEGFA/VEGFR2 axis may be a promising strategy after stimulation with NDRG1.

According to the literature, the membrane bound by the NDRG1 protein is close to the adhesion junction [14]. In cancers, the *NDRG1* gene is considered to be involved in inhibiting metastasis, which is negatively correlated with the migration of metastatic cancer cells [15–17]. Therefore, NDRG1 reduces metastatic potential by forming adhesion boundaries, increasing cell–cell adhesion, and inhibiting migration and invasion. The expression of EMT-related proteins, including vimentin, N-cadherin, and E-cadherin, as invasive markers is significantly increased in glioma cells and surgically resected specimens [18]. By analyzing migration and invasion capacities, we found that NDRG1 overexpression significantly decreased all these capacities. As a limitation, we failed to detect the expression level of EMT-related proteins.

The regulation of NDRG1 is highly complex under hypoxia, and its cellular function is still controversial. It has been demonstrated that reducing NDRG1 expression in GSCs can inhibit self-renewal, promote differentiation, and significantly inhibit tumor occurrence. In contrast, overexpression of NDRG1 in GSCs can induce PN-to-MES transition and improve the highly malignant phenotype [19]. In this study, overexpressed NDRG1 inhibited malignant behaviors, including proliferation, colony formation, tumor formation, migration, and invasion. These effects were further promoted by the addition of the VEGFR2 inhibitor Ki8751, which is similar to the effects of VEGFA knockdown. Overexpression of VEGFA is a critical regulator of EMT activation. NDRG1-induced VEGFA may promote migration and invasion; however, overexpression of NDRG1 obviously decreased migration and invasion, which is controversial regarding the effect of VEGFA on EMT. These results indicated that NDRG1 exerts regulatory roles in a VEGFA-independent manner, which is worth investigating in further studies.

Some studies have pointed out that the expression and function of NDRG1 are affected by conventional GBM treatment; thus, NDRG1 may be a promising target for GBM treatment if methods that can reduce these effects are developed in the future.

In humans, the VEGF family consists of several members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E (viral VEGF), VEGF-F (snake venom VEGF), and placental growth factor (PlGF). Recently, endocrine gland-derived vascular endothelial growth factor (e.g., VEGF) has been added to this family. These factors show a different affinity for VEGFR subtypes. VEGF-A can activate VEGFR-1 and VEGFR-2, while VEGF-B and PlGF can only bind to VEGFR-1. Moreover, VEGF-C and VEGF-D can only bind to VEGFR-3. In this study, we revealed that NDRG1 positively correlated with the expression of VEGFA but not VEGFB or VEGFC. Overexpressed NDRG1 binds to the VEGFA promoter region and exerts transcriptional activating ability. This finding indicates its specific roles in regulating VEGFA. We hypothesized that overexpressed NDRG1 may promote angiogenesis by transcriptionally activating VEGFA. As a limitation, the expression level of VEGFA-related downstream targets involved in regulating migration and invasion should be detected in further investigation.

5. Conclusion

Our study demonstrates that NDRG1 exerts tumor-suppressing roles in GBM. It was also found that overexpression of NDRG1 transcriptionally activates VEGFA, which is a positive regulator of migration and invasion capacities in GBM. Stimulation of NDRG1 suppressed malignant behaviors, which was further suppressed by inhibiting VEGFA/VEGFR2 signaling. All these results provide a novel strategy for GBM therapy by stimulating NDRG1 and inhibiting VEGFA simultaneously.

Data Availability

All data generated or analyzed during this study are included in this published article.

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.

Authors' Contributions

Xufan Zhang and Qian Chen contributed equally to this work and share first authorship. Qin Jiang and Qiongying Hu contributed equally.