Journal of Environmental and Public Health

# Application of Gene Testing for Public Health

Lead Guest Editor: Fenglin Liu
Guest Editors: Weiguo Li and Xuncai Chen

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Tongzhang Zheng, USA

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*Retraction*

# Retracted: Correlation between High Myopia Susceptibility and Polymorphisms of RASGRF1 Gene among College Students in Zhejiang

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## References

[1] J. Yi, Y. Dai, S. Ma, Y. Zheng, Y. Liang, and X. Huang, "Correlation between High Myopia Susceptibility and Polymorphisms of RASGRF1 Gene among College Students in Zhejiang," *Journal of Environmental and Public Health*, vol. 2023, Article ID 6767410, 6 pages, 2023.

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# Retracted: Effects of DNA Immunoadsorption Combined with Medication on Immune Function and Renal Function in Patients with Systemic Lupus Erythematosus

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# Retracted: Identification of Differentially Methylated Genes Associated with Clear Cell Renal Cell Carcinoma and Their Prognostic Values

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[1] B. Wan, Y. Yang, and Z. Zhang, "Identification of Differentially Methylated Genes Associated with Clear Cell Renal Cell Carcinoma and Their Prognostic Values," *Journal of Environmental and Public Health*, vol. 2023, Article ID 8405945, 10 pages, 2023.

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# Retracted: The Role of C-Reactive Protein in the Prognosis of Prostate Cancer: A Meta-Analysis

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[1] T. Liu and L. Zhuo, "The Role of C-Reactive Protein in the Prognosis of Prostate Cancer: A Meta-Analysis," *Journal of Environmental and Public Health*, vol. 2023, Article ID 6222324, 8 pages, 2023.

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# Retracted: The Diagnostic Accuracy of Transabdominal and Transvaginal Color Doppler Ultrasound for Pregnant Women with Vasa Previa and Velamentous Cord Insertion

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# Retracted: Impacts of Ultrasound-Guided Nerve Block Combined with General Anesthesia with Laryngeal Mask on the Patients with Lower Extremity Fractures

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# Retracted: Circulating miR-340-5p and miR-506-3p as Two Osteo-miRNAs for Predicting Osteoporosis in a Cohort of Postmenopausal Women

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# Retracted: MicroRNA-340 and MicroRNA-450b-5p: Plasma Biomarkers for Detection of Non-Small-Cell Lung Cancer

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# Retracted: Effects of Modified Duhuo Jisheng Decoction Combined with Arthroscopic Surgery on Bone Metabolism, Oxidative Stress, and Serum TLR4 and TGF-$\beta$1 in Patients with Knee Osteoarthritis

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# Retracted: Clinical Effect of Open Reduction and Internal Fixation for Femoral Neck Fracture in Young Adults and Related Factors of Femoral Head Necrosis

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# Retracted: Retrospective Case Analysis of 104 Cases of Talipes Equinus

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# Retracted: Chemical Structures and Pharmacological Properties of Typical Bioflavonoids in *Polygonati Rhizoma* (PGR)

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# Retracted: Effects of DNA Immunoadsorption Combined with Medication on Immune Function and Renal Function in Patients with Systemic Lupus Erythematosus

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*Research Article*

# Effects of DNA Immunoadsorption Combined with Medication on Immune Function and Renal Function in Patients with Systemic Lupus Erythematosus

**Lijie Bai,[1] Mingxia Sun,[2] Guiying Wu,[1] Jing Wang,[1] Yong Wang,[1] Jun Shi,[3] and Liying Zhang[4]**

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*Objective*. At present, glucocorticoids combined with cyclophosphamide are still used for the clinical treatment of systemic lupus erythematosus (SLE). However, long-term practice has shown that drug treatment currently has the phenomena of long treatment duration, uncontrollable conditions in a short period of time, and unsatisfactory efficacy. DNA immunoadsorption therapy is a newly developed therapy. The combination of drugs and DNA immunoadsorption has been reported for the treatment of SLEN in clinics for a long time. In this study, we observed the effects of DNA immunoadsorption combined with drug therapy on immune function and renal function in patients with systemic lupus erythematosus (SLE). The results showed that the DNA immunosorbent assay combined with medication in the treatment of SLE could quickly and specifically remove pathogenic substances from patients, improve renal function, immune function, and complement levels in patients, and help to relieve disease activity.

## 1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune, inflammatory connective tissue disease involving multiple organs that occurs mostly in young women. Its clinical manifestations are complex and varied, which can lead to changes in brain, kidney, blood, skin, and joints [1]. Immunosuppressive agents are mainly used in clinics to inhibit abnormal immune and inflammatory responses in order to treat SLE [2]. In recent years, with the continuous improvement of treatment methods, the use of hormones and immunosuppressants, and the emergence of biological agents, the prognosis of SLE patients has greatly improved. However, immunosuppressive agents have poor efficacy for patients with high activity of SLE, especially for patients with combined nervous system lesions. Moreover, such patients have become the difficulties in the treatment of SLE due to their rapid disease progression, poor treatment response, and poor clinical prognosis [3]. At present, the early removal of autoantibodies from patients' serum, control of disease activity, and protection of renal function are the keys to treatment.

DNA immunoadsorption is a new therapeutic method developed on the basis of plasma exchange. DNA is fixed on the carrier as a ligand to form an adsorption column, which can specifically remove the anti-DNA antibody or immunoglobulin by the biological affinity of antigen and antibody, thereby reducing the damage of pathogenic antibodies and immune complexes to tissues and organs [4]. A single treatment with a DNA immunosorbent assay can effectively eliminate endogenous pathogenic factors in blood of SLE patients, help patients survive an immune storm, and

promote disease remission. Stummvoll et al. [5] observed that 16 patients with SLE nephritis had significantly improved resistance after three months of immunoadsorption treatment, with the SLE disease activity index (SLEDAI) score decreased, proteinuria significantly reduced, and anti-ds-DNA antibody titer decreased. These results indicated that the DNA immunosorbent assay could effectively control the condition of SLE patients and create the conditions for later drug treatment. In order to further verify this result, in this study, we investigated the effects of DNA immunoadsorption combined with glucocorticoids, cyclophosphamide, and other drugs on the immune function and renal function in patients with SLE in order to provide more evidence for the clinical treatment of SLE.

## 2. Data and Methods

*2.1. General Information.* A total of 84 patients with SLE who visited our hospital from May 2018 to May 2021 were selected. According to the difference in treatment methods, all patients were divided into an observation group and a control group, with 42 cases in each group.

*2.2. Inclusion and Exclusion Criteria*

*2.2.1. Inclusion Criteria.* The inclusion criteria were as follows: all patients met the diagnostic criteria for SLE, no treatment with glucocorticoids or immunosuppressive drugs within 2 months before treatment, patients with 24 h urine protein quantification in the urine test ≥1 g, and patients with normal coagulation function and no bleeding tendency or active bleeding.

*2.2.2. Exclusion Criteria.* The exclusion criteria were as follows: patients with combined renal malignant tumor, patients with severe cardiovascular and cerebrovascular diseases, patients with severe bacterial or active viral infections such as hepatitis B and C, patients with a history of acute rheumatic fever and rheumatoid arthritis, patients who are allergic to the drugs used in this study, and women who are pregnant or nursing.

*2.3. Treatment Methods.* Patients in the control group were treated with the conventional medication for SLE, namely, glucocorticoids combined with cyclophosphamide pulse therapy. Methylprednisolone tablets were administered at a dose of 0.8 mg/(kg·d) once per day. Cyclophosphamide (0.5 g) for injection was added into 250 mL of 0.9% sodium chloride solution for intravenous infusion once every 2 weeks and changed to once every 4 weeks after 6 weeks according to the degree of disease of the patient. Continuous treatment was given for 6 months.

On the basis of the control group, patients in the observation group were treated with DNA immunoadsorption. A DNA immunoadsorption column, a hemoperfusion machine, and extracorporeal circulation equipment were used for the adsorption treatment. Specific steps were as follows: 500 mL of 5% glucose injection was added into the adsorption column and allowed to stand for 30 min. During the static period, gently tap and rotate the adsorption column every 10 minutes for 1 to 2 minutes. After the adsorbent particles are saturated, use 4000 mL of heparin sodium and sodium chloride solution to flow in the adsorption system of the adsorption column from top to bottom, with a flow rate of 50 to 100 mL/min. Gently tap and rotate the adsorption column with your hand until the exhaust is exhausted. Finally, use 500 mL of heparin sodium chloride solution (including 100 mg of heparin) to close the circulation for 30 minutes to make the adsorption column completely heparinized. After successful deep venipuncture of bilateral iliac venous access, intravenous heparin was started at a dose of 1 mg/kg body weight with a total dose of 16–20 mg/h, and heparin was stopped 30 min before the end. After the deep vein indwelling catheter was effectively connected to the adsorption column as the vascular access, a preflush was performed and connected to the venous line so that the patient could establish effective cardiopulmonary bypass and anticoagulation. The blood pump was started at an initial speed of 80–100 mL/min and then gradually increased to 100–150 mL/min. After adsorption, blood was returned using the air-to-blood method, and protamine was slowly injected intravenously to neutralize the heparin. The single adsorption time was 2-3 h, and the next treatment could be carried out after an interval of 3 d. According to the patient's tolerance and serological indicators, DNA immunoadsorption therapy was performed two to three times.

*2.4. Observation Indicators*

(1) Health status evaluation: before and after treatment, clinical analysis was performed on 24 indicators of nine organ systems in patients according to the SLEDAI, with a total score of 105 points [6]. The basic inactive period is 0–4 points, the mild active period is 5–9 points, the moderate active period is 10–14 points, and the severe active period is ≥15 points. Meanwhile, using the MOSF-36 scale as a measurement tool and an anonymous survey, the physical function (PF) and mental health (MH) scores of the two groups before and after treatment were compared.

(2) Detection of immune function: before and after treatment, 3 mL of fasting venous blood was collected from the patients. After centrifugation, the levels of immunoglobulins (IgA, IgG, and IgM), complement C3 and C4 were detected by electrochemical luminescence assay.

(3) Detection of inflammatory factor indicators: before and after treatment, 3 mL of venous fasting blood was collected and centrifuged. Serum levels of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) were measured by enzyme-linked immunosorbent assay.

(4) Renal function test: before and after treatment, the peripheral blood of patients was collected, and after centrifugation, the blood urea nitrogen (BUN) and

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

| | Control group ($n = 42$) | Observation group ($n = 42$) | $x^2$ /$t$ | $P$ |
|---|---|---|---|---|
| Gender ($n$ (%)) | | | 0.060 | 0.806 |
| Male | 11 | 12 | | |
| Woman | 30 | 29 | | |
| Mean age (years, $x \pm s$) | $33.95 \pm 4.29$ | $34.16 \pm 4.07$ | 0.230 | 0.819 |
| Mean course of disease (years, $x \pm s$) | $2.16 \pm 0.67$ | $2.14 \pm 0.64$ | 0.140 | 0.889 |
| SLEDAI score (score, $x \pm s$) | $22.07 \pm 0.94$ | $21.92 \pm 0.87$ | 0.759 | 0.450 |
| Organ involvement ($n$ (%)) | | | 0.135 | 0.987 |
| Central nervous system | 29 | 30 | | |
| Heart | 27 | 28 | | |
| Lungs | 21 | 19 | | |
| Kidney | 41 | 41 | | |
| White blood cells ($\times 10^9$/L, $x \pm s$) | $5.35 \pm 1.14$ | $5.28 \pm 1.37$ | 0.255 | 0.799 |
| Hemoglobin (g/l, $x \pm s$) | $96.84 \pm 12.53$ | $95.71 \pm 10.96$ | 0.051 | 0.960 |
| Platelets ($\times 10^9$/L, $x \pm s$) | $216.74 \pm 41.27$ | $224.89 \pm 42.73$ | 0.889 | 0.377 |

serum creatinine (SCr) contents were measured by the electrochemical luminescence method. The 24 h urine samples of patients were collected before and after treatment, and the urine protein content was detected by an automatic urine analyzer.

(5) Adverse reactions: during the treatment, mild rash, thrombocytopenia, fever, malignant vomiting, and decreased blood pressure in the two groups were recorded.

*2.5. Statistical Methods.* SPSS 22.0 software was used for processing. The measurement data that conformed to the normal distribution of the experimental data were expressed as mean ± SD. An independent sample $t$-test was used for comparison between groups. A paired $t$-test was used for intragroup comparison. Experimental data were counted and expressed as (%) and compared by the $x^2$ test. The test level was $\alpha = 0.05$, and $P < 0.05$ indicated that the difference was statistically significant.

## 3. Results

*3.1. General Baseline.* There was no significant difference in general baseline data between the two groups ($P > 0.05$), as shown in Table 1.

*3.2. Assessment of the Health Status of Patients in Two Groups.* Before treatment, the SLEDAI score, PF score, and MH score between the two groups were not statistically significant ($P > 0.05$). After treatment, the SLEDAI score of patients in the observation group was lower than that of the control group, and the PF score and MH score of patients in the observation group were higher than those of patients in the control group (both $P < 0.05$), as shown in Figure 1.

*3.3. Comparison of Immune Indexes between the Two Groups.* Before treatment, the levels of IgA, IgG, IgM and complement C3 and C4 between the two groups were not statistically significant ($P > 0.05$). After treatment, the levels of IgA, IgG, and IgM in patients of the observation group were lower than those of the control group, and the levels of complement C3 and C4 were higher than those of the control group (all $P < 0.05$), as shown in Table 2.

*3.4. Comparison of Inflammatory Factor Levels between the Two Groups.* Before treatment, the levels of IL-6, IL-8, and TNF-$\alpha$ between the two groups were not statistically significant ($P > 0.05$). The levels of IL-6, IL-8, and TNF-$\alpha$ in the two groups of patients after treatment were lower than those before treatment, and the levels of IL-6, IL-8, and TNF-$\alpha$ in the observation group were lower than those in the control group (all $P < 0.05$), as shown in Figure 2.

*3.5. Comparison of Renal Function Indexes between the Two Groups.* Before treatment, the levels of BUN and SCr and the 24 h urinary protein quantity between the two groups were not statistically significant ($P > 0.05$). The levels of BUN and SCr and 24 h urinary protein quantity in the two groups after treatment were lower than those before treatment, and the levels of BUN and SCr and 24 h urinary protein quantity in the observation group were lower than those in the control group (all $P < 0.05$), as shown in Figure 3.

*3.6. Adverse Reactions in Two Groups during Treatment.* In the observation group, there were three cases of mild rash, one case of thrombocytopenia, three cases of generate heat, four cases of nausea and vomiting, and one case of decreased blood pressure, with the total incidence rate of 28.57%. In the control group, there were two cases of mild rash, two cases of generating heat, and three cases of nausea and vomiting, with a total incidence rate of 16.67%. There was no statistical significance in the incidence rate of various adverse reactions or the total incidence between the two groups (all $P > 0.05$), as shown in Table 3.

## 4. Discussion

At present, the principle of clinical treatment of SLE is "classification, staging, combination, and long-term," and the drugs used target control immunosuppressants and

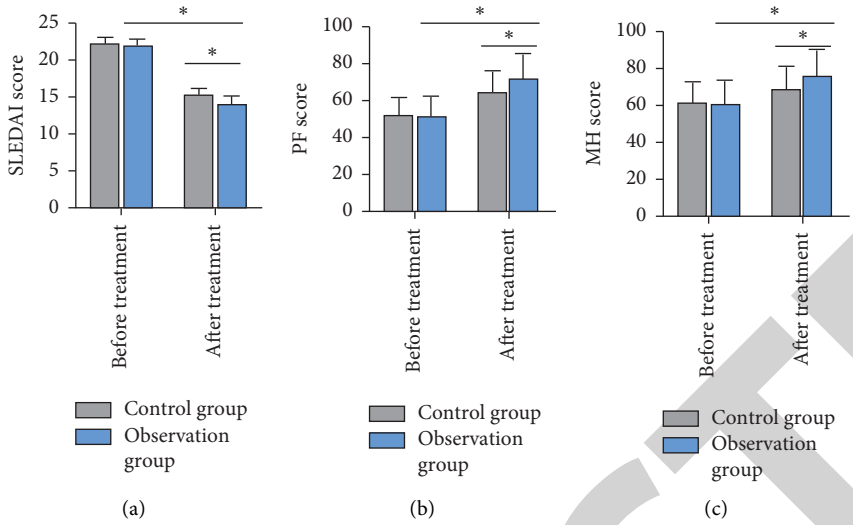


Figure 1: Health status evaluation of two groups of patients. (a) SLEDAI score. (b) PF score. (c) MH score. ($^*P < 0.05$).

Table 2: Comparison of immune indexes between the two groups.

| Group | Time | IgA (g/L) | IgG (g/L) | IgM (g/L) | C3 (g/L) | C4 (g/L) |
|---|---|---|---|---|---|---|
| Control group ($n = 42$) | Before treatment | $2.63 \pm 0.41$ | $20.95 \pm 3.38$ | $1.84 \pm 0.42$ | $0.51 \pm 0.07$ | $0.07 \pm 0.02$ |
| | After treatment | $2.54 \pm 0.38^{a}$ | $18.52 \pm 3.12^{a}$ | $1.72 \pm 0.33^{a}$ | $0.54 \pm 0.02^{a}$ | $0.08 \pm 0.01^{a}$ |
| Observation group ($n = 42$) | Before treatment | $2.61 \pm 0.43$ | $20.49 \pm 3.26$ | $1.86 \pm 0.45$ | $0.50 \pm 0.06$ | $0.07 \pm 0.01$ |
| | After treatment | $2.42 \pm 0.29^{ab}$ | $16.37 \pm 2.81^{ab}$ | $1.63 \pm 0.30^{ab}$ | $0.57 \pm 0.05^{ab}$ | $0.09 \pm 0.03^{ab}$ |

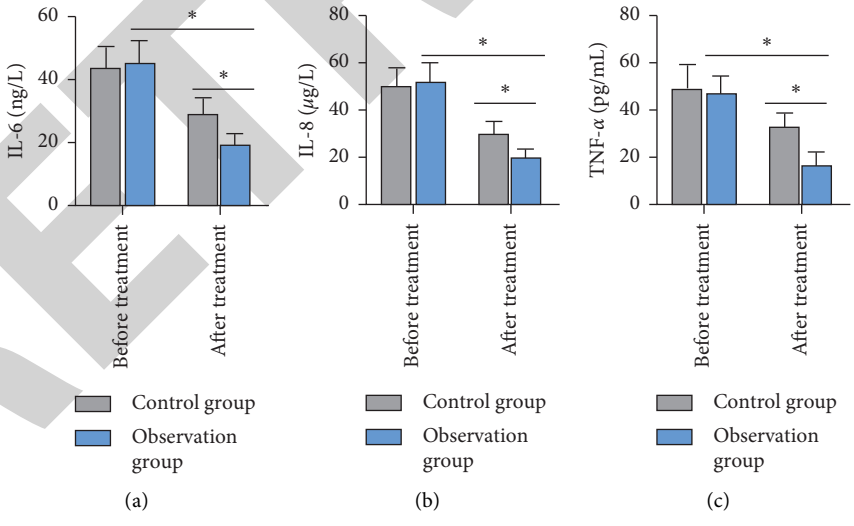


Figure 2: Comparison of inflammatory factor levels between the two groups. (a) IL-6. (b) IL-8. (c) TNF-$\alpha$. ($^*P < 0.05$).

cytotoxic drugs with the ultimate goal to inhibit excessive autoimmune responses [7, 8]. Autoantibodies in SLE patients can attack their cells and tissues, forming antigen-antibody complexes that are deposited in the vascular wall, glomerular basement membrane, and other areas, eventually leading to target organ function damage [9, 10]. Glucocorticoids combined with cyclophosphamide have anti-inflammatory and anti-T-lymphocyte proliferation effects, which can alleviate the clinical symptoms of patients [11, 12]. However, in the process of conventional drug treatment, it will inhibit the body's immune function and the resulting cytotoxicity, resulting in a poor anti-inflammatory effect. In recent years, biological agents for the treatment of SLE have appeared, but most of them are still in the initial stages of

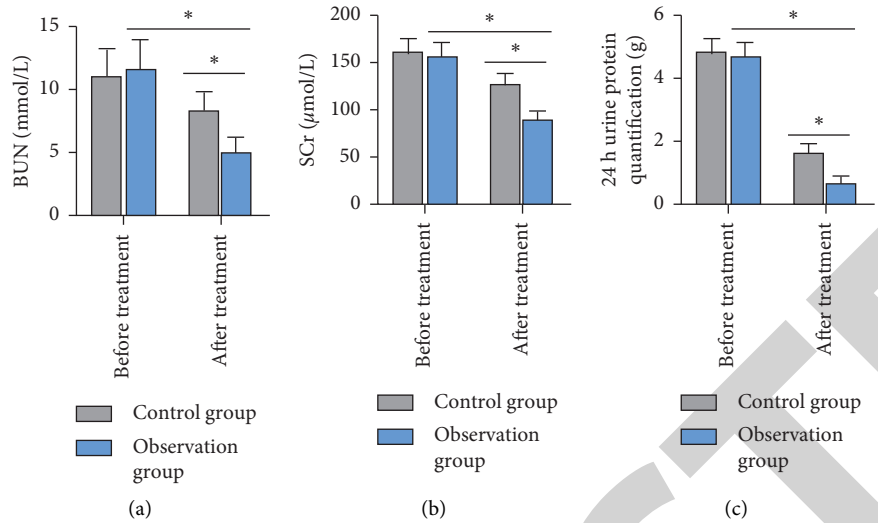


Figure 3: Comparison of renal function indicators between the two groups. (a) BUN. (b) SCr. (c) 24 h urine protein quantification. ($^*P < 0.05$).

Table 3: Comparison of adverse reactions between the two groups.

| Group | Mild rash | Thrombocytopenia | Generate heat | Nausea and vomiting | Decreased blood pressure | Total incidence |
|---|---|---|---|---|---|---|
| Control group ($n = 42$) | 2 (4.76) | 0 (0.00) | 2 (4.76) | 3 (7.14) | 0 (0.00) | 7 (16.67) |
| Observation group ($n = 42$) | 3 (7.14) | 1 (2.38) | 3 (7.14) | 4 (9.52) | 1 (2.38) | 12 (28.57) |
| $x^2$ | 0.213 | 1.012 | 0.213 | 0.156 | 1.012 | 1.700 |
| $P$ | 0.645 | 0.314 | 0.645 | 0.693 | 0.314 | 0.192 |

research and clinical application, and their efficacy and safety await follow-up and evaluation in large-scale double-blind controlled trials.

The results of this study showed that the improvement in SLEDAI, PF, and MH scores was better in the treatment group than in the control group. SLEDAI is recognized as a reliable and effective tool for evaluating the activity of SLE [13]. Therefore, this result indicates that the clinical application of immunoadsorption, hormones, and immunosuppressants can effectively remove antibodies from the body and alleviate the symptoms of patients with exact clinical efficacy. DNA immunoadsorption therapy is an emerging method for the treatment of autoimmune diseases in recent years, which belongs to the field of blood purification treatment [14, 15]. DNA immunoadsorption therapy uses antigens or other substances with specific physicochemical affinity as ligands, which are combined with the carrier and connected to the adsorption column. Specific adsorption is used to eliminate endogenous pathogenic factors in patients' blood, so as to exert the effects of purifying blood, eliminating immune complexes and immunoglobulins in patients with SLE, alleviating target organ damage, and achieving the effects of targeted therapy for SLE [16, 17].

Studies have found that the body's immune function, complement, and inflammatory factor levels are closely related to the occurrence and development of SLE [18]. The insufficient production of inhibitory T lymphocytes will result in the weakened inhibition of CD8+ T cells on B lymphocytes, which in turn leads to the abnormal proliferation of B lymphocytes and the secretion of a large amount of Ig, thereby increasing the content of Ig in the body and accelerating the further development of the patient's condition [19]. In addition, complement is also involved in the regulation of immune function and the formation of antigen-antibody complexes. Complement C3 and C4 are glycoproteins with enzyme activity in body fluids. There are a large number of autoantibodies in SLE patients, and their phagocytosis in the formed antigen-antibody complex will consume a large amount of complement, resulting in a reduction of complement content in the body [20, 21]. In this study, DNA immunoadsorption combined with medication significantly reduced IgA, IgG, and IgM levels in patients and increased complement C3 and C4 levels in patients. It indicated that DNA immunoadsorption therapy combined with medication could improve the high immune function of patients. The reason for this is that DNA immunoadsorption therapy could eliminate autoantibodies in vivo in time, so as to regulate immune function and restore balance.

The results of this study showed that the levels of inflammatory factors were decreased after treatment in both groups compared with those before treatment, and they were significantly better in the observation group than in the control group patients. IL-6 can stimulate the activation and differentiation of inflammatory cells, aggravating the

inflammatory damage to the target organs in SLE patients and the progression of the disease. The massive release of IL-8 in the active stage of SLE disease further aggravates the renal inflammatory response [22, 23]. TNF-$\alpha$ is a widely used cytokine in clinics; its level can be significantly elevated when the body is stimulated by external bacteria and viruses. The significant difference in IL-6, IL-8 and TNF-$\alpha$ after treatment between the two groups in this study may be due to the fact that DNA immunosorbent assay could remove endogenous pathogenic factors such as autoantibodies and inflammatory factors in blood through specific adsorption and reduce complement consumption in patients' bodies, which plays a role in improving immune function of patients, increasing complement level, and reducing inflammatory factor level in vivo.

SLE can involve multiple organs throughout the body, with kidney involvement being the most severe. When the kidneys are involved, SLE patients will present with such symptoms as hematuria, proteinuria, and edema or even lead to end-stage renal disease, which will endanger the patients' lives [24, 25]. The local deposition of antigen-antibody complexes in the glomeruli is the most fundamental pathological change leading to renal impairment [26, 27]. Braun et al. [28] adopted immunoadsorption to treat SLE patients with routine immunosuppressive resistance, and 70% of the patients recovered within three weeks after treatment with rapid reduction of circulating immune complexes and immunoglobulins, serum SCr reduction, and significantly reduced urine protein. DNA immunoadsorption therapy can directly remove autoantibodies, especially anti-ds-DNA antibodies, which are closely related to the prognosis, so as to reduce the damage of the antigen-antibody complex to the glomerulus [29, 30]. Therefore, the results of this study show that the BUN and SCr levels and 24 h urine protein quantity in the observation group were lower than those in the control group. This further confirms that DNA immunosuppression combined with glucocorticoid and cyclophosphamide treatment might help to improve the renal function in patients with SLE.

Our study further observed the occurrence of adverse reactions in the two groups and found that the combination of DNA immunosuppression and drug treatment did not increase the adverse reactions of the patients, which is beneficial for the patients to safely survive the highly active clinical risk period of the condition. It should also be noted that although the use of glucocorticoids and immunosuppressive agents during treatment can significantly improve the clinical outcome and prognosis of patients, the 5-year survival rate of approximately 10% of patients is still poor. Therefore, once clinically diagnosed, effective treatment measures that inhibit lupus activity are taken immediately to ensure the improvement of clinical symptoms and further improve the prognosis. At the same time, shortening the medication time as much as possible during the induction treatment stage is also the key to ensure the long-term prognosis of patients and reduce complications [31].

To sum up, a DNA immunosorbent assay combined with drugs in the treatment of SLE can quickly and specifically remove pathogenic substances from patients, improve renal function, immune function, and complement levels in patients, and help to relieve disease activity. However, its exact effect and long-term efficacy require further evidence from large samples and multicenter prospective trials.

## Data Availability

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

## Disclosure

Lijie Bai and Mingxia Sun are the co-first authors.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Acknowledgments

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*Retraction*

# Retracted: Correlation between High Myopia Susceptibility and Polymorphisms of RASGRF1 Gene among College Students in Zhejiang

**Journal of Environmental and Public Health**

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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.

## References

[1] J. Yi, Y. Dai, S. Ma, Y. Zheng, Y. Liang, and X. Huang, "Correlation between High Myopia Susceptibility and Polymorphisms of RASGRF1 Gene among College Students in Zhejiang," *Journal of Environmental and Public Health*, vol. 2023, Article ID 6767410, 6 pages, 2023.

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*Research Article*

# Correlation between High Myopia Susceptibility and Polymorphisms of RASGRF1 Gene among College Students in Zhejiang

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*Objective*. The aim of the study is to analyze the correlation between high myopia susceptibility and Ras protein-specific guanine nucleotide-releasing factor-1(RASGRF1) gene polymorphism among college students in Zhejiang. *Methods*. A stratified whole-group sampling method was used to select 218 cases of college students in Zhejiang who met the inclusion and exclusion criteria from January, 2019, to December, 2021, and they were divided into 77 cases (154 eyes) in the high myopia group and 141 cases (282 eyes) in the medium-low myopia group according to the degree of myopia, and 109 cases of college volunteers without myopia from the same period of medical examination in the region were included in the control group. The single nucleotide polymorphisms (SNPs) located in functional regions were selected by searching the literature and genetic databases, and the base sequences of rs939658, rs4778879, and rs8033417 loci were obtained by genotyping candidate SNPs using multiplex ligase detection reaction technique. The cardinality test was used to compare the differences in genotype frequency distribution of each locus of the RASGRF1 gene between the high myopia group and the low to moderate myopia group and the control group. *Results*. The genotype frequencies and allele frequencies of the RASGRF1 gene rs939658 locus in the high myopia group compared with the moderate-low myopia group and the control group were not statistically significant ($P > 0.05$). The genotype frequencies and allele frequencies of the rs4778879 locus of the RASGRF1 gene were compared among the three groups, and the differences were not statistically significant ($P > 0.05$). The genotype frequency and allele frequency of the rs8033417 locus of the RASGRF1 gene differed significantly among the three groups ($P < 0.05$). *Conclusion*. The polymorphism of the rs8033417 locus of the RASGRF1 gene was significantly correlated with the susceptibility of high myopia among college students in Zhejiang.

## 1. Introduction

High myopia refers to pathological myopia with a refractive error of -6D and above; its main symptoms are progressive vision loss and, in severe cases, irreversible pathological changes that cannot be optically corrected, such as chorioretinal degeneration, glaucoma, cataract, and retinal detachment [1, 2]. Some studies have found that the prevalence of high myopia among college students in China has shown a significant upward trend in recent years, which has a negative impact on their quality of life and employment [3, 4]. The formation of high myopia is more genetically related, and the latest human genetic library data show that hundreds of genetic factors associated with myopia have been determined by genome-wide association studies and whole-exome sequencing [5], among which Ras protein-specific guanine nucleotide-releasing factor 1 (RASGRF1) is a gene closely associated with myopia as confirmed by several studies [6]. RASGRF1, located on chromosome 15, is highly expressed in the retina and optic neurons and is important for eye development and visual signaling; mutations in this gene can activate Ras, causing overgrowth of the eye and leading to the development of high myopia [7]. Kim and Baek [8] showed that the association studies and linkage analysis of RASGRF1 gene polymorphisms with high myopia varied widely in different populations, so the association of RASGRF1 gene with myopia needs to be further validated in different populations. Based on this, this study

was conducted to analyze the association between high myopia susceptibility and RASGRF1 gene polymorphism among college students in Zhejiang, with the aim of further clarifying whether RASGRF1 gene is an important pathogenic gene affecting the occurrence of high myopia among college students in this region.

## 2. Materials and Methods

*2.1. General Information.* A stratified whole-group sampling method was used to randomly select three universities from the Zhejiang region from January, 2019, to December, 2021, and all freshman students within five classes from each university who volunteered to participate in this study were randomly selected. A total of 529 college students voluntarily participated in this study, and 218 cases finally met the inclusion and exclusion criteria, including 121 males and 97 females, with an average age of $(20.86 \pm 3.47)$ years.

Inclusion criteria were as follows: aged 18–24 years old; Han nationality; met the diagnostic criteria for myopia [9]; all had binocular onset; no strabismus or amblyopia; no history of ocular trauma or surgery; and patients and their families understood and gave informed consent.

Exclusion criteria were as follows: combined with severe heart, liver, kidney, and other organ dysfunction and other immune-related diseases; combined with systemic acute and chronic diseases affecting vision such as diabetes; combined with glaucoma, cataract, retinal, or optic neuropathy; and combined with malignant tumor or psycho-psychiatric diseases. They were divided into 77 cases (154 eyes) in the high myopia group and 141 cases (282 eyes) in the medium-low myopia group according to the myopia grading standard, and 109 college volunteers without myopia from the same period of medical examination in Zhejiang were included in the control group. Myopia grading standard [10]: high myopia was determined by the equivalent spherical lens of both eyes ≥−8.0 D and the axis length (AL) ≥26 mm; low-moderate myopia was determined by the equivalent spherical lens of both eyes −0.5 D to −7.75 D.

*2.2. Methods*

*2.2.1. Routine Ophthalmic Examination.* All study subjects underwent routine ophthalmic examinations and special instrumental examinations, including ① naked distance and near visual acuity and corrected visual acuity in both eyes. ② Topcon RM8800 computerized optometry was used for binocular computerized optometry, and Topcon comprehensive optometry was used for binocular dilated optometry and trial lenses to check refractive status, determine refractive error, and calculate spherical equivalent (SE). ③ Using Topcon NCT CT-80 tonometer, the intraocular pressure of both eyes was detected. ④ The corneal status, anterior chamber depth, pupil size and shape, and crystal transparency were observed by slit-lamp microscope Topcon SL-1E. ④ After the pupil was dilated fully with the front lens, fundus examination was performed with the front lens under the slit lamp, focusing on the macular area. ⑤ The eye movements of both eyes were examined. ⑥ AL was examined in both eyes using a diagnostic A-ultrasound machine, and each eye was measured three times to obtain the mean value for analysis.

*2.2.2. RASGRF1 Gene SNP Selection.* By searching the literature and gene databases, single nucleotide polymorphisms (SNPs) located in functional regions were selected, and loci with disease susceptibility were selected in combination with the literature, and the minimum allele frequency (MAF) of SNP was screened, and SNP loci with MAF > 10% were selected for function prediction, with priority given to loci with larger MAF values. RASGRF1 and its upstream 100 kb range of ccRE sequences were screened from the gene database, and two SNPs were finally selected for genotyping analysis in combination with existing literature studies. There were 5 inheritance patterns, namely, allelic model ($A_1$ vs $A_2$), homozygous model ($A_1$ $A_1$ vs $A_2A_2$), heterozygous model ($A_1$ $A_1$ vs $A_1A_2$), dominant model ($A_1$ $A_1 + A_1$ $A_2$ vs $A_2A_2$), and implicit model ($A_2A_2$ vs $A_1$ $A_2 + A_2$ $A_2$).

*2.2.3. SNP Genotyping and Sequencing.* SNP typing was performed using a modified multiplex ligase detection reaction (LDR) technique with polymerase chain reaction (PCR) primers designed using Primer3v.0.4.0 and synthesized by Dalian Baocheng Biological Company. Primer sequences: rs939658 Forward 5′-CCACGCAGCATTCAT TCACTTG-3′ and Reverse 5′-CCTCCCCTCATGGGTACC TGTC-3′; rs4778879 Forward 5′-GAAACTGGGCAGGCT GAGAACA-3′ and Reverse 5′-GCTGGTATTCCAAAA CTCCATGTAGAA-3′; and rs8033417 Forward 5′ -TGG AGCAGCTGGGGATGGGG-3′ and reverse 5′-AGCCGA GATGACACCACTGCA-3′. The ABI3730XL sequencer from Applied Biosystems was used to perform the assay, and the typing data were analyzed using GeneMapper software. The typing process ensured that the negative control was band-free, and in addition, 10% of the samples were randomly selected for sequencing and validation of replicate experiments to ensure the reliability of the assay results.

*2.3. Statistical Processing.* SPSS 22.0 statistical software was used for data analysis, and the Hardy–Weinberg equilibrium test of the genotypes of each SNPs locus in the high myopia group and the control group and the moderate-low myopia group was used to determine the population representativeness of the samples by the $\chi^2$ test. Measurement data were expressed by $(\overline{x} \pm s)$ and the differences between groups were expressed by two-sample independent $t$-test; the count data were expressed as rate and the differences between groups were expressed by $\chi^2$ test; the difference was considered statistically significant by two-sided $P < 0.05$.

## 3. Results

*3.1. Basic Situation.* This study included 218 college students in Zhejiang, of which female students were more common, accounting for 59.74%. The grouping according to the degree of myopia could be divided into 77 cases (154 eyes) in the high

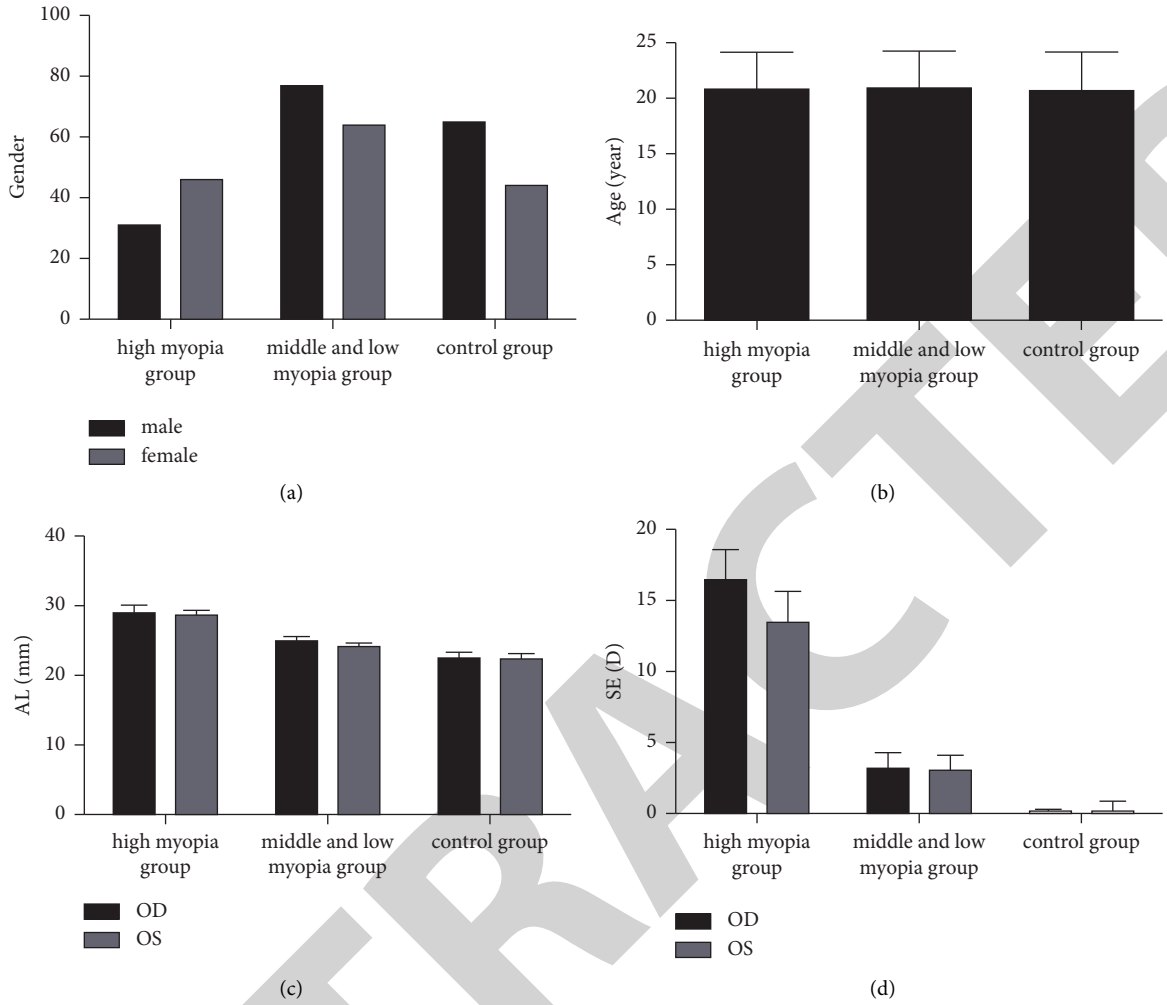


Figure 1: Demographic characteristics among the three groups.

myopia group and 141 cases (282 eyes) in the low to moderate myopia group, and 109 college students with eyes without myopia were selected as a normal control group. Statistical analysis of age (Figure 1(b)) and gender (Figure 1(a)) among the three groups showed that there was no statistically significant difference between the three groups in the above-mentioned aspects of comparison ($P > 0.05$); the axial length (Figure 1(c)) and SE (Figure 1(d)) of each group were different ($P < 0.05$). As shown in Figure 1.

*3.2. Hardy–Weinberg Equilibrium Test and Distribution of RASGRF1 Gene SNP Loci.* The results of the H–W balance test showed that the genotype distribution of SNP loci in the high myopia group, low to moderate myopia group, and control group were not statistically significant ($P > 0.05$) compared with the distribution in the H-W theoretical state. It indicated that the distribution of genotypes in the high myopia group, moderate-low myopia group, and control group had reached a genetic balance, and the population was representative, and further analysis could be carried out as shown in Table 1.

*3.3. Comparison of Genotype Distribution and Allele Frequency of the rs939658 Locus of RASGRF1 Gene among Three Groups.* The genotype frequencies and allele frequencies of the rs939658 locus of the RASGRF1 gene in the high myopia group compared with the low-moderate myopia group and the control group were not statistically significant. ($P > 0.05$), as shown in Table 2.

*3.4. Comparison of Genotype Distribution and Allele Frequency of RASGRF1 Gene rs4778879 Locus among Three Groups.* The genotype frequencies and allele frequencies of the RASGRF1 gene rs4778879 locus in the high myopia group compared with the low-moderate myopia group and the control group were not statistically significant ($P > 0.05$), as shown in Table 3.

*3.5. Comparison of Genotype Distribution and Allele Frequency of RASGRF1 Gene rs8033417 Locus among Three Groups.* The genotype frequency and allele frequency of the rs8033417 locus of the RASGRF1 gene in the high myopia

Table 1: Hardy–Weinberg equilibrium test for SNP loci of RASGRF1 gene.

| SNP ID | *High myopia group (n = 77)* | | *Moderate-low myopia group (n = 141)* | | *Control group (n = 109)* | |
|---|---|---|---|---|---|---|
| | $A_1A_1/A_1A_2/A_2A_2$ | *P* | $A_1A_1/A_1A_2/A_2A_2$ | *P* | $A_1A_1/A_1A_2/A_2A_2$ | *P* |
| rs 939658 | 21/15/41 | 0.257 | 44/23/74 | 0.386 | 34/26/49 | 0.163 |
| rs 4778879 | 17/22/38 | 0.581 | 25/43/73 | 0.356 | 24/39/46 | 0.465 |
| rs 8033417 | 12/16/49 | 0.096 | 32/67/42 | 0.065 | 23/47/39 | 0.291 |

$A_1$ means mutant type, $A_2$ means wild type, $A_1A_1$ means mutant homozygous type, $A_1A_2$ means heterozygous genotype, and $A_2A_2$ means wild type homozygous type.

Table 2: Comparison of genotype distribution and allele frequency of the rs939658 locus of RASGRF1 gene among three groups.

| Genotype/alleles | | High myopia group ($n = 77$) | Moderate-low myopia group ($n = 141$) | Control group ($n = 109$) | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|
| Genotype | GG | 21 | 44 | 34 | 2.974 | 0.562 |
| | GA | 15 | 23 | 26 | | |
| | AA | 41 | 74 | 49 | | |
| Alleles | G | 57 | 111 | 94 | 1.502 | 0.472 |
| | A | 97 | 171 | 124 | | |

Table 3: Comparison of genotype distribution and allele frequency of RASGRF1 gene rs4778879 locus among three groups.

| Genotype/alleles | | High myopia group ($n = 77$) | Moderate-low myopia group ($n = 141$) | Control group ($n = 109$) | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|
| Genotype | GG | 17 | 25 | 24 | 2.820 | 0.588 |
| | GA | 22 | 43 | 39 | | |
| | AA | 38 | 73 | 46 | | |
| Alleles | G | 56 | 93 | 87 | 2.567 | 0.277 |
| | A | 98 | 189 | 131 | | |

Table 4: Comparison of genotype distribution and allele frequency of RASGRF1 gene rs8033417 locus among three groups.

| Genotype/alleles | | High myopia group ($n = 77$) | Moderate-low myopia group ($n = 141$) | Control group ($n = 109$) | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|
| Genotype | TT | 12 | 32 | 23 | 25.684 | <0.001 |
| | CT | 16 | 67 | 47 | | |
| | CC | 49 | 42 | 39 | | |
| Alleles | T | 40 | 131 | 93 | 18.070 | <0.001 |
| | C | 114 | 151 | 125 | | |

group compared with the low to moderate myopia group and the control group were statistically significant ($P < 0.05$), as shown in Table 4.

## 4. Discussion

High myopia is an eye disease caused by the interaction of genetic, environmental, and individual differences. In China, the prevalence of high myopia among college-level students accounts for about 20% of the number of myopic college students, and the accompanying complications such as chorioretinopathy and glaucoma are common causes of vision loss and even blindness in the naked eyes of adolescents [10, 11]. With the application of molecular genetics and genotyping technology in clinical medical research, the study of genetic susceptibility and pathogenesis of myopia has entered a new phase of exploration. The application of molecular genetic methods to study and analyze the genetic factors and susceptibility genes of high myopia provides a molecular genetic basis for clinical development of high myopia prevention and treatment programs [12]. Various gene sequence-mediated signaling pathways have been found to be involved in the development of myopia, among which genetic variants at the RASGRF1 locus have been associated with visual function and several of its SNP loci may be closely associated with high myopia [13], but analysis of the correlation between RASGRF1 gene polymorphisms and susceptibility to high myopia has been less frequently reported.

This study considered college students in Zhejiang as the research subject and screened out the genes by searching the relevant literature in NCBI PubMed; we screened the genes and SNP loci that might be associated with high myopia and finally identified rs939658, rs4778879, and rs8033417 loci on RASGRF1 gene, and analyzed their relationship with the susceptibility to high myopia of college students in this

region. The Hardy–Weinberg equilibrium test showed that the genotype distributions of SNP loci in the three groups were not significantly different from those in the H–W theory state, indicating that the genotype distributions in all three groups reached genetic equilibrium and the populations were representative. In this study, the genotype frequency and allele frequency of SNP rs939658 and rs4778879 of the RASGRF1 gene between the myopia group and the control group were not significantly different, but the genotype frequencies and allele frequencies of the rs8033417 locus of the RASGRF1 gene were significantly different between the two groups, in which the risk of high myopia was significantly higher in C allele carriers than in T allele carriers, indicating that the C allele of the rs8033417 locus was associated with myopia. The RASGRF1 gene, a protein-coding gene localized at 15q25.1, is highly expressed in neurons and the retina, and its expression is regulated by retinol and muscarinic receptors and plays an important role in retinal function and enhanced visual process [14, 15]. Defects in the RASGRF1 gene cause impaired regulation of retinol and muscarinic receptors, resulting in impaired visual development and increased risk of high myopia [16, 17]. Kunceviciene et al. [18] found that the RASGRF1 gene was associated with the heritability of myopia, in which the rs8027411GT type carriers were 2.7-fold more likely to develop myopia, similar to the results of the present study, suggesting that the focus should be on the rs8033417 locus C carriers and timely and effective preventive measures should be given to slow down the development of myopia.

In this study, we further analyzed the genotype distribution and allele frequency of RASGRF1 gene polymorphism SNP loci in patients with different degrees of myopia, and the results showed that there was no significant difference in the genotype and allele frequencies of SNPs rs939658 and rs4778879 in the RASGRF1 gene in the high myopia group and low to moderate myopia group, while the genotype frequencies and allele frequencies of rs8033417 loci of RASGRF1 gene in both groups were significantly different. This suggests that the genetic susceptibility to high myopia among college students in Zhejiang is not significantly associated with the rs939658 and rs4778879 loci of the RASGRF1 gene, while the rs8033417 locus may be a risk gene for high myopia among college students in this region while carrying the C allele, and college students carrying the C allele have an increased risk of myopia. However, no evidence was found in the study of Fernandez-Medarde and Santos [19] to support the association of high myopia with the rs8033417 locus of the RASGRF1 gene, and analysis of the reasons for this may be related to the different single nucleotide polymorphism loci selected in this study, and differences in the inclusion criteria for high myopia can also cause changes in gene frequency [20]. The study of SNPs and genetic susceptibility of specific myopia groups is important for understanding the molecular genetic mechanisms underlying the development of high myopia in different populations in various regions. The disadvantage of this study is that the number of samples selected is relatively limited, and the included research subjects are all Han college students in the region. Considering that high myopia is a complex process involving multiple genes and pathways, the subsequent experimental validation of the function of the rs8033417 locus of the RASGRF1 gene is still needed to increase the sample size [21].

In conclusion, this study confirmed that the high myopia susceptibility of college students in Zhejiang was associated with the rs8033417 locus of the RASGRF1 gene and that college students carrying the C allele were at increased risk of myopia. In this study, we identified the rs8033417 locus variation in the RASGRF1 gene in a population of college students with high myopia in Zhejiang, which provided a reliable molecular genetic basis for the later gene diagnosis and treatment and prevention of high myopia for college students in the region.

## Data Availability

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

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Acknowledgments

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*Retraction*

# Retracted: Identification of Differentially Methylated Genes Associated with Clear Cell Renal Cell Carcinoma and Their Prognostic Values

**Journal of Environmental and Public Health**

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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.

## References

[1] B. Wan, Y. Yang, and Z. Zhang, "Identification of Differentially Methylated Genes Associated with Clear Cell Renal Cell Carcinoma and Their Prognostic Values," *Journal of Environmental and Public Health*, vol. 2023, Article ID 8405945, 10 pages, 2023.

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*Research Article*

# Identification of Differentially Methylated Genes Associated with Clear Cell Renal Cell Carcinoma and Their Prognostic Values

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*Objective*. Renal cell carcinoma (RCC) is a heterogeneous disease comprising histologically defined subtypes among which clear cell RCC (ccRCC) accounts for 70% of all RCC cases. DNA methylation constitutes a main part of the molecular mechanism of cancer evolution and prognosis. In this study, we aim to identify differentially methylated genes related to ccRCC and their prognostic values. *Methods*. The GSE168845 dataset was downloaded from the Gene Expression Omnibus (GEO) database to identify differentially expressed genes (DEGs) between ccRCC tissues and paired tumor-free kidney tissues. DEGs were submitted to public databases for functional and pathway enrichment analysis, protein-protein interaction (PPI) analysis, promoter methylation analysis, and survival correlation analysis. *Results*. In the setting of $|\log2FC| \geq 2$ and adjusted $p$ value <0.05 during differential expression analysis of the GSE168845 dataset, 1659 DEGs between ccRCC tissues and paired tumor-free kidney tissues were sorted out. The most enriched pathways were "*T* cell activation" and "cytokine-cytokine receptor interaction." After PPI analysis, 22 hub genes related to ccRCC stood out, among which CD4, PTPRC, ITGB2, TYROBP, BIRC5, and ITGAM exhibited higher methylation levels, and BUB1B, CENPF, KIF2C, and MELK exhibited lower methylation levels in ccRCC tissues compared with paired tumor-free kidney tissues. Among these differentially methylated genes, TYROBP, BIRC5, BUB1B, CENPF, and MELK were significantly correlated with the survival of ccRCC patients ($p < 0.001$). *Conclusion*. Our study indicates the DNA methylation of TYROBP, BIRC5, BUB1B, CENPF, and MELK may be promising results for the prognosis of ccRCC.

## 1. Introduction

Cancer originating in the kidney afflicts more than 400,000 individuals each year and becomes the 13th most common cancer across the world [1]. The incidence rate of kidney cancer is raising with age, and a peak of incidence occurred at approximately 75 years of age [2]. Men have a 2-fold higher incidence of kidney cancer than women. Smoking, obesity, and high blood pressure are deemed as the main risk factors of kidney cancer, all of which are avoidable to reduce the risk of developing kidney cancer [3]. Renal cell carcinoma (RCC) represents over 80% of all kidney tumors and possesses several subtypes with unique characteristics, such as clear cell (ccRCC), papillary (pRCC), and chromophobe (chRCC), among which ccRCC is the most common subtype and accounts for 70% of all RCC cases [4]. The treatment strategies of metastatic RCC have evolved over the past two decades, switching from vascular endothelial growth factor-targeted therapies to immune-checkpoint inhibitors and novel combination strategies [5, 6]. However, many metastatic patients treated with mTOR and TK inhibitors develop multidrug resistance, showing poor 5-year survival rates [7]. In light of steady progress in dissecting the molecular features of ccRCC development, personalized care according to the genetic and molecular features of an individual and their tumor should be expanded to improve patient outcomes [8].

DNA methylation represents a pertinent epigenetic modification of the human genome and is also considered as a critical disease-specific characteristic in many cancers, unmasking the cell-of-origin of cancer and predicting the outcome [9]. DNA methylation alternations occurring in cancer commonly follow two principal axes. One is global hypomethylation inducing genome stability as well as retroviral elements. Another is hypermethylation within the

promoter regions of a broad range of tumor suppressor genes in turn silencing their transcriptions [10]. Unlike static genetic risk estimates, DNA methylation data offer a valuable source for biomarker development due to DNA methylation varying dynamically along with many exogenous and endogenous factors [11]. DNA hypermethylation or hypomethylation exerts a different influence on ccRCC prognosis, and the methylation extent of key methylation sites leads to gene expression changes [12]. However, previous evidence to prove the roles of methylation-driven genes in ccRCC is limited. In this study, we analyzed mRNA data from public microarray datasets and performed database analysis of methylation-driven genes in ccRCC, in a bid to understand the carcinogenesis mechanism related with DNA methylation and to ulteriorly developing novel therapeutic targets for ccRCC.

## 2. Materials and Methods

*2.1. Analysis of Microarray Data.* The GSE168845 dataset was downloaded from the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/) database, consisted of the microarray-based transcriptome of 4 ccRCC tissue samples (labeled as GSM5171251, GSM5171253, GSM5171255, and GSM5171257) and paired tumor-free kidney tissue samples (labeled as GSM5171252, GSM5171254, GSM5171256, and GSM5171258), and was processed on the GPL21185 platform (public on March 14, 2021). The corresponding platform annotation information file was obtained from the GEO official website. The ccRCC tissue samples of patients were compared with paired tumor-free kidney tissue samples to identify the differentially expressed genes (DEGs) which should fulfill the screening criteria of $|\log_2$ fold change (FC)$| \geq 2$ (adjusted $p$ value $<0.05$). Differential gene analysis was performed using the limma Bioconductor *R* package, and the $p$ value was corrected by using the Benjamini–Hochberg false discovery rate (FDR). The volcano maps and heatmaps for all DEGs and representative DEGs were generated using the base package in the *R* software.

*2.2. Functional and Pathway Enrichment Analysis.* The clusterProfiler package in the R software was employed to run GO and KEGG pathway enrichment analysis based on DEGs between ccRCC tissues and paired tumor-free kidney tissues, in a bid to investigate the biological functions and related pathways of DEGs. Result interpretation for GO analysis primarily refers to the three domains: biologic process (BP), cellular component (CC), and molecular function (MF). The KEGG analysis offers a systematic analysis of gene functions and genomic information in relation to gene signal transduction and disease pathways. A $q$ value (adjusted $p$ value) less than 0.5 denoted significantly enriched GO terms and KEGG-defined pathways. Enrichment results were visualized using the ggplot2 R package. The top 10 GO terms for each domain and the top 20 KEGG pathways were visualized as bubble plots using the ggplot2 R package.

*2.3. Protein-Protein Interaction (PPI) Analysis and Identification of Hub Genes.* The DEGs between ccRCC tissues and paired tumor-free kidney tissues were subject to the prediction of PPIs by using the STRING (https://string-db.org/). The PPI network was constructed using the Cytoscape software (v3.9.0), with a filter condition of 0.7. The CytoHubba plugin in the Cytoscape was applied to calculate the degree values of nodes in the PPI network, and a higher degree value reflects more central genes in the network's topology. Candidate hub genes were selected with a filter condition of degree value $\geq 50$.

*2.4. Methylation Levels of Hub Genes in ccRCC.* The candidate hub genes were imported into the UALCAN database (https://ualcan.path.uab.edu/) which is a comprehensive, user-friendly, and interactive database to evaluate epigenetic regulation of gene expression by promoter methylation.

*2.5. Survival Correlation Analysis.* Differentially methylated hub genes between ccRCC tissues and paired tumor-free kidney tissues were mapped into the Kaplan–Meier plotter which can evaluate the correlation between gene expressions and survival in more than 30 thousand samples from 21 tumor types using sources from the GEO, EGA, and TCGA.

## 3. Results

*3.1. Identification of DEGs Related to ccRCC.* When we set the screening criteria as $|\log_2 FC| \geq 2$ and adjusted $p$ value $<0.05$ during differential expression analysis of the GSE168845 dataset, a total of 1659 DEGs (Figure 1(a)) between ccRCC tissues and paired tumor-free kidney tissues were sorted out, including 776 upregulated genes and 883 downregulated genes in ccRCC tissues compared with paired tumor-free kidney tissues. Figure 1(b) shows representative 50 DEGs among 1659 DEGs between ccRCC tissues and paired tumor-free kidney tissues.

*3.2. Enrichment Analysis of DEGs Related to ccRCC.* We then submitted 1659 DEGs related to ccRCC to undergo GO annotation and KEGG pathway analyses to characterize the main functional pathways associated with ccRCC. As the results of GO analysis denoted, a total of 910 GO terms were significantly enriched ($p < 0.05$), consisting of 786 terms referring to the BP domain, 43 terms referring to the CC domain, and 81 terms referring to the MF domain. The top 10 GO terms for each domain are presented in Figure 2(a). The most enriched GO terms at the BP domain were "*T* cell activation" (enriched by 100 DEGs), followed by "regulation of *T* cell activation" (enriched by 91 DEGs) and then "negative regulation of immune system process" (enriched by 83 DEGs). The most enriched GO terms at the CC domain were "external side of plasma membrane" (enriched by 75 DEGs) and "apical part of cell" (enriched by 71 DEGs). The most enriched GO terms in the MF domain were "channel activity" (enriched by 58 DEGs) and "passive transmembrane transporter activity" (enriched by 58 DEGs). As the results of the

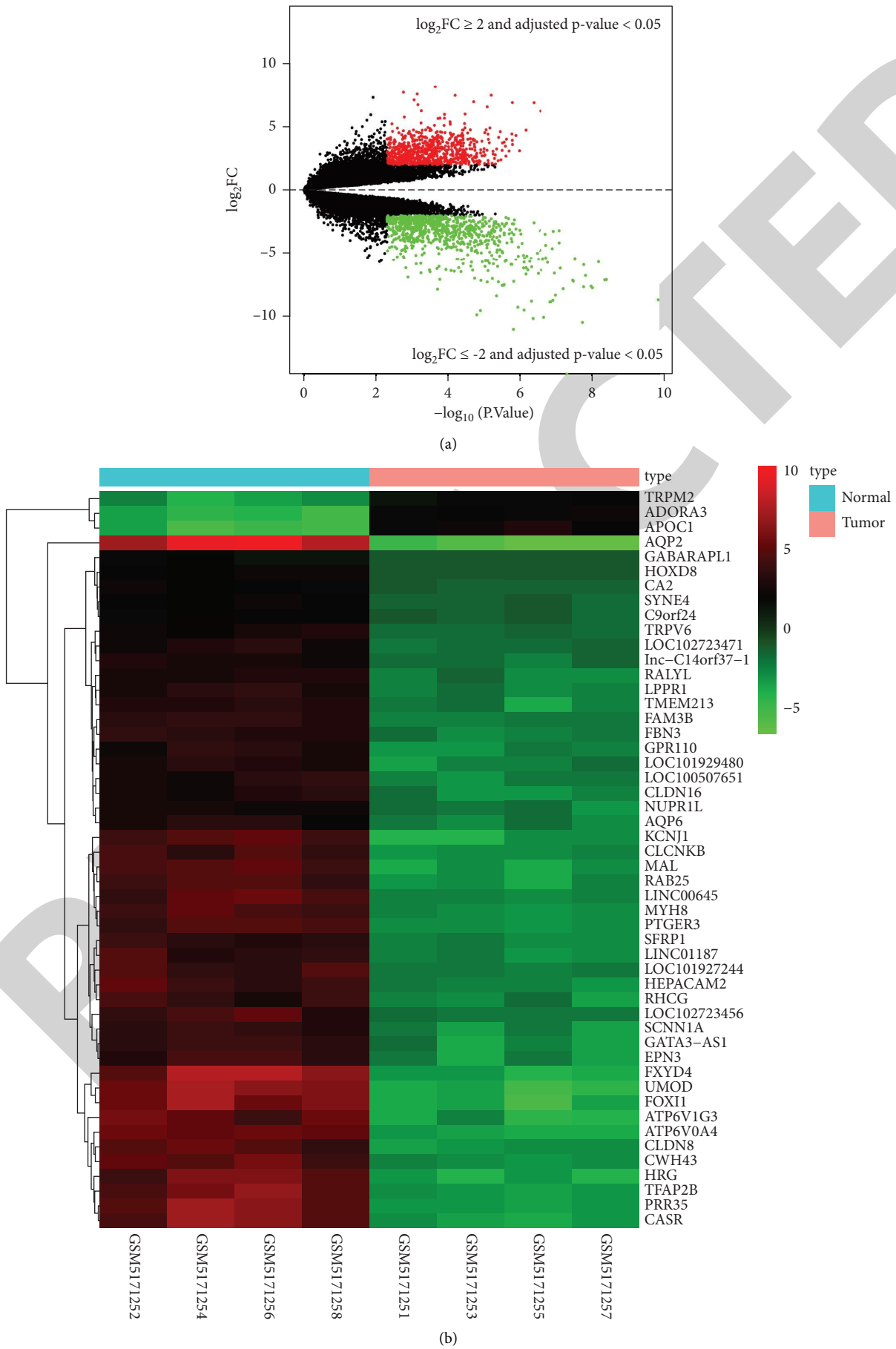
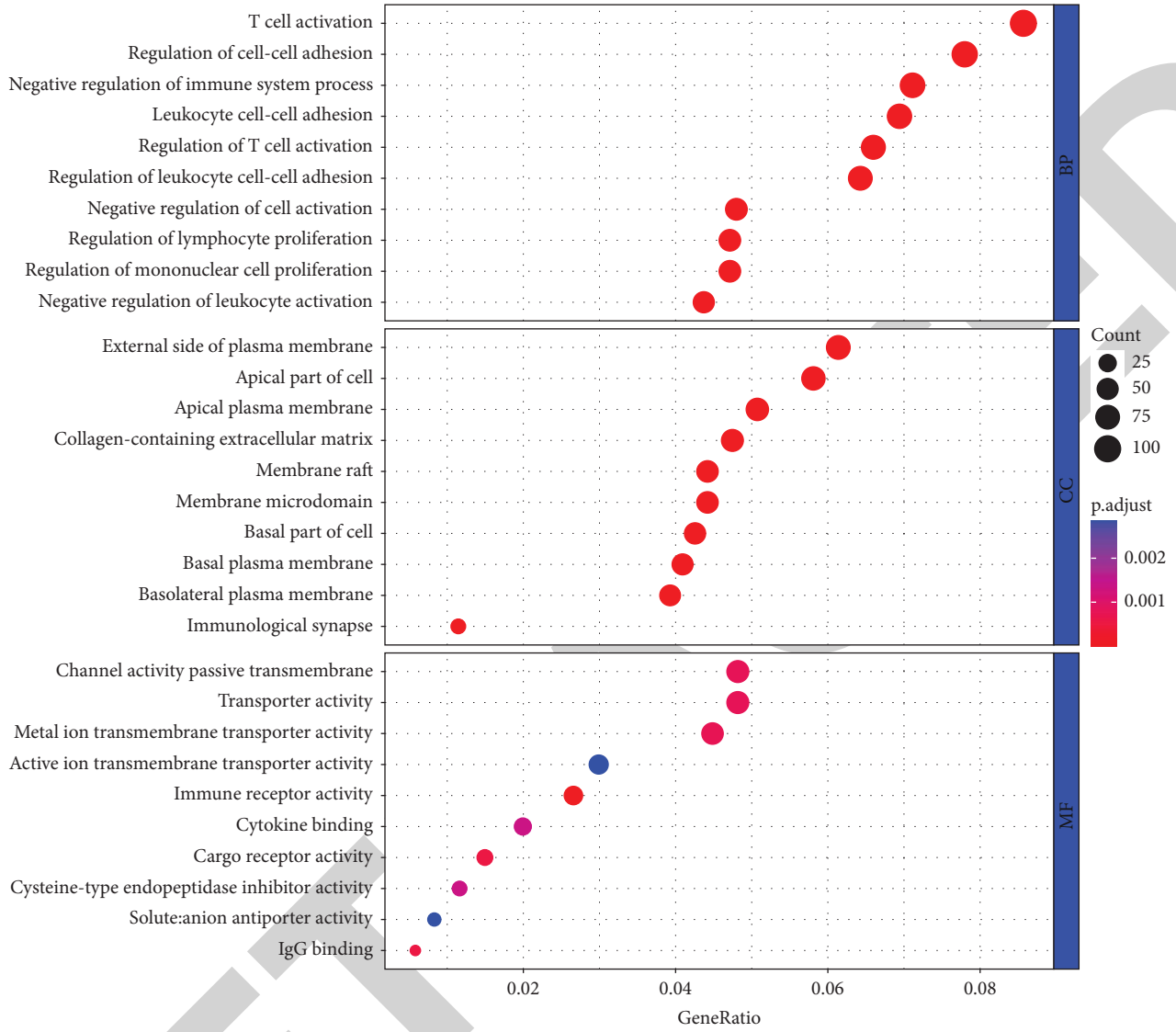
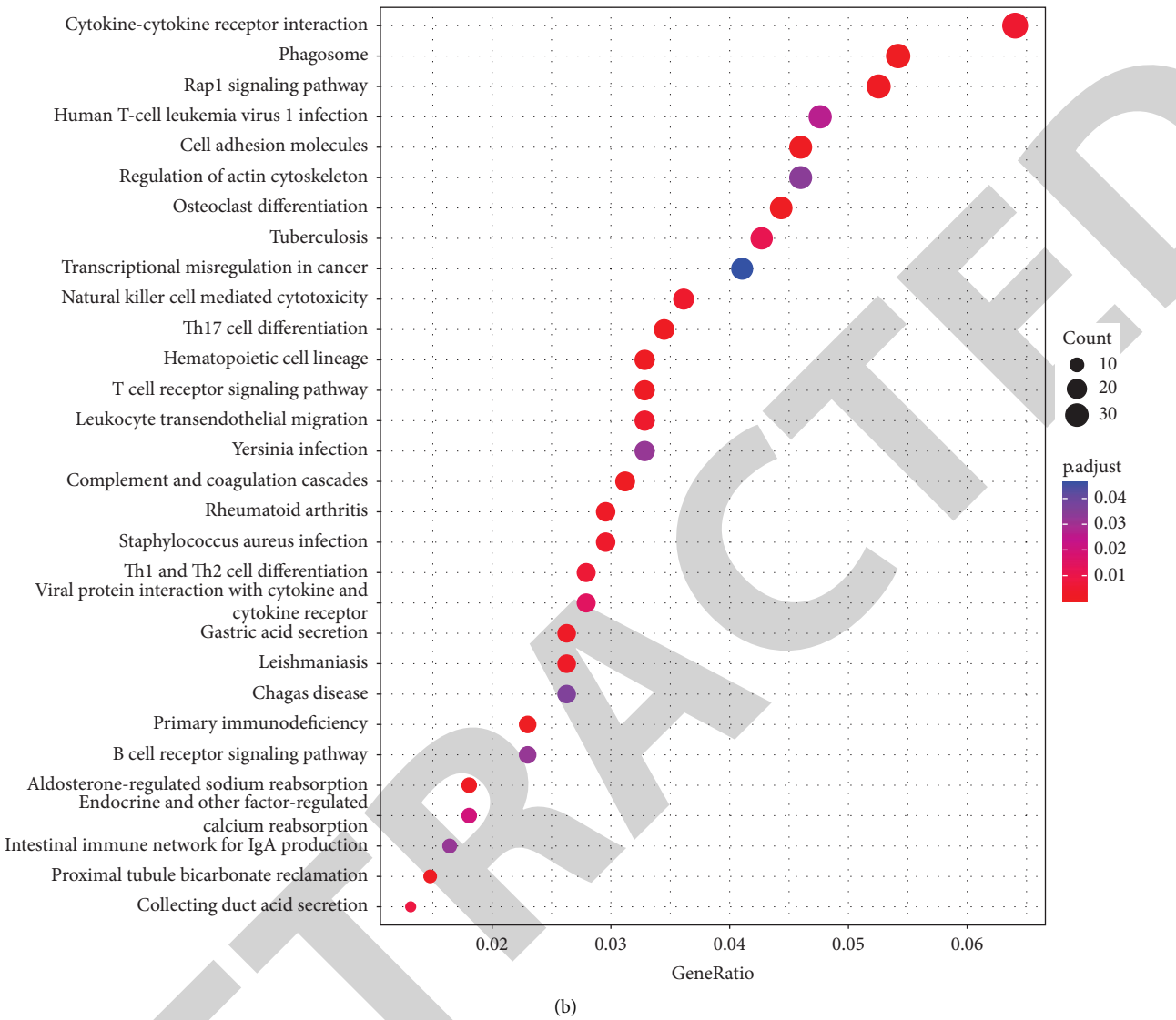



Figure 1: The volcano map (a) and heatmap (b) showing a total of 1659 DEGs (776 upregulated genes and 883 downregulated genes) and representative 50 DEGs between ccRCC tissues and paired tumor-free kidney tissues.




(a)

Figure 2: Continued.




(b)

Figure 2: The bubble plots showing the top 10 GO terms at the BP, CC, and MF domains (a) and the top 20 KEGG-defined pathways (b) significantly enriched by DEGs between ccRCC tissues and paired tumor-free kidney tissues.

KEGG pathway were shown, a total of 32 KEGG pathways were significantly enriched ($p < 0.05$). The most enriched KEGG-defined pathways were "cytokine-cytokine receptor interaction" (enriched by 39 DEGs) and "phagosome" (enriched by 33 DEGs). The top 20 KEGG-defined pathways enriched by DEGs are presented in Figure 2(b).

*3.3. Identification of Hub Genes Related to ccRCC.* With the aid of the STRING database, 1659 DEGs related to ccRCC were submitted for PPI analysis. The PPI network was made, comprising 298 nodes with 3349 edges. The most central gene in the PPI network was CD4 with a degree value of 86 (Figure 3). There were 22 genes with degree values not less than 50 and they were deemed as hub genes related to ccRCC. These 22 DEGs were found to be upregulated in ccRCC tissues compared with paired tumor-free kidney tissues (Table 1).

*3.4. Methylation Levels of Hub Genes in ccRCC.* With the aid of the UALCAN database, 22 DEGs related to ccRCC were submitted for differential methylation analysis. CD4, PTPRC, CCNA2, CD8A, BUB1, ASPM, BUB1B, KIF20A, CENPF, DLGAP5, ITGB2, KIF2C, TYROBP, BIRC5, CEP55, ITGAM, MELK, NUSAP1, and TPX2 were found to differentially methylated genes between ccRCC tissues and paired tumor-free kidney tissues ($p < 0.05$). The DNA methylation level was indicated by the $\beta$ value ranging from 0 (unmethylated) to 1 (fully methylated). Hypermethylation was deemed as $\beta$ value cut-off ($\beta$ value: 0.7–0.5) including CD4, PTPRC, ITGB2, TYROBP, BIRC5, and ITGAM, and all exhibited higher methylation levels in ccRCC tissues compared with paired tumor-free kidney tissues (Figure 4). Hypomethylation was deemed as $\beta$ value cut-off ($\beta$ value: 0.3–0.25) including CCNA2, CD8A, BUB1, ASPM, BUB1B, KIF20A, CENPF, DLGAP5, KIF2C, CEP55, MELK, and NUSAP1, and TPX2. BUB1B, CENPF, KIF2C, and MELK

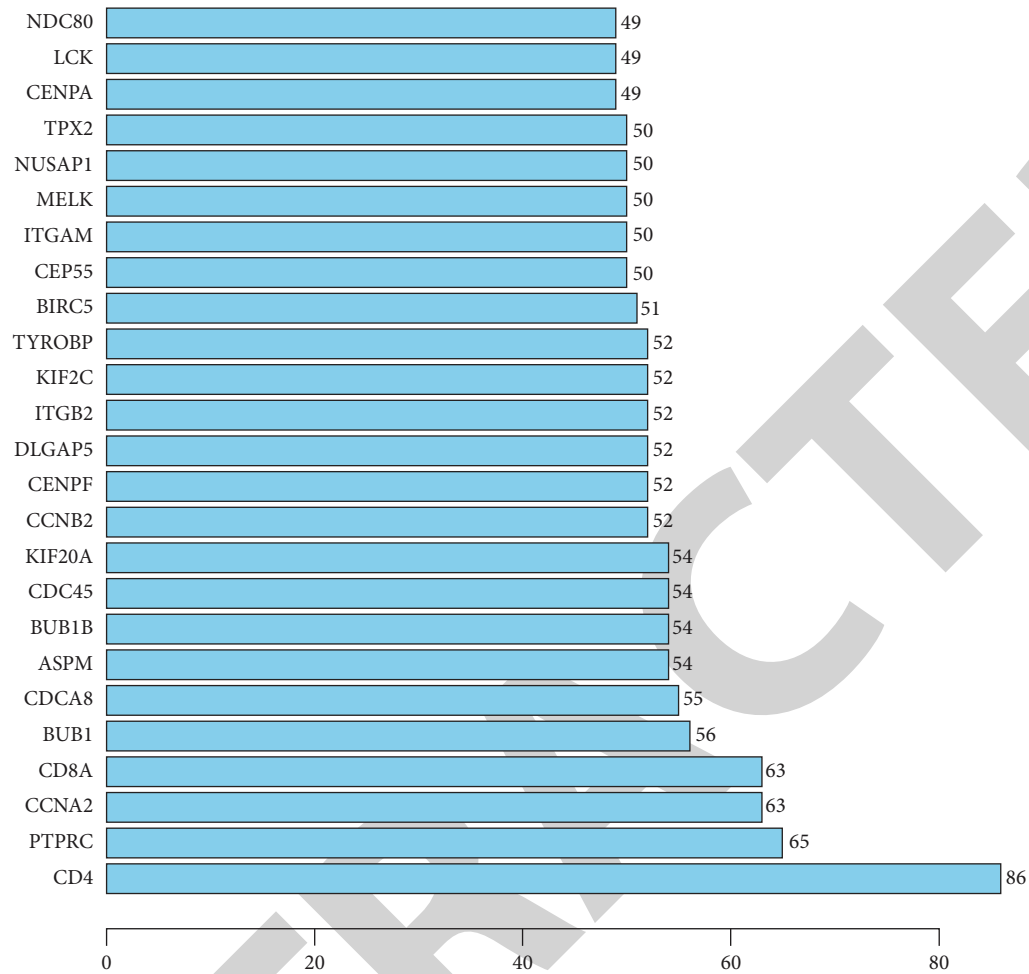



Figure 3: The PPI network containing 22 genes with degree values not less than 50 which were deemed as hub genes related to ccRCC.

exhibited lower methylation levels in ccRCC tissues compared with paired tumor-free kidney tissues (Figure 4).

*3.5. Survival Correlation Analysis of Hub Genes with ccRCC.* Accordingly, we imported CD4, PTPRC, ITGB2, TYROBP, BIRC5, ITGAM, BUB1B, CENPF, KIF2C, and MELK into the Kaplan–Meier plotter to evaluate the correlations between these differentially methylated genes and ccRCC patient survival. Results of survival analysis, it was found that TYROBP, BIRC5, BUB1B, CENPF, and MELK were significantly correlated with the survival of ccRCC patients (Figure 5, $p < 0.001$).

## 4. Discussion

Abnormal DNA methylation usually occurs during early carcinogenesis, being one of the hallmarks of some human cancers, including ccRCC [13]. DNA methylation profiling may reveal important new therapeutic targets for cancer diagnosis and prognosis prediction. In this study, we performed differential expression analysis using the expression profile of the GSE168845 dataset and obtained 1659 DEGs between ccRCC tissues and paired tumor-free kidney tissues. After PPI analysis, 22 hub genes related to ccRCC stood out, among which CD4, PTPRC, CCNA2, CD8A, BUB1, ASPM, BUB1B, KIF20A, CENPF, DLGAP5, ITGB2, KIF2C, TYROBP, BIRC5, CEP55, ITGAM, MELK, NUSAP1, and TPX2 were found to differentially methylated genes between ccRCC tissues and paired tumor-free kidney tissues. Among these differentially methylated genes, TYROBP, BIRC5, BUB1B, CENPF, and MELK were upregulated in ccRCC tissues compared with paired tumor-free kidney tissues significantly correlated with the survival of ccRCC patients.

TYRO protein tyrosine kinase-binding protein (TYROBP), also named as killer cell activating receptor-associated protein (KARAP) or DNAX activating protein of 12 kDa (DAP12), is an immunoreceptor tyrosine-based activation motif (ITAM) that is mainly expressed in natural killer cells as well as various myeloid cells [14]. As an ITAM-bearing transmembrane adaptor, TYROBP can bind to several activating receptors recognizing MHC class I molecules and regulate various biological functions [15]. As shown by previous animal studies, when the mice underwent TYROBP knockout, NKG2D, a DAP12-dependent NK cell receptor, was found to affect the antitumoral activity and modulate NK cell function, thus mainly engaging in the recognition and elimination of tumor cells [16]. Concurring with our findings [17], TYROBP was considered as a

Table 1: A total of 22 genes with degree values not less than 50 were deemed as hub genes related to ccRCC, and they were found to be upregulated in ccRCC tissues compared with paired tumor-free kidney tissues.

| Gene symbol | $Log_2\|FC\|$ | Adjusted $p$ value |
|---|---|---|
| CD8A | 2.838996022 | 0.003249294 |
| CEP55 | 4.192570999 | 0.003452655 |
| CENPF | 3.621102901 | 0.0038734 |
| TYROBP | 4.115558646 | 0.004355457 |
| BIRC5 | 3.965466193 | 0.005350871 |
| TPX2 | 3.652378883 | 0.0072194 |
| CDC45 | 3.447878167 | 0.00783151 |
| NUSAP1 | 3.144174107 | 0.008370445 |
| DLGAP5 | 4.058408375 | 0.008892258 |
| ITGB2 | 2.782041562 | 0.009088639 |
| MELK | 4.830346117 | 0.010130527 |
| BUB1 | 4.668321017 | 0.010191001 |
| CCNB2 | 3.86197456 | 0.010273159 |
| CCNA2 | 3.008112629 | 0.011503765 |
| CD4 | 2.229504475 | 0.013388999 |
| KIF20A | 4.525246826 | 0.014945035 |
| PTPRC | 2.480557811 | 0.01900056 |
| CDCA8 | 2.135758288 | 0.019032544 |
| ASPM | 3.343095344 | 0.023214685 |
| ITGAM | 2.311626971 | 0.024122534 |
| BUB1B | 2.096177963 | 0.026408703 |
| KIF2C | 2.473022677 | 0.033689531 |

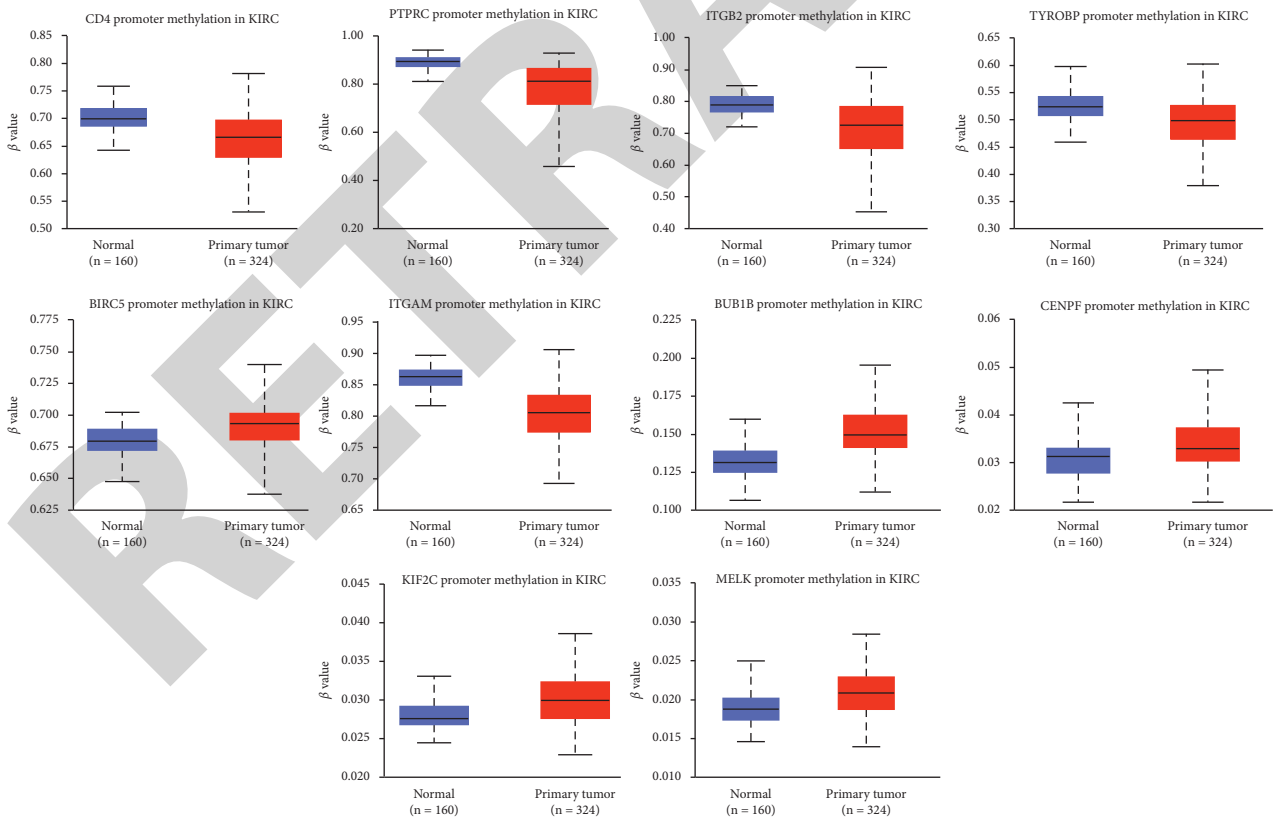



Figure 4: The UALCAN database analysis of methylation levels of hub genes in ccRCC tissue samples ($n = 324$) compared with normal kidney tissue samples ($n = 160$) derived from TCGA.

potential prognostic factor of ccRCC. BIRC5 is also recognized as surviving, which is an important member of the protein family to inhibit cell apoptosis in human cancers but is not expressed in normal differentiated tissues. When highly expressed, BIRC5 allows cancer cells to resist apoptotic checkpoints and anticancer agents [18]. Xu et al. also

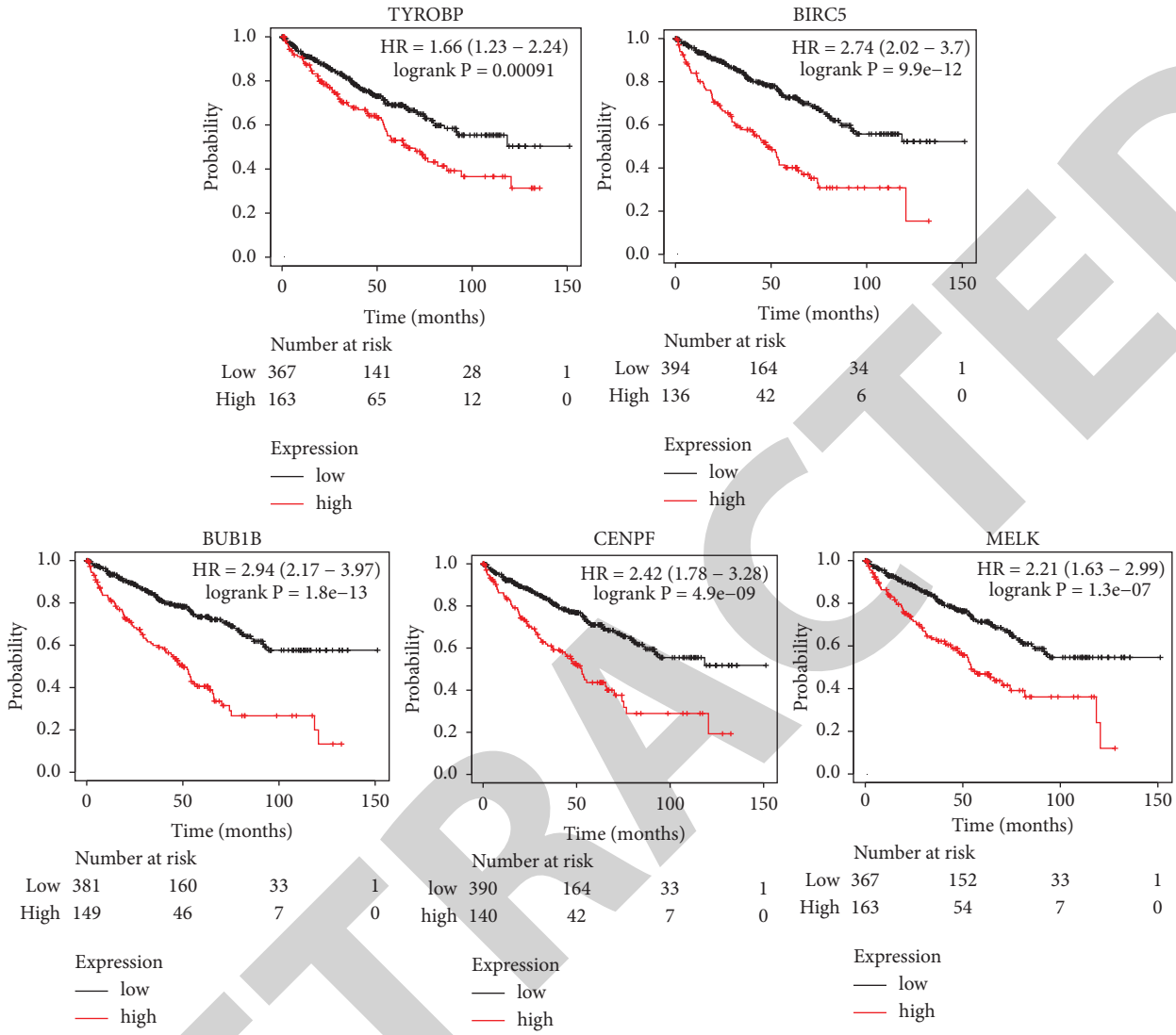



Figure 5: The Kaplan–Meier plotter analysis of the correlations between differentially methylated genes and ccRCC patient survival ($n = 530$).

demonstrated BICR5 is related with the development of ccRCC, which is consistent with our results [19]. BUB1 mitotic checkpoint serine/threonine kinase B (BUB1B) has the ability to modulate the spindle assembly checkpoint (SAC) family [20]. High expression of BUB1B may be correlated with intrachromosomal instability and thus contribute to the tumorigenesis and development of many human tumors, including breast cancer, prostate cancer, and brain tumors [21–24]. Sekino et al. demonstrated that BUB1B could be served as an independent prognostic marker of RCC patients and related with the expressions of CD44, p53, and PD-L1 [25]. Centromere-associated protein E (CENPE) is one of the mitosis-associated genes that are dysregulated in many types of cancers, such as acute myeloid leukemia [26], cutaneous melanoma [27], adrenocortical carcinoma [28], and ccRCC [29]. Maternal embryonic leucine zipper kinase (MELK) is a key component of the sucrose-nonfermenting/AMP-activated protein kinase family belonging to serine-threonine protein kinases that are implicated in many cellular processes [30, 31]. MELK shows a high abundance in multiple human tumors, including gastric tumor [31], Wilms' tumor [32], and breast tumor [33], as well as colorectal cancer [34], and its high abundance is linked to unfavorable prognoses in patients. Zhang et al. found that MELK phosphorylated an inhibitory subunit of mTORC1 PRAS40 and then activated the mTORC1, thus promoting the malignant phenotype of ccRCC cells [35].

In conclusion, our study indicates the DNA methylation of TYROBP, BIRC5, BUB1B, CENPF, and MELK may be implicated in the carcinogenesis or progression of ccRCC and provide promising results for the prognosis of ccRCC. The present study also provides the carcinogenesis mechanism related with DNA methylation and to ulteriorly developing novel therapeutic targets for ccRCC. However, PCR detection of TYROBP, BIRC5, BUB1B, CENPF, and MELK in clinical ccRCC samples should be available in future work. Methylation-related mechanisms are complex, and the specific mechanisms, such as DNA methylation or histone

methylation, responsible for DNA methylation of TYROBP, BIRC5, BUB1B, CENPF, and MELK are still needed to be further investigated through methylation-specific PCR detection of clinical ccRCC samples.

## Data Availability

The GSE168845 datasets were downloaded from the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo) that is a public database. Other data used to support the findings of this study are included within the article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Volume 2023, Article ID 9753869, 1 page
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*Retraction*

# Retracted: The Role of C-Reactive Protein in the Prognosis of Prostate Cancer: A Meta-Analysis

**Journal of Environmental and Public Health**

Received 12 December 2023; Accepted 12 December 2023; Published 13 December 2023



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

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

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

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

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

## References

[1] T. Liu and L. Zhuo, "The Role of C-Reactive Protein in the Prognosis of Prostate Cancer: A Meta-Analysis," *Journal of Environmental and Public Health*, vol. 2023, Article ID 6222324, 8 pages, 2023.

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Journal of Environmental and Public Health
Volume 2023, Article ID 6222324, 8 pages
https://doi.org/10.1155/2023/6222324



*Research Article*

# The Role of C-Reactive Protein in the Prognosis of Prostate Cancer: A Meta-Analysis

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*Objective*. To investigate the role of C-reactive protein (CRP) in the prognosis of prostate cancer (PCa). *Methods*. The studies related to C-reactive protein and prostate cancer were searched by computer, including PubMed and Web of Science. The retrieval time was from the establishment of the database to August 2022. QUADAS score was employed to assess the studies' quality, funnel plot was employed to analyze the bias of the included studies, and RevMan and STATA statistical software programs were used to draw forest maps to represent the analysis results. *Results*. In the initial examination, 432 articles were obtained. After removing the duplicate articles, reading the abstract and theme, and then reading the full text, 12 articles finally met the inclusion criteria. The results revealed that serum C-reactive protein (CRP) levels were associated with overall survival (OS) in patients with PCa (OR = 1.47 [1.19, 1.82], $P < 0.05$), and patients with high CRP levels had an increased risk of developing prostate cancer (HR = 0.26, 95% CI: 0.23, 0.29). However, there was no obvious difference in circulating CRP levels between patients with prostate cancer and healthy controls ($P > 0.05$). *Conclusions*. CRP levels are associated with PCa patients′ OS. High CRP levels have an elevated incidence of PCa, but there was no obvious distinction in circulating CRP levels between patients with prostate cancer and healthy controls. Therefore, C-reactive protein has certain reference value for judging the prognosis of prostate cancer.

## 1. Introduction

Prostate cancer (PCa) is a common malignant tumor of the male prostate epithelium [1]. According to statistics, the incidence of PCa increases year by year, which has become one of the major malignant tumor diseases threatening men's health [2]. Due to the lack of typical clinical manifestations, once discovered, most patients are in the advanced stage, and the prognosis is poor [3]. Therefore, finding sensitive markers for early screening of the disease has become the focus of clinical research [4]. C-reactive protein (CRP) is an acute phase-reaction protein synthesized by liver cells when the body suffers from injury or pathogenic microorganism infection [5]. CRP concentration in blood of healthy people is very low. However, when inflammation and injury occur, CRP in plasma rises sharply to play a role in activating complement and strengthening the phagocytosis of phagocytes, which can clear the pathogenic microorganisms invading the body and the damaged, necrotic, and apoptotic histiocytes. These are typical nonspecific but sensitive indicators of inflammation [6].

It has been reported that a variety of inflammatory mediators are involved in the development of malignant tumor diseases, among which IL-6 is considered to be the most core inflammatory factor connecting inflammation and tumor [7]. IL-6 plays a vital role in promoting tumor angiogenesis and increases the production of acute phase proteins, leading to tumor staging and poor prognosis [8]. However, CRP is mainly synthesized by hepatocytes under the regulation and induction of IL-1, IL-6, and tumor necrosis factor, which can characterize the content of IL-6 and indirectly reflect the level of local inflammatory activity of tumors [9]. Clinically, the elevated CRP concentrations are found in tissue injury, infection, arterial hypertension and atherosclerosis, diabetes, obesity, and malignant tumor, as well as a series of other acute and chronic inflammatory

diseases [10]. Our team has been investigating the relationship between CRP and malignant tumor. Studies have pointed out that CRP plays an essential role in the occurrence and development of malignant tumors such as PCa, breast cancer, renal cell carcinoma, and gastrointestinal tumor [11, 12]. This study summarized the studies related to CRP and PCa and discussed their significance in PCa diagnosis in order to provide reference for clinical practice.

## 2. Methods

*2.1. Literature Retrieval.* English databases such as PubMed and Web of Science were selected, and the retrieval date was up to August 2022. For the English database, our search keywords were as follows: "c-reactive protein," "C-reactive protein," "CRP," and "PCa."

*2.2. Inclusion Criteria.* Inclusion criteria were as follows: (1) study methods including prospective and retrospective studies; (2) all subjects were patients diagnosed with PCa; and (3) data can be acquired.

*2.3. Exclusion Criteria.* Exclusion criteria were as follows: (1) repeated studies and materials; (2) reviews and meta-analyses; and (3) the experimental design was defective, and the quality of literature was low.

*2.4. Data Extraction.* Basic information of the literature was extracted, including the first author, publication year, country, average age, study type, total number of patients, and prostate-specific antigen level. At the same time, the value of CRP and the hazard ratio (HR) of PCa were also extracted from all enrolled patients.

*2.5. Literature Quality Assessment.* Two investigators were assigned to conduct a literature search, review the entire article, and then filter in accordance to the inclusion and exclusion criteria. The results of screening between the two investigators were cross-compared, and if there were differences, the final results were discussed and determined by a third investigator. The quality of the included literature was assessed according to the QUADAS score.

*2.6. Statistical Methods.* RevMan and STATA software programs were used for analysis. The $I^2$ test was employed to identify the heterogeneity. If $I^2$ was less than 60%, all studies were considered homogeneous, and the included data were analyzed by the fixed-effect model. If $I^2 \geq 60\%$, heterogeneity between studies was considered and included data were analyzed using a random-effect model. $P < 0.05$ denoted that the distinction was statistically obvious. Bias analysis of the enrolled research studies was carried out using funnel plots, and the analysis results were represented by forest maps.

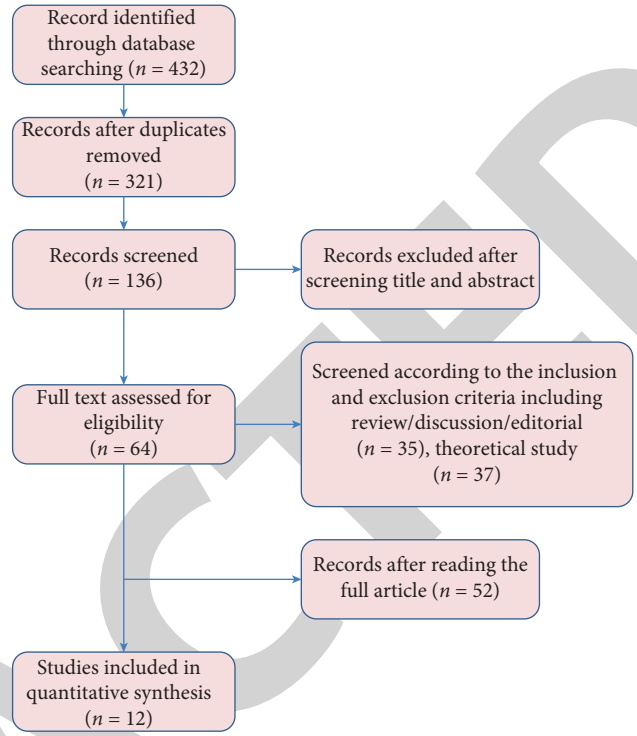


Figure 1: The process of literature inclusion.

## 3. Results

*3.1. The Process of Literature Collection and Literature Quality.* In accordance to the search strategy, a total of 432 articles were obtained, and 321 articles were left after removing the duplicate articles. After reading the abstract and article title, 12 articles were finally included, as shown in Figure 1. The QUADAS score was employed to evaluate the quality of the articles, and the results revealed that the articles included in the analysis were of high quality (Table 1).

The basic information of the articles included in the meta-analysis is summarized in Table 2. As can be seen from the risk of bias map, the included articles have low bias (Figure 2).

*3.2. Correlation between CRP Level and OS Rate in Patients with PCa.* We used RevMan to make forest map; because of the large heterogeneity (df = 5 ($P < 0.0001$), $I^2 = 81\%$), the random-effect model was employed. OS is a dichotomous variable, and we use OR as the final result. The findings revealed that the level of CRP was correlated with OS rate of PCa patients (OR = 1.47 [1.19, 1.82], $P < 0.05$) (Figure 3).

*3.3. Predictive Value of CRP Level on PCa.* The forest map was made by STATA, and the random-effect model was employed because of the large heterogeneity ($I^2 = 89.5\%$). We used HR to assess the risk of PCa. The results revealed that patients with high CRP level had an increased risk of PCa (HR = 0.26, 95% CI: 0.23~0.29) (Figure 4). RevMan is used for funnel plot, which shows basic symmetry, indicating small bias (Figure 5).

Table 1: Quality assessment.

| | Spectrum composition | Selection criteria | Reference standard | Disease progression bias | Partial verification | Differential verification | Incorporation bias | Index test execution | Reference standard execution | Test review bias | Reference standard review bias | Clinical review bias | Uninterpretable test result | Withdrawals | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ito et al. [13] | Yes | Yes | Yes | Yes | Whole sample | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | 13/14 |
| Yamada et al. [14] | Yes | Yes | Yes | Yes | Whole sample | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 14/14 |
| Merriel et al. [15] | Yes | Yes | Yes | Yes | Whole sample | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes | 12/14 |
| Prins et al. [16] | Yes | Yes | Yes | Yes | Whole sample | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 14/14 |
| Beer et al. [17] | Yes | Yes | Yes | Yes (up to 4 weeks) | Whole sample | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | 13/14 |
| Hall et al. [18] | Yes | Yes | Yes | Yes | Whole sample | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 14/14 |
| Ilktac et al. [19] | Yes | Yes | Yes | Yes | Whole sample | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 13/14 |
| Stikbakke et al. [20] | Yes | Yes | Yes | Yes | Whole sample | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 13/14 |
| Stark et al. [21] | No | Yes | Yes | Yes | Whole sample | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 13/14 |
| Xu et al. [22] | Yes | Yes | Yes | Yes | Whole sample | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 14/14 |
| Benli et al. [23] | Yes | Yes | Yes | Yes | Whole sample | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 13/14 |
| Tulloch-Reid et al. [10] | Yes | Yes | Yes | Yes | Whole sample | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 13/14 |

Table 2: Basic information of the included literature.

| Number | Study | Year | Country/region | Age median | Study type | Number of patients | Prostate-specific antigen level |
|---|---|---|---|---|---|---|---|
| 1 | Ito et al. [13] | 2011 | Japan | 70 | Prospective | 80 | 40 ng/mL |
| 2 | Yamada et al. [14] | 2019 | Japan | 75 | Retrospective | 196 | 397.15 ng/mL |
| 3 | Merriel et al. [15] | 2021 | England | 74.38 | Retrospective | 10 901 | — |
| 4 | Prins et al. [16] | 2012 | USA | 71.9 | Prospective | 119 | 80.8 (0.8–2113) ng/mL |
| 5 | Beer et al. [17] | 2008 | USA | 69.5 | Prospective | 160 | 107 (4–6288) ng/mL |
| 6 | Hall et al. [18] | 2013 | USA | 64 | Retrospective | 206 | 14.7 [0.48–166] ng/mL |
| 7 | Ilktac et al. [19] | 2021 | Turkey | 66.85 | Retrospective | 149 | — |
| 8 | Stikbakke et al. [20] | 2019 | Norway | 71.7 | Prospective | 7356 | 14.3 $\mu$g/L |
| 9 | Stark et al. [21] | 2009 | USA | 59.4 | Prospective | 22071 | — |
| 10 | Xu et al. [22] | 2015 | China | 65 | Retrospective | 135 | 80 ng/mL |
| 11 | Benli et al. [23] | 2018 | Turkey | 67.6 | Retrospective | 231 | $6.87 \pm 7.27$ (PCa) and $0.91 \pm 0.6$ ng/dl (control) |
| 12 | Tulloch-Reid [10] | 2017 | Africa | 65.4 | Retrospective | 481 | — |

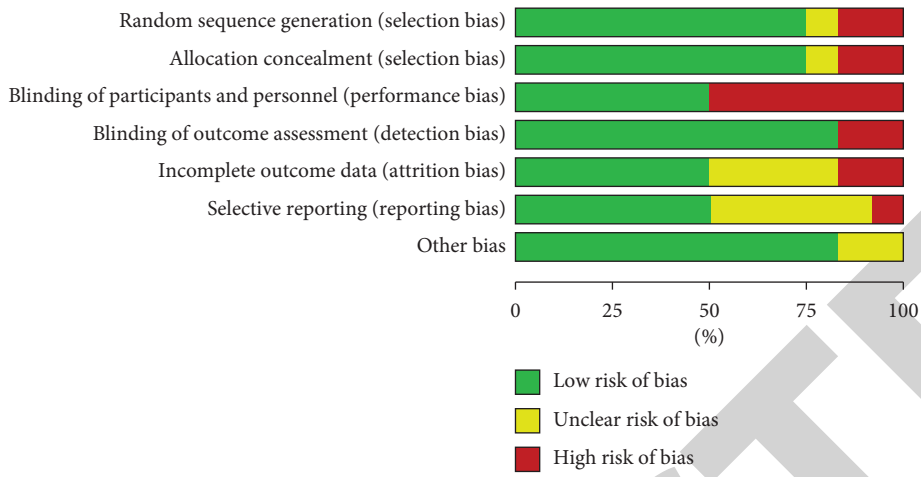


Figure 2: Risk of Bias map.

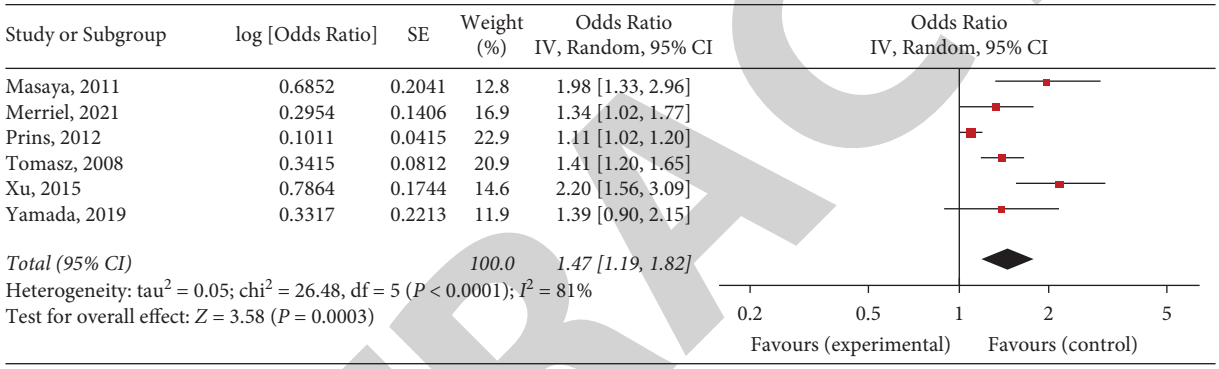


Figure 3: Relationship between CRP level and OS rate in PCa patients.

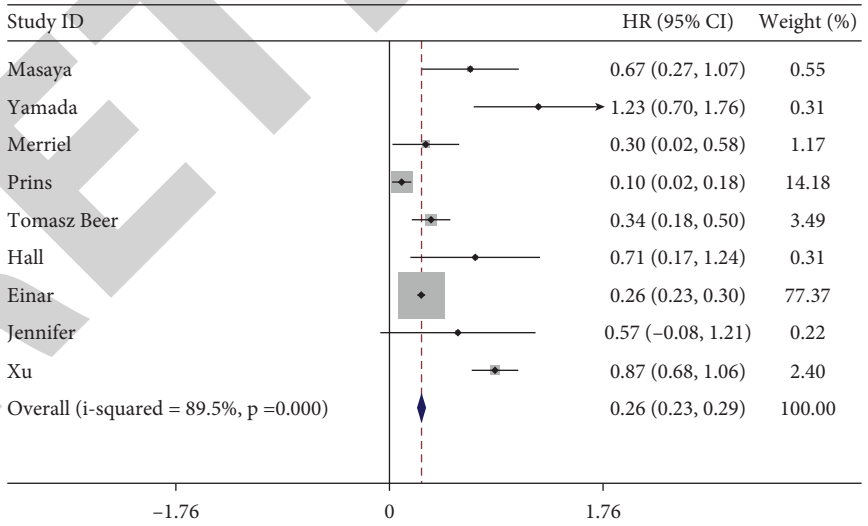


Figure 4: HR of CRP level and OS rate in PCa patients.

*3.4. Circulating CRP Levels between PCa Patients and Healthy Controls.* We made forest plots by RevMan and used a fixed-effect model because of the small heterogeneity (df = 3 ($P = 0.10$), $I^2 = 52\%$). Since the units were consistent, we used MD instead of SMD to assess the distinction in circulating CRP levels between PCa patients and healthy controls. It was found that there was no obvious distinction in circulating CRP levels between PCa patients and healthy controls ($P > 0.05$) (Figure 6). A funnel plot with RevMan shows basic symmetry, indicating less bias (Figure 7).

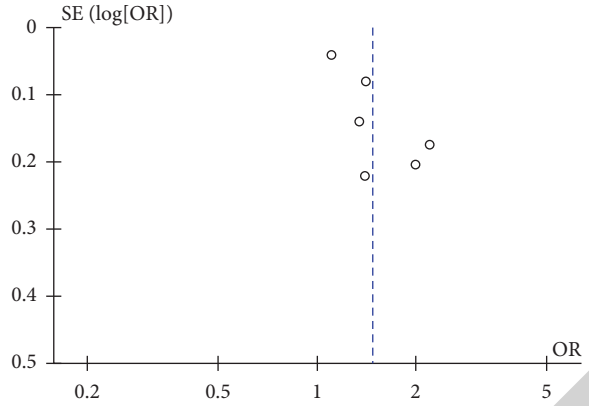


Figure 5: Funnel plot of CRP level and OS rate in PCa patients.

| Study or Subgroup | prostate cancer Mean | SD | Total | Control Mean | SD | Total | Weight (%) | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Abdullah, 2021 | 4.07 | 1.5 | 31 | 3.3 | 1.3 | 118 | 10.0 | 0.77 [0.19, 1.35] |
| Einar, 2019 | 2.17 | 2.47 | 509 | 2.1 | 2.46 | 6761 | 67.5 | 0.07 [−0.15, 0.29] |
| Erdal, 2018 | 2.4 | 3.7 | 117 | 1.8 | 3.3 | 114 | 4.1 | 0.60 [−0.30, 1.50] |
| Marshall, 2017 | 2.11 | 2.34 | 229 | 2.09 | 2.42 | 252 | 18.4 | 0.02 [−0.41, 0.45] |
| *Total (95% CI)* | | | *886* | | | *7245* | *100.0* | *0.15 [−0.03, 0.34]* |

Heterogeneity: chi$^2$ = 6.23, df = 3 ($P$ = 0.10); $I^2$ = 52%
Test for overall effect: $Z$ = 1.64 ($P$ = 0.10)

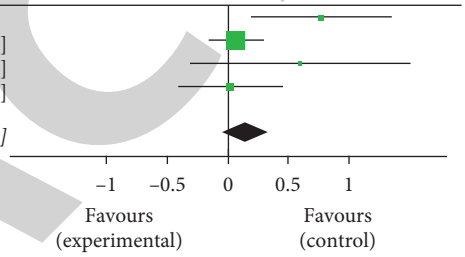


Figure 6: Forest plot of circulating CRP levels between PCa patients and healthy controls.

## 4. Discussion

Relevant studies have shown that the incidence rate of PCa among Chinese men shows a rising trend [24]. However, there is no unified standard of detection index standard for relevant prognosis evaluation such as local lesion control and imaging examination, and the prognosis of PCa cannot be evaluated [25]. Currently, prostate-specific antigen (PSA) is only a marker for evaluating disease progression after PCa antitumor treatment, but this indicator cannot be used to evaluate disease status of PCa patients [26]. Therefore, the search for appropriate bioclinical markers has become a more important topic in PCa research.

According to our results, patients with high CRP levels had an increased risk of PCa (HR = 0.26, 95% CI: 0.23–0.29). This indicates a close association between CRP and PCa. CRP may be used as one of the indicators of high risk of PCa. CRP, a cyclic pentamer formed by five identical subunits relying on non-covalent bonds, is characterized by the ability to specifically bind to phosphocholine group in the presence of calcium ions [27]. As an acute temporal protein released by inflammatory response, CRP is often used as an important indicator for the diagnosis, efficacy observation, and prognosis of clinical infections and tissue damage [28]. Some scholars have found that when tumors develop, the level of CRP will increase obviously, while inflammatory metaplasia and tumor deterioration will stimulate the increase in its indicators. The presence of proinflammatory factors and tumor necrosis factors in the tumor microenvironment is one of the reasons for the increased serum CPR concentration in patients with malignant tumors [29]. Many patients with malignant tumors have varying degrees of CRP concentration increase, and the increase in CRP concentration may increase the risk of cancer, and the change of CRP concentration is very important for the diagnosis, progression, treatment, and prognosis of different malignant tumors. Yet, our results revealed that circulating CRP levels did not differ obviously between PCa patients and healthy controls. It is important for patients with malignant tumor, especially for patients lacking specific tumor markers [30].

Among the included literature in this study, data on OS were available in most articles, and hazard ratio (HR) values were provided. In fact, measures of efficacy for risk assessment of PCa included overall survival (OS) and cancer-specific survival (CSS). However, there are those that take the last one into account, so this article only analyzes the operating system. We used two methods, one is HR, and the other is OR. HR is often used in oncology randomized clinical trials (RCTs) to assess the effect of treatment on the time endpoint of an event. All HR data were recorded in KM′s life curve to summarize the treatment effect during the whole RCT period [31]. In contrast, the median survival only focused on one point on the survival curve for the treatment group. Therefore, HR is very appropriate to demonstrate the effect of CRP on PCa. However, our results show no significant differences in circulating CRP levels between patients with PCa and healthy controls. In fact, previous studies have reported that circulating levels of genetically

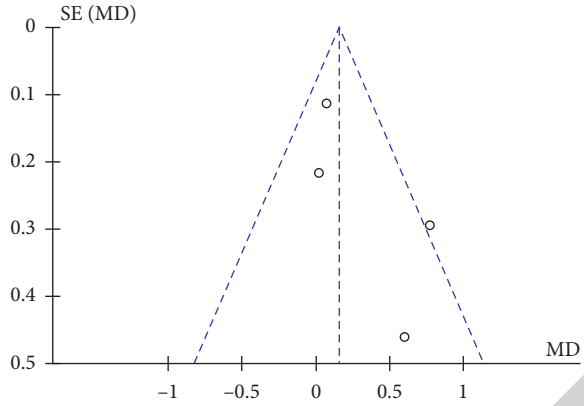


Figure 7: Funnel plot of circulating CRP levels between PCa patients and healthy controls.

predicted CRP are not associated with PCa risk, possibly because CRP circulating levels are affected by a variety of factors [32].

CRP promotes the chronic inflammatory stimulation to induce excessive cell proliferation and DNA damage [33]. The elevated CRP level in PCa patients may be caused by tumor necrosis, local tissue damage, and tumor-related inflammation, but the specific regulatory mechanism needs further investigation. In addition, as a marker of inflammation, whether CRP has a direct carcinogenic effect remains to be further studied [34]. In addition, the limitations of this meta-analysis are as follows. First, due to the difficulty in obtaining data from unpublished reports or ongoing studies, only published literature resources were included in this analysis. Second, the sources of research sites are not rich enough. The large volume of literature from the United States means that more research is needed to prove that the conclusions drawn from this meta-analysis are universally applicable to all ethnic groups. Finally, most of the studies we included were not followed up long enough, so studies with longer follow-up are needed.

Inflammation and PCa are intertwined and influence each other. In the tumor microenvironment, the malignant proliferation of tumor will destroy tissue structure, destroy the function of tissue barrier, and invade the vascular system and immune system of the whole body. During this period, cancer cells will destroy the repair and defense process of inflammatory reaction, stimulate the inflammatory reactions, and promote the malignant proliferation and metastasis of cancer cells [35]. As one of the members involved in the above process, CRP can be used as an ideal marker to reflect the inflammatory reactions. n conclusion, CRP levels are associated with PCa patients′ OS. High CRP levels have an elevated incidence of PCa, but there was no obvious distinction in circulating CRP levels between patients with prostate cancer and healthy controls. Therefore, C-reactive protein has certain reference value for judging the prognosis of prostate cancer.

## Data Availability

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

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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*Retraction*

# Retracted: Circulating miR-340-5p and miR-506-3p as Two Osteo-miRNAs for Predicting Osteoporosis in a Cohort of Postmenopausal Women

**Journal of Environmental and Public Health**

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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] Z. Lu, H. Cao, and X. Hu, "Circulating miR-340-5p and miR-506-3p as Two Osteo-miRNAs for Predicting Osteoporosis in a Cohort of Postmenopausal Women," *Journal of Environmental and Public Health*, vol. 2023, Article ID 7571696, 8 pages, 2023.

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*Research Article*

# Circulating miR-340-5p and miR-506-3p as Two Osteo-miRNAs for Predicting Osteoporosis in a Cohort of Postmenopausal Women

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*Objective*. An increasing risk of developing osteoporosis which is characterized by bone production weakness and microarchitectural deterioration is found among postmenopausal women. MicroRNAs (miRNAs) are secreted into the circulation from cells of various tissues in response to local disease severity including bone diseases. Herein, we set out to identify candidate miRNAs predictable for osteoporosis incidence in postmenopausal elderly women. *Methods*. The circulating miRNA expression profiles deposited in the dataset accessioned as GSE201543 were downloaded from the GEO database. The study included 176 postmenopausal women who underwent BMD testing, including 96 women reporting osteoporosis and 70 women reporting normal BMD. All subjects were submitted their serum samples for measurements of bone metabolism markers. *Results*. The miRNA expression profiles of the GSE201543 dataset were differentially analyzed and found 97 miRNAs being upregulated concomitantly with 31 miRNAs being downregulated in the serum samples between osteoporotic postmenopausal women and postmenopausal women with normal BMD. Osteoporotic postmenopausal women were demonstrated with elevated serum levels of miR-340-5p and miR-506-3p when compared to normal postmenopausal women. Pearson correlation analysis demonstrated that circulating miR-340-5p and miR-506-3p expressions were increased as BAP, $\beta$-CTx, and PINP levels increased, but osteocalcin and 25-(OH)VitD levels are declined in osteoporotic postmenopausal women. Results of the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) showed circulating miR-340-5p and miR-506-3p expressions alone or combined together produced 0.843 AUC, 0.851 AUC, and 0.935 AUC, respectively, when used to predict the incidence of osteoporosis in postmenopausal women. *Conclusion*. Our work suggested that circulating miR-340-5p and miR-506-3p function as osteo-miRNAs in postmenopausal women and may serve as potential noninvasive biomarkers for the incidence of osteoporosis in postmenopausal women.

## 1. Introduction

Osteoporosis is a skeletal disease arising from a diseased condition that bone formation is overwhelmed by bone resorption and has a high morbidity rate among elderly individuals, particularly, women of postmenopausal age [1, 2]. Osteoporosis and subsequent fractures involve half of women and one-fifth of men who are aged more than 50 years worldwide, leading to substantial morbidity and an unsatisfactory quality of life [3]. Osteoporosis is characterized by bone production weakness along with microarchitectural deterioration leading to a higher risk of fracture [4]. The past half-century has witnessed the development of scanning modalities for BMD and bone microarchitecture measurements, such as dual-energy X-ray absorptiometry or quantitative CT [5]. The gradual imbalance between bone formation and resorption can be caused by multiple factors, including aging, estrogen deficiency, and prolonged immobilization, followed by disruption of normal apoptosis and autophagy with excessive inflammation [6].

Preventing the occurrence and minimizing the risk of fractures are the main goals of several pharmacological agents for osteoporosis management either by inducing bone formation or by reducing bone resorption, including zoledronic acid, calcitonin, and salmon calcitonin [7]. Interestingly, bone mineral density (BMD), osteoporosis, and osteoporotic fracture are shown to bind avidly to heritability [8]. However, it is still challenging to determine the genetic architecture, especially the genomic and molecular mechanisms contributing to osteoporosis.

Detections of circulating microRNAs (miRNAs) as potential biomarkers for the risk of osteoporosis and subsequent fractures by next-generation sequencing (NGS) and global miRNA expression have recently attracted much attention [9]. miRNAs have the ability to post-transcriptionally regulate and silence target gene expression and thus play osteoclast differentiation and survival, as well as osteoblast-to-osteoclast communication [10]. For example, two miRNAs, miR-485-3p and miR-491-5p, were reported to protect osteoporotic postmenopausal women against vertebral fractures [11]. miR-340-5p is localized in 5q35 and has been demonstrated to target many genes, such as ROCK1, FHL2, and SKP2, and to regulate the relevant mechanisms involving several signaling pathways, such as JAK-STAT, and Wnt/$\beta$-catenin pathways, thus contributing to in the initiation of several diseases [12]. miR-506-3p was reported to regulate RAB3D expression and repress osteosarcoma cell proliferation and growth [13]. In the beginning, we analyzed the raw data sourced from the GSE201543 dataset and found that miR-340-5p and miR-506-3p were two osteoporosis-related miRNAs (osteo-miRNAs) among postmenopausal women. Herein, we set out to validate the diagnostic values of these two osteo-miRNAs as noninvasive biomarkers in osteoporotic postmenopausal women.

## 2. Materials and Methods

*2.1. Bioinformatics Analysis.* The Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/gds) was thoroughly retrieved to acquire miRNA expression profiles associated with osteoporosis in postmenopausal women. The circulating miRNA expression profiles deposited in the dataset accessioned as GSE201543 were downloaded for further analysis. The GSE201543 dataset encompassed 10 serum samples being made up of 6 postmenopausal women with osteoporosis (sample labels: GSM6067330-GSM6067335) and 4 postmenopausal women without osteoporosis (sample labels: GSM6067336-GSM6067339) and generated on the GPL20712 platform (Agilent-070156 Human miRNA). Differentially expressed miRNAs in the serum sample between postmenopausal women with osteoporosis and postmenopausal women without osteoporosis must fulfill $\log2|\text{fold change (FC)}| > 2$ and adjusted $p < 0.05$ by using the GEO2R bioinformatics tool [14]. The volcano maps and heatmaps were generated to present all differentially expressed miRNAs and expression diversity of representative differentially expressed miRNAs.

*2.2. Study Subjects.* The study included 176 postmenopausal women who underwent BMD testing at the Heilongjiang Beidahuang Group General Hospital between January 2021 and December 2022. The diagnosis of osteoporosis was confirmed based on the classification criteria of the World Health Organization (WHO) based on T-score of BMD testing [15]: T-scores not less than −1.0 were deemed as normal BMD, T-scores ranging from −1.0 to −2.5 as osteopenia, and T-scores not more than −2.5 as osteoporosis. Exclusion criteria for study subjects were as follows: complications such as rheumatoid arthritis or collagen, diabetes mellitus, endocrine disorders, and chronic liver diseases, which influence bone mass; systemic lupus erythematosus, metabolic and endocrine diseases, connective tissue disease, hyperthyroidism, spondylitis, bone tumors, or previous history of hormone replacement therapy, corticosteroid therapy, and stress hormones, which affect bone metabolism; previous history of bisphosphonates. Additionally, patients with common fractures, family history of bone disorder, or low physical activity, and mental illness were also excluded from the study. All included subjects were informed of the medical record review and study design and signed consent documents before data collection. The Ethics Committee of the Heilongjiang Beidahuang Group General Hospital approved and reviewed the study protocol.

*2.3. Human Serum Sample Collection.* Blood samples (5 ml venous blood) were obtained from all subjects on the next day from 9:00 to 11:30 a.m. after an overnight fast to avoid potential diurnal influence. The serum was obtained following centrifugation (3000 r/min, 5 min) of blood samples and equally submitted for bone metabolism marker detection and RNA extraction, respectively.

*2.4. BMD Measurements and Bone Metabolism Evaluation.* BMD measurements of the femoral neck, lumbar spine, total hip, and 1/3 radius applied the DPX-MD dual-energy X-ray bone densitometry (LUNA, USA). The serum levels of bone alkaline phosphatase (BAP) and osteocalcin were measured with the aid of a colorimetric analyzer (Cobas Integra, Roche, Switzerland) using the immunoenzymetric assay kits (MicroVue BAP, USA) and immunoassay ELISA kits (MicroVue Osteocalcin, USA), respectively. The serum levels of $\beta$-carboxyl terminal peptide ($\beta$-CTx), propeptide of type I procollagen (PINP), and 25-hydroxyvitamin D (25-(OH)VitD) were detected using the patented electrochemiluminescence (ECLIA) method by a Cobas Integra colorimetric analyzer with the aid of kits (USCN Life Science, Wuhan, China).

*2.5. RNA Extraction, cDNA Synthesis, and Quantitative Real-Time PCR (qRT-PCR).* Total RNA was extracted from the serum samples using TRIzol reagent (Invitrogen, USA). The reverse transcription was applied to the PrimeScript RT Master Mix (Takara, Japan). The PCR amplification of candidate miRNAs was carried out by the ABI 7300 machine

Table 1: The primer sequences for miR-340-5p, miR-506-3p, and the endogenous reference U6 used for qRT-PCR.

| Name | Primer sequences (5′-3′) |
|---|---|
| miR-340-5p | Forward: 5′-CTGGTAGGTTATAAAGCAATGA-3′<br>Reverse: 5′-TCAACTGGTGTCGTGGAG-3′ |
| miR-506-3p | Forward: 5′-TAAGGCACCCTTCTGAGTAGA-3′<br>Reverse: 5′-GCGAGCACAGAATTAATACGAC-3′ |
| U6 | Forward: 5′-GTGCTCGCTTCGGCAGCACAT-3′<br>Reverse: 5′-TACCTTGCGAAGTGCTTAAAC-3′ |

Table 2: The demographics and baseline bone parameters of study subjects.

| Name | Osteoporosis ($n = 96$) | Normal ($n = 70$) | $p$ value |
|---|---|---|---|
| Age (year) | 64.88 ± 4.30 | 63.81 ± 3.63 | 0.093 |
| BMI (kg/m$^2$) | 22.65 ± 2.58 | 24.75 ± 3.70 | <0.001 |
| Menopause year | 9.92 ± 3.30 | 8.68 ± 2.40 | 0.008 |
| BMD femoral neck (g/cm$^2$) | 0.62 ± 0.29 | 0.76 ± 0.41 | 0.018 |
| $T$-score for femoral neck | −2.63 ± 0.68 | 0.34 ± 0.43 | <0.001 |
| BMD lumbar spine (g/cm$^2$) | 0.69 ± 0.47 | 0.98 ± 0.70 | 0.003 |
| $T$-score for lumbar spine | −2.81 ± 0.95 | 0.71 ± 1.22 | <0.001 |
| BMD total hip (g/cm$^2$) | 0.71 ± 0.46 | 0.86 ± 0.73 | 0.043 |
| BMD 1/3 radius (g/cm$^2$) | 0.50 ± 0.35 | 0.69 ± 0.20 | <0.001 |

BMI, body mass index; BMD, bone mineral density.

(Applied Biosystems, USA) with the aid of the SYBR Green I Master Mix kit (Invitrogen, USA), with results presented by the $2^{-\Delta\Delta C}$ method. The primer sequences for miR-340-5p, miR-506-3p, and the endogenous reference U6 are listed in Table 1.

*2.6. Statistical Analysis.* All data produced in the study were shown as mean ± standard deviation and submitted into the SPSS 21.0 software for statistical comparisons. The studied variables include age, BMI, menopause years, BMD of the femoral neck, lumbar spine, total hip, and 1/3 radius, and the serum levels of bone metabolism markers, circulating miR-340-5p and miR-506-3p expressions between osteoporotic women and normal postmenopausal women, were compared by using two independent sample $t$-test. Pearsom correlation analysis was applied to estimate associations between circulating miR-340-5p expression, miR-506-3p expression, and the studied independent variables in osteoporotic women. Osteoporosis diagnosis using miR-340-5p and miR-506-3p alone or in combination at a baseline expression level applied the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). The level of $p < 0.05$ denoted a statistically significant difference.

## 3. Results

*3.1. The Demographics and Baseline Bone Parameters of Study Subjects.* There were 176 postmenopausal women in this study, among which 96 postmenopausal women (54.55%) reported osteoporosis with $T$-score ≤ −2.5, 10 postmenopausal women (5.68) reported osteopenia with $T$-score ranging from −1.0 to −2.5, and 70 postmenopausal women (39.77%) reported normal $T$-score ≥ −1.0. Osteoporotic postmenopausal women exhibited decreased BMI, longer years of menopause, declined BMD in the femoral neck, lumbar spine, total hip, and 1/3 radius, lower $T$-scores of the femoral neck and lumbar spine compared with normal postmenopausal women ($p < 0.001$, Table 2). With regard to baseline bone parameters, it was found that the serum levels of BAP, $\beta$-CTx, and PINP were higher, but the serum levels of osteocalcin, 25-(OH)VitD, were lower in osteoporotic postmenopausal women than normal postmenopausal women ($p < 0.001$, Figure 1).

*3.2. High Circulating miR-340-5p and miR-506-3p in Osteoporotic Postmenopausal Women.* To study molecular alternations related to the incidence of osteoporosis in postmenopausal women, we submitted miRNA expression profiles of the GSE201543 dataset for differential analysis and found 97 miRNAs being upregulated concomitantly with 31 miRNAs being downregulated in the serum samples between osteoporotic postmenopausal women and postmenopausal women with normal BMD. The top 5 upregulated circulating miRNAs ranked by $p$ values in osteoporotic postmenopausal women were miR-4527, miR-5186, miR-340-5p, miR-506-3p, and miR-4770 (Table 3). After reviewing relevant literature about these miRNAs in osteoporosis, we selected miR-340-5p and miR-506-3p for further detection in the serum samples of 96 osteoporotic postmenopausal women and 70 normal postmenopausal women. Osteoporotic postmenopausal women were demonstrated with upregulated miR-340-5p and miR-506-3p when compared to normal postmenopausal women ($p < 0.001$, Figure 2).

*3.3. Circulating miR-340-5p and miR-506-3p Correlated with Bone Metabolism Markers in Osteoporotic Postmenopausal Women.* Pearson correlation analysis demonstrated that

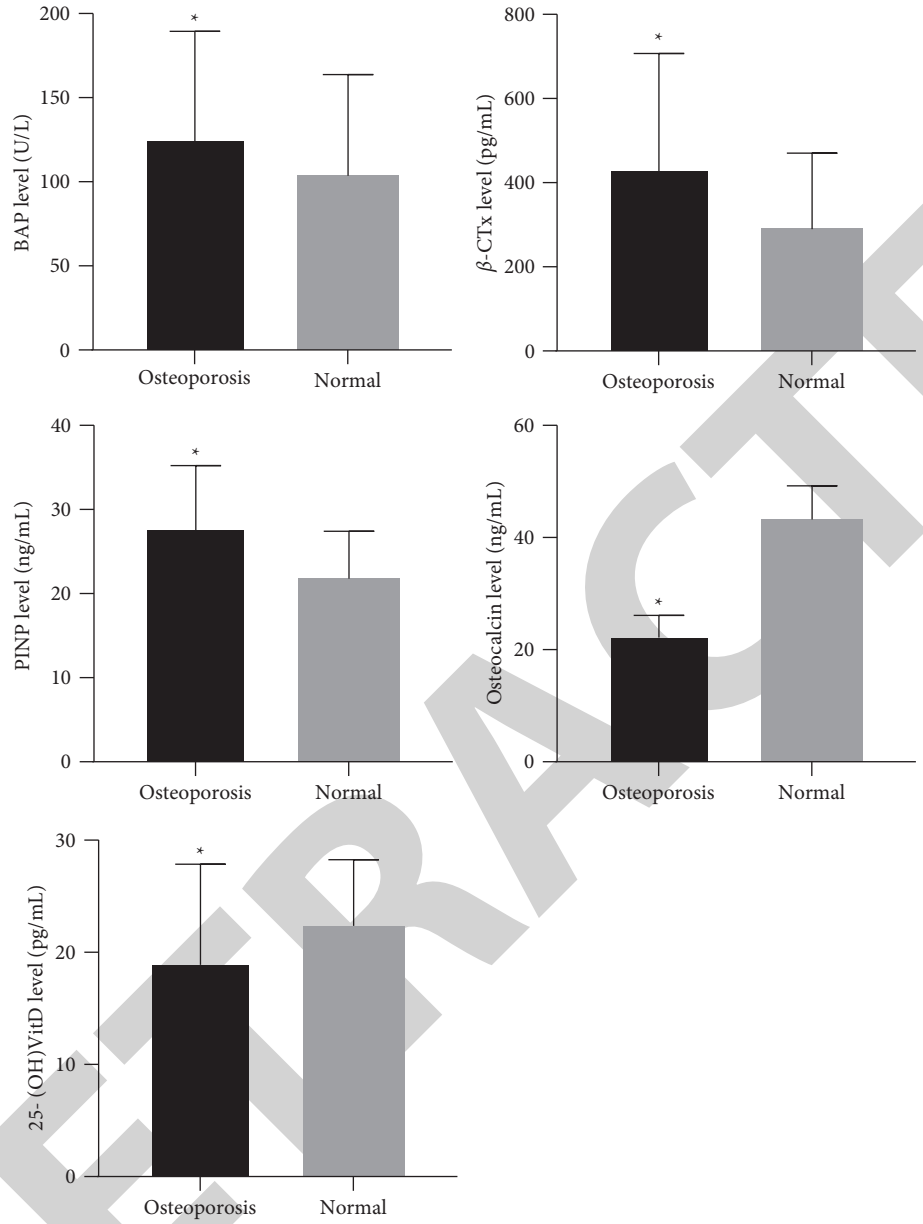


Figure 1: The serum levels of baseline bone parameters between osteoporotic postmenopausal women ($n = 96$) and postmenopausal women with normal BMD ($n = 70$). $^{*}p < 0.05$, compared with postmenopausal women with normal BMD (by the unpaired $t$-test).

Table 3: The top 5 upregulated circulating miRNAs ranked by $p$ values in osteoporotic postmenopausal women after analyzing miRNA expression profiles of the GSE201543 dataset.

| ID | Log2FC | $p$ value |
|---|---|---|
| hsa-miR-4527 | 6.42075 | $1.03E-09$ |
| hsa-miR-5186 | 6.568372 | $1.29E-09$ |
| hsa-miR-340-5p | 5.796601 | $1.57E-09$ |
| hsa-miR-506-3p | 5.707624 | $1.57E-09$ |
| hsa-miR-4770 | 5.797031 | $1.68E-09$ |

FC, fold change.

circulating miR-340-5p and miR-506-3p expressions were increased as BAP, $\beta$-CTx, and PINP levels increased, but osteocalcin and 25-(OH)VitD levels declined in osteoporotic postmenopausal women ($p < 0.001$, Figure 3 and Table 4).

*3.4. The Diagnostic Values of Circulating miR-340-5p and miR-506-3p in Osteoporotic Postmenopausal Women.* The diagnostic performance for circulating levels of miR-340-5p and miR-506-3p in clinical serum samples for osteoporotic postmenopausal women was determined using the AUC. Results showed that circulating miR-340-5p and miR-506-3p expressions produced 0.843 AUC (Figures 4(a) and 4(b), $p < 0.01$) and 0.851 AUC ($p < 0.01$), respectively. Additionally, we found a much stronger diagnostic value for the incidence of osteoporosis in postmenopausal women with an AUC of 0.935 ($p < 0.001$, Figure 4(c)) produced by circulating miR-340-5p and miR-506-3p levels in combination compared to a single miRNA ($p < 0.01$). Circulating miR-340-5p expression conferred 72.90% sensitivity and 87.10% specificity for osteoporotic postmenopausal women.

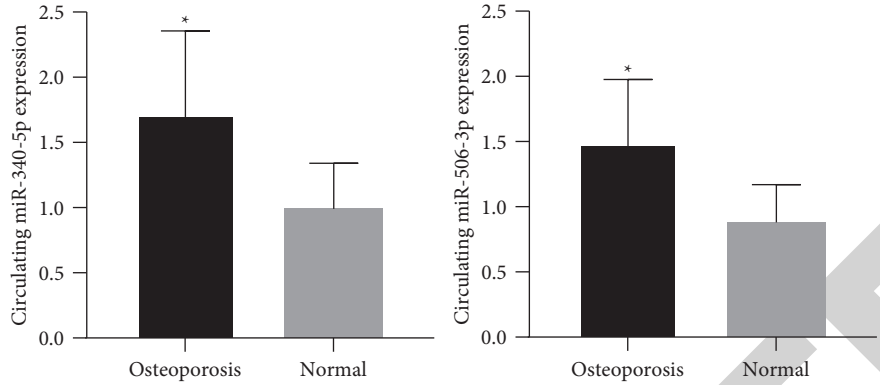


Figure 2: Circulating miR-340-5p and miR-506-3p expressions in clinical samples between osteoporotic postmenopausal women ($n = 96$) and postmenopausal women with normal BMD ($n = 70$). $^* p < 0.05$, compared with postmenopausal women with normal BMD (by the unpaired $t$-test).

Circulating miR-506-3p expression conferred 74.00% sensitivity and 85.70% specificity for osteoporotic postmenopausal women. Circulating miR-340-5p and miR-506-3p combined together conferred 84.40% sensitivity and 92.90% specificity for osteoporotic postmenopausal women.

## 4. Discussion

Osteoporosis represents a common public health burden among elderly individuals, especially among postmenopausal women. Considering excellent stability, tissue specificity, as well as easy detection of circulating miRNAs, they have been widely applied for the prediction and early diagnosis of human diseases, including metabolic bone disease [16]. miRNAs are shown to be closely associated with osteoblast and osteoclast differentiation and survival in the context of bone formation [17]. We performed differential expression analysis using miRNA expression profiles of the GSE201543 dataset and found the top 5 upregulated circulating miRNAs ranked by $p$ values in osteoporotic postmenopausal women compared with postmenopausal women with normal BMD, miR-4527, miR-5186, miR-340-5p, miR-506-3p, and miR-4770. Clinical validation demonstrated acceptable diagnostic values of miR-340-5p and miR-506-3p alone or in combination for osteoporosis incidence among postmenopausal women.

Bone turnover markers can be employed alone or in combination with other bone parameters to evaluate bone resorption and bone formation in aged postmenopausal women [18]. As demonstrated by Thejaswi et al., the BAP level was helpful as a screening biomarker to predict osteoporosis in postmenopausal women [19]. $\beta$-CTx as a key resorption marker was shown to be more predictive for fracture risk than formation markers in very elderly women [20]. Serum PINP is designated as an important bone formation marker in osteoporosis, and it, with CTX, was commonly utilized to evaluate the offset of drug action after bisphosphonate therapy [21]. Osteocalcin is considered as a bone matrix protein, and osteoporosis patients exhibited a decreased osteocalcin level when compared to those with normal BMD [22]. A decreasing level of serum 25-(OH) VitD is regarded as one of the most events predicting the incidence of fractures in elderly women [23]. In the study, the levels of BAP, $\beta$-CTx, and PINP notably elevated, and the levels of osteocalcin and 25-(OH)VitD significantly declined in osteoporotic postmenopausal women compared with normal postmenopausal women.

It is believed that molecular alternations were associated with bone metabolism. We found that osteoporotic postmenopausal women were demonstrated with elevated serum levels of miR-340-5p and miR-506-3p when compared to normal postmenopausal women, and circulating levels of miR-340-5p and miR-506-3p had positive correlations with the serum levels of BAP, $\beta$-CTx, and PINP, but negative correlations with the serum levels of osteocalcin and 25-(OH)VitD in osteoporotic postmenopausal women. A study of type I diabetes found high expression of miR-340-5p proportional to inflammatory cytokine-stimulated $\beta$ cell damage [24]. The study reported by Du et al. showed that miR-340-5p inhibition could increase $\beta$-catenin expression and thus promote osteogenesis of bone marrow-derived mesenchymal stem cells [25]. Loss of miR-340-5p was also shown to enhance the levels of ALP, osteocalcin, collagen-I, and RUNX2 and increase calcium deposition, thus promoting osteogenesis of MC3T3-E1 [26]. miR-506-3p could inhibit osteogenic differentiation by modulating bone morphogenetic protein 7 [27]. All these previous reports showed similar results as our study, and thus, we believed that high circulating 340-5p and miR-506-3p expression may be linked with the incidence of osteoporosis among postmenopausal women.

In conclusion, the study supports the notion that circulating miR-340-5p and miR-506-3p along with bone turnover markers such as BAP, $\beta$-CTx, PINP, osteocalcin, and 25-(OH)VitD as potential diagnostic biomarkers for the occurrence of osteoporosis in postmenopausal women. However, further investigations with RNA sequencing or miRNA arraying will be performed to identify more specific miRNAs as diagnostic biomarkers for postmenopausal osteoporosis. Further investigations will also focus on miRNA

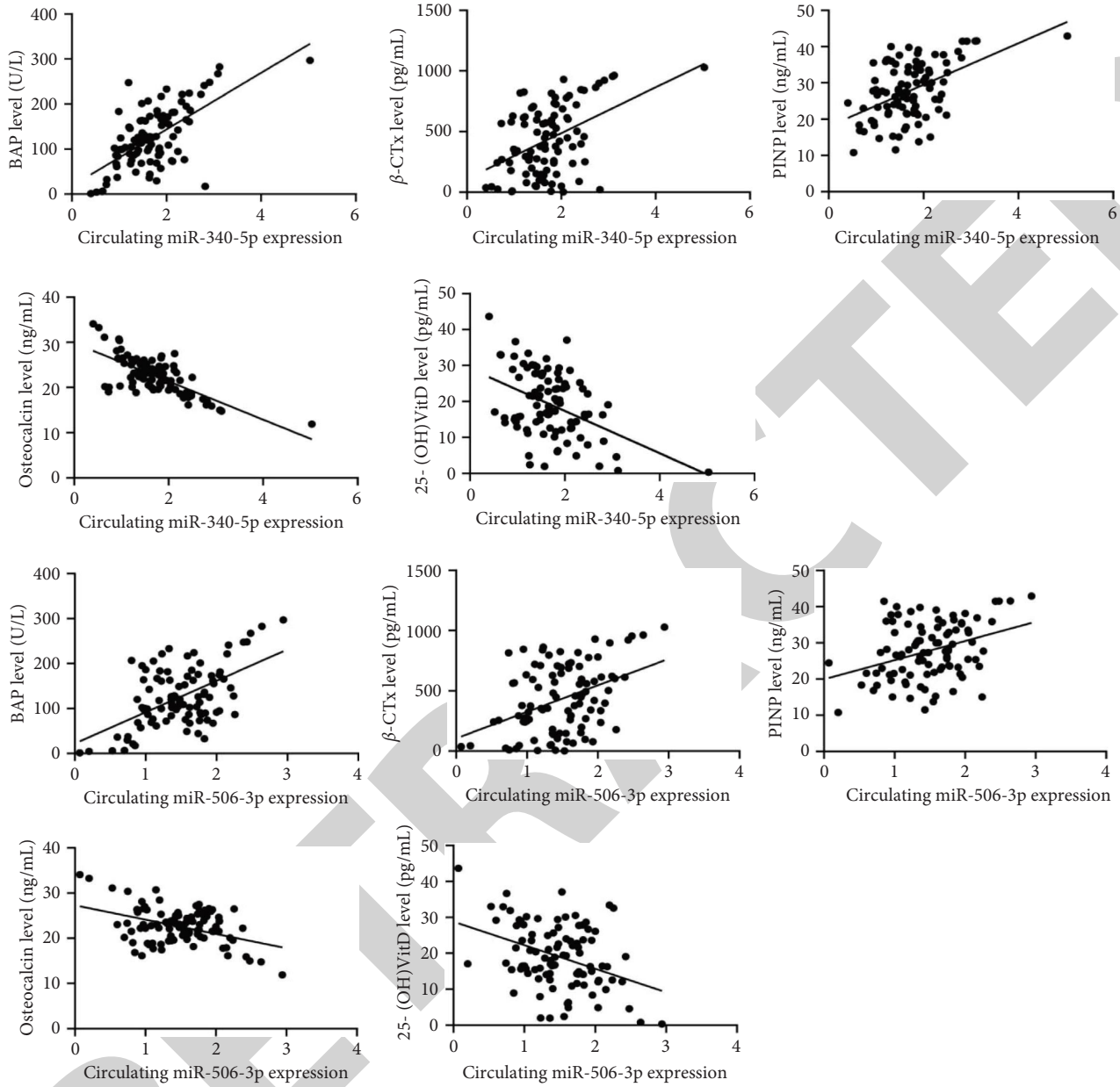


Figure 3: Correlation analysis between circulating miR-340-5p, miR-506-3p, and bone metabolism markers in osteoporotic postmenopausal women ($n = 96$).

Table 4: Pearson correlation analysis of circulating miR-340-5p, miR-506-3p, and bone metabolism markers in osteoporotic postmenopausal women.

| Bone metabolism markers | Circulating miRNA | |
|---|---|---|
| | miR-340-5p | miR-506-3p |
| BAP | $r$ (95% CI) = 0.635 (0.498–0.741) | $r$ (95% CI) = 0.552 (0.395–0.677) |
| $\beta$-CTx | $r$ (95% CI) = 0.445 (0.269–0.593) | $r$ (95% CI) = 0.405 (0.223–0.560) |
| PINP | $r$ (95% CI) = 0.489 (0.320–0.628) | $r$ (95% CI) = 0.352 (0.163–0.516) |
| Osteocalcin | $r$ (95% CI) = −0.715 (−0.801–0.601) | $r$ (95% CI) = −0.417 (−0.570–0.236) |
| 25-(OH)VitD | $r$ (95% CI) = −0.436 (−0.585–0.258) | $r$ (95% CI) = −0.378 (−0.538–0.192) |

BAP, bone alkaline phosphatase; $\beta$-CTx, $\beta$-carboxyl terminal peptide; PINP, propeptide of type I procollagen; 25-(OH)VitD, 25-hydroxyvitamin D.

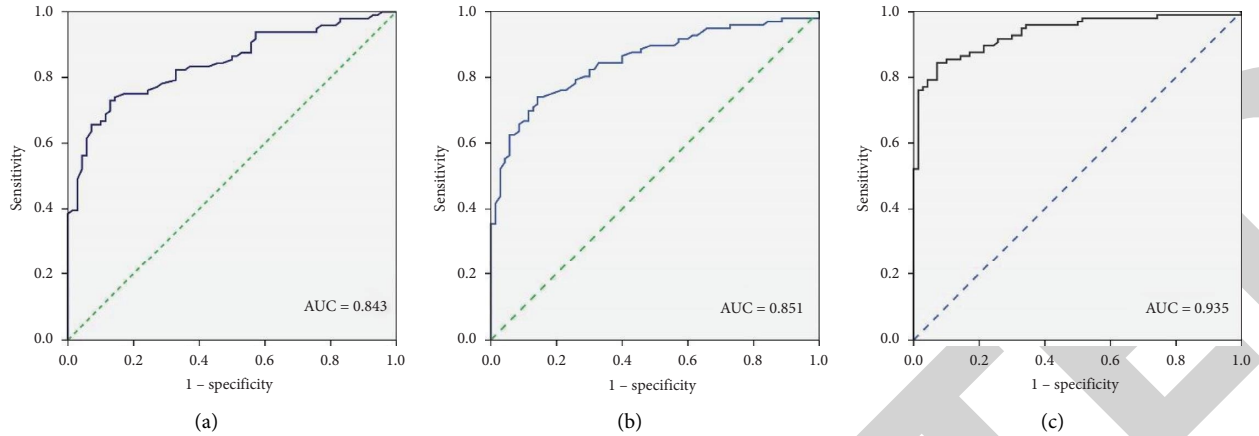


Figure 4: The diagnostic values of circulating miR-340-5p (a) and miR-506-3p (b) alone or combined together (c) in osteoporotic postmenopausal women ($n = 96$).

control of mRNA in bone metabolism regulation of miR-340-5p and miR-506-3p, as well as more functional studies using ovariectomized mice.

## Data Availability

The GSE201543 dataset was downloaded from the Gene Expression Omnibus database (GEO, https://www.ncbi.nlm.nih.gov/geo) that is a public database. Other data supporting this study are included within the article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Zifeng Lu and Haiou Cao equally contributed to this work.

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*Retraction*

# Retracted: MicroRNA-340 and MicroRNA-450b-5p: Plasma Biomarkers for Detection of Non-Small-Cell Lung Cancer

**Journal of Environmental and Public Health**

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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] Y. Wu, H. Jing, and J. Zhang, "MicroRNA-340 and MicroRNA-450b-5p: Plasma Biomarkers for Detection of Non-Small-Cell Lung Cancer," *Journal of Environmental and Public Health*, vol. 2022, Article ID 8024700, 8 pages, 2022.

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*Research Article*

# MicroRNA-340 and MicroRNA-450b-5p: Plasma Biomarkers for Detection of Non-Small-Cell Lung Cancer

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*Objective*. Since the inefficient cancer management is caused by inaccurate diagnoses, there is a need for minimally invasive method to improve the diagnostic accuracy of non-small-cell lung (NSCLC). This study intended to detect miR-340 and miR-450b-5p levels in plasma from NSCLC patients and to assess the potential values for the prediction of tumor development and prognosis. *Methods*. A GSE64591 dataset included 200 samples (100 early-stage NSCLC patients and 100 noncancer control) aimed to identify a panel of circulating miRNAs in plasma. The levels of miR-340 and miR-450b-5p in plasma from NSCLC patients ($n = 120$) and healthy controls ($n = 120$) were detected by quantitative real-time polymerase chain reaction (qRT-PCR). The diagnostic and prognostic value of plasma miR-340 and miR-450b-5p were performed using receiver operating curves (ROC), Kaplan-Meier method, and Cox regression analysis. *Results*. miR-450b-5p and miR-340 in plasma was significant difference between early-stage NSCLC patients and noncancer control by searching the GSE64591 dataset. When compared with the healthy controls, the plasma miR-340 was decreased in the NSCLC patients, but the plasma miR-450b-5p was increased. NSCLC patients could be distinguished accurately from healthy controls by the circulating miR-340 and miR-450b-5p with the AUC of 0.740 (95% CI: 0.677~0.804) and of 0.808 (95% CI: 0.754~0.861), respectively. With these two markers, the specificity and sensitivity were 78.33% and 77.5% with the AUC of 0.862. Patients with advanced T, N, and TNM stage demonstrated lower plasma miR-340 and higher plasma miR-450b-5p, and both of them were correlated with the prognosis of NSCLC patients. Furthermore, plasma miR-340 was also negatively correlated with tumor grade. All clinicopathological variables significantly associated to prognosis were T stage, N stage, TNM stage, tumor grade, and plasma levels of miR-340 and miR-450b-5p in univariate Cox regression analysis. The variables that retained their significance in the multivariate model were T stage, plasma miR-340, and plasma miR-450b-5p. *Conclusion*. The plasma levels of miR-340 combined with miR-450b-5p potentially define core biomarker signatures for improving the accuracy of NSCLC diagnosis. Moreover, circulating miR-340 and miR-450b-5p are independent biomarkers of survival in nonmetastatic NSCLC patients.

## 1. Introduction

Lung cancer continues to be the leading cause of cancer-related mortality worldwide, with an estimated 1.8 million people dying every year, resulting in huge burden in public health care and personal quality of life [1]. As the most common histological subtype of lung cancer, non-small-cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma, bronchoalveolar cell carcinoma, large cell carcinoma, and carcinoid, is responsible for approximately 85% of lung cancer occurrence [2]. Adenocarcinoma plays a significant proportion of NSCLC, accounting for 40% of the prevalence [3]. Lung cancer, especially NSCLC, is often diagnosed at an advanced stage and presents a poor prognosis with an average five-year survival rate of 15%, which is related to increasing mortality [4]. The 5-year overall survival for NSCLC patients in IB stage and IVA-IVB stage is 68% and 0%~10%, respectively [5]. The occurrence of NSCLC is the result of mutual leasing of various factors, including cigarette smoking, dust pollution, occupational carcinogens, and genetic susceptibility [6].

With the deepening understanding of the molecular changes and genomic biomarkers that promote the development of lung cancer, the treatment of NSCLC is no longer

limited to traditional methods such as chemotherapy, radiotherapy, and surgery [7]. In the past two decades, the clinical application of targeted therapy has greatly changed the therapeutic prospect of advanced NSCLC [8, 9]. MicroRNA (miRNA) is a small nonprotein coding RNA with a length of 22 nt, which suppresses gene expression by targeting messenger RNA (mRNA) for translation inhibition and/or cleavage and participates in oncogenesis through regulating cell cycle, apoptosis, and migration [10]. Studies have shown that miRNAs could exhibit tumor-promoting (e.g., miR-155-5p and miR-223-3p [11]) or tumor-inhibiting functions (e.g., miR-590-5p [12] and miR-625-5p [13]) in NSCLC.

Recently, miR-340 was reported to contribute to the inhibition of proliferation and invasion of tumor cells, including hepatocellular carcinoma [14], ovarian cancer [15], and NSCLC [16]. Besides, lower expression of miR-450b-5p was found to be associated with the inhibition of the malignant process of lung adenocarcinoma [17]. The usage of circulating miRNAs may serve as diagnostic tools in NSCLC [18]. However, whether the plasma levels of miR-340 and miR-450b-5p identified as diagnostic and prognostic biomarkers for NSCLC is still unknown. Therefore, we explored the plasma levels of miR-340 and miR-450b-5p in the early-stage NSCLC patients according to a miRNA dataset (GSE64591) and discovered the correlations between miR-340 and miR-450b-5p plasma levels and clinical characteristics of NSCLC patients, as well as the prognosis.

## 2. Methods and Materials

*2.1. Microarray Data Information.* A miRNA dataset (GSE64591; Platform: GPL18942, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE64591) included 200 samples [100 stage I~IIIA NSCLC patients (65 patients with lung squamous cell carcinoma, 35 patients with lung adenocarcinoma), and 100 non-cancer control] intended to identify a panel of circulating miRNAs in plasma. There was a difference in gender (more men among NSCLC patients), age (patients were on average 1.5 years older than controls), smoking status (15% more current smokers among NSCLC patients), and alcohol drinking status (patients included 12% more former alcohol consumers). The plasma samples were screened for 754 circulating miRNAs via quantitative real-time polymerase chain reaction (qRT-PCR), using TaqMan MicroRNA Arrays.

*2.2. Patient Selection.* A total of 120 patients were diagnosed histologically as NSCLC with the age of $66.45 \pm 7.83$ years (range: 47~84 years). The patients consisted of 36 (30.00%) cases with squamous cell carcinoma and 84 (70.00%) cases with adenocarcinoma. The disease stages were classified as follows: stage I $(A + B)$ ($n = 50$, 41.67%), stage II $(A + B)$ ($n = 59$, 49.17%), and stage IIIA ($n = 11$, 9.7%) according to *The 8$^{th}$ edition of the tumor, node and metastasis (TNM) classification* [19]. Tumor differentiation was reported in 15 patients (12.50%) with G1, 73 patients (60.83%) with G2, and 32 patients (26.67%) with G3. The patients were excluded if (1) they had lung metastases from other malignancies; (2) they received previous neoadjuvant therapy for NSCLC before surgery; and (3) they had unresectable IIIB and IV stage NSCLC. In addition, age, sex, and smoking habits-matched healthy controls ($n = 120$) participated in this study (Table 1).

*2.3. Plasma Sample Collection.* Plasma samples were obtained from 120 NSCLC patients before surgical resection and healthy controls for the detection of miR-340 and miR-450b-5p. The samples collected using ethylenediaminetetraacetic acid (EDTA)-blood tubes were separated through centrifugal isolation at 1,500 g for 15 min followed by being aliquoted immediately to fresh tubes and stored at -80°C.

*2.4. RNA Extraction from Plasma and qRT-PCR Detection.* Total RNA from plasma containing small RNA was extracted using the miRNeasy Plasma Kit (Qiagen GmbH, Hilden, Germany). The concentration and purity of the RNA were determined with a NanoDrop 1000 (Thermo Fisher Scientific, Wilmington, DE). After the synthetization of cDNA using miScript II RT Kit with abidance by the manufacturer's protocol, the performance of qRT-PCR was done by miScript SYBR Green PCR Kit (Qiagen) on a Bio-Rad IQ5 Multicolor RT-PCR Detection System (Bio-Rad, Hercules, CA, USA). The relative levels of miR-340 (Forward: 5′-GCGCGTCCGTCTCAGTTACTT-3′; Reverse: 5′-AGTG CAGGGTCCGAGGTATT-3′) and miR-450b-5p (Forward: 5′-CGCGTTTTGCAATATGTTCC-3′; Reverse: 5′- AGTG CAGGGTCCGAGGTATT-3′) were calculated via the $2^{-\Delta\Delta Ct}$ method [20] using miR-16-5p (Forward: 5′-CGCGTAGCA GCACGTAAATA-3′; Reverse: 5′- AGTGCAGGGTCCGA GGTATT-3′) as reference gene, which has been reported to be a marker of hemolysis for its high and stable in the test environment [11, 21].

*2.5. Statistical Analysis.* All data were presented as mean ± standard deviation (SD) or percentage (%). The baseline data between healthy controls and NSCLC patients was analyzed using $\chi^2$ test or $t$-test. Receiver operating curves (ROC) and area under the curve (AUC) analyses were used to determine the diagnostic value of miR-340 and miR-450b-5p in distinguishing between plasma from healthy controls and NSCLC patients. The Student's $t$ -test as well as one-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) test were used to analyze the correlation between the miR-340 and miR-450b-5p plasma levels and clinicopathological features of the patients. Survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariable Cox regression model was used to determine HRs and 95% confidence intervals (CIs) for overall survival, which was defined as the time from the first diagnosis to death from any cause or last follow up. A bilaterally shown $P$ value $<0.05$ was considered statistically significant using the SPSS 22.0 software (SPSS Inc., Chicago, IL) and the GraphPad Prism 8.00 (GraphPad Software Inc., San Diego, CA) for the statistical analyses.

Table 1: Clinicopathological features of NSCLC patients and healthy controls.

| | NSCLC patients | Healthy controls | $P$ |
|---|---|---|---|
| Age | | | |
| ≤60 | 28 | 32 | |
| >60 | 92 | 88 | 0.551 |
| Gender | | | |
| Female | 28 | 35 | |
| Male | 92 | 85 | 0.304 |
| Smoke habits | | | |
| Never smoker | 9 | 10 | |
| Former smoker | 59 | 51 | |
| Smoker | 52 | 59 | 0.584 |

## 3. Result

*3.1. MicroRNA Profiles in Plasma by Searching the GSE64591 Dataset.* Of the 294 biomarker candidates in GSE64591 dataset, the expression of 17 miRNAs in plasma showed significant correlation with the occurrence of NSCLC (miR-28, miR-25, miR-193a-5p, miR-200c, miR-203, miR-218, miR-323-3p, miR-450b-5p, miR-642, miR-766, miR-661, miR-34b, miR-340, miR-22, miR-590-3p, miR-191, and miR-1290, Figure 1). Among these microRNAs, we chose miR-450b-5p and miR-340 for the further investigation, which were served as risk factors for NSCLC in the logistic model [22].

*3.2. Plasma Levels of miR-340 and miR-450b-5p in NSCLC Patients and Healthy Controls.* When compared with the healthy controls ($0.956 \pm 0.410$), plasma miR-340 was decreased in the NSCLC patients ($0.638 \pm 0.280$, $t = 7.023$, $P < 0.001$), while the plasma miR-450b-5p was increased ($1.540 \pm 0.466$ vs. $1.032 \pm 0.339$, $t = 9.658$, $P < 0.001$). We then analyzed the diagnostic power of circulating miR-340 and miR-450b-5p, and the result showed NSCLC patients could be distinguished accurately from healthy controls. The AUC was 0.740 (95% CI: 0.677~0.804; $P < 0.001$, Figure 2(a)) for the plasma miR-340, and 0.808 (95% CI: 0.754~0.861; $P < 0.001$, Figure 2(b)) for the plasma miR-450b-5p. Moreover, the ROC test showed 51.69% sensitivity and 87.5% specificity at the cut-off point of 0.926 for the plasma level of miR-340. At the optimal cut-off point of 1.383, the test sensitivity was 60.83%, and the specificity was 85.83% for the plasma level of miR-450b-5p. With these two markers, the specificity and sensitivity were 78.33% and 77.5% with the AUC of 0.862 ($P < 0.001$, Figure 2(c)).

*3.3. Correlation of Plasma Levels of miR-340 and miR-450b-5p with Clinical and Pathological Characteristics of NSCLC Patients.* As shown in Table 2, no significance was found between the plasma levels of miR-340 and miR-450b-5p with the following clinical and pathological characteristics, including age, gender, smoke habits, histotype, adjuvant chemotherapy, and radiotherapy (all $P > 0.05$). Patients with advanced T stage, N stage, and TNM stage demonstrated lower miR-340 plasma level and higher miR-450b-5p plasma level (all $P < 0.05$). Furthermore, plasma miR-340 was also adversely correlated with tumor grade ($P < 0.05$).

*3.4. Plasma miR-340 and miR-450b-5p Levels Are Associated with Survival in NSCLC Patients.* Based on the median value of miR-340 and miR-450b-5p plasma levels, NSCLC patients were classified into the high-class group and the low-class group. The results revealed that the 5-year OS in the miR-340 low class were significantly shorter than the miR-340 high class ($\chi^2 = 37.14$, $P < 0.001$, Figure 3(a)). On the contrary, the 5-year OS in the miR-450b-5p low class were significantly longer than the miR-450b-5p high class ($\chi^2 = 73.15$, $P < 0.001$, Figure 3(b)). We then addressed the prognostic value of combined miR-340 and miR-450b-5p in plasma of NSCLC patients. As shown in Figure 3(b), patients from the miR-340 high class/miR-450b-5p low class group had the longest survival, and those from the miR-340 low class/miR-450b-5p high class had worst prognosis ($\chi^2 = 81.70$, $P < 0.001$).

*3.5. Univariate and Multivariate Cox Regression Analyses of the NSCLC Patients.* Next, univariate analyses for OS with all clinicopathological variables, described in Table 3 and Figure 4(a), were conducted. Those significantly associated to OS were T stage ($P < 0.001$), N stage ($P < 0.001$), TNM stage ($P < 0.001$), tumor grade ($P = 0.002$), and plasma levels of miR-340 ($P < 0.001$) and miR-450b-5p ($P < 0.001$). Variables found to be significantly associated to OS at the $P < 0.05$ level in the univariate analysis were entered into a multivariate model (Table 3 and Figure 4(b)). The variables that retained their significance in the multivariate OS model were T stage ($P = 0.038$), miR-340 plasma level ($P = 0.008$), and miR-450b-5p plasma level ($P < 0.001$).

## 4. Discussion

Previous evidences indicated that some miRNAs as oncogenes or tumor suppressors were identified as potential biomarkers involved in the development and treatment of NSCLC [23, 24], because they are highly stable for their resistance to endogenous and exogenous RNase activity, as well as to extreme temperatures, extremes of pH (pH 1 or 13), extended storage in frozen conditions, and repeated freeze-thaw cycles [25].

In our study, we preformed data analysis on plasma samples of 100 patients with early-stage NSCLC and 100 health controls based on public dataset platform and obtained 17 miRNAs that were significantly related to the occurrence of NSCLC, including miR-28, miR-25, miR-193a-5p, miR-200c, miR-203, miR-218, miR-323-3p, miR-450b-5p, miR-642, miR-766, miR-661, miR-34b, miR-340, miR-22, miR-590-3p, miR-191, and miR-1290. As reported in a prior study on the predictability of miRNAs for NSCLC [22], miR-340 and miR-450b-5p were selected for further exploration in the present study. Human miR-340 is a tumor suppressor miRNA associated with a variety of cancers. For instance, miR-340 suppressed cancer progression via inactivating signal pathways related to tumorigenesis, such as AKT pathway in gastric cancer [26], Wnt/$\beta$-catenin signaling in ovarian cancer [27],

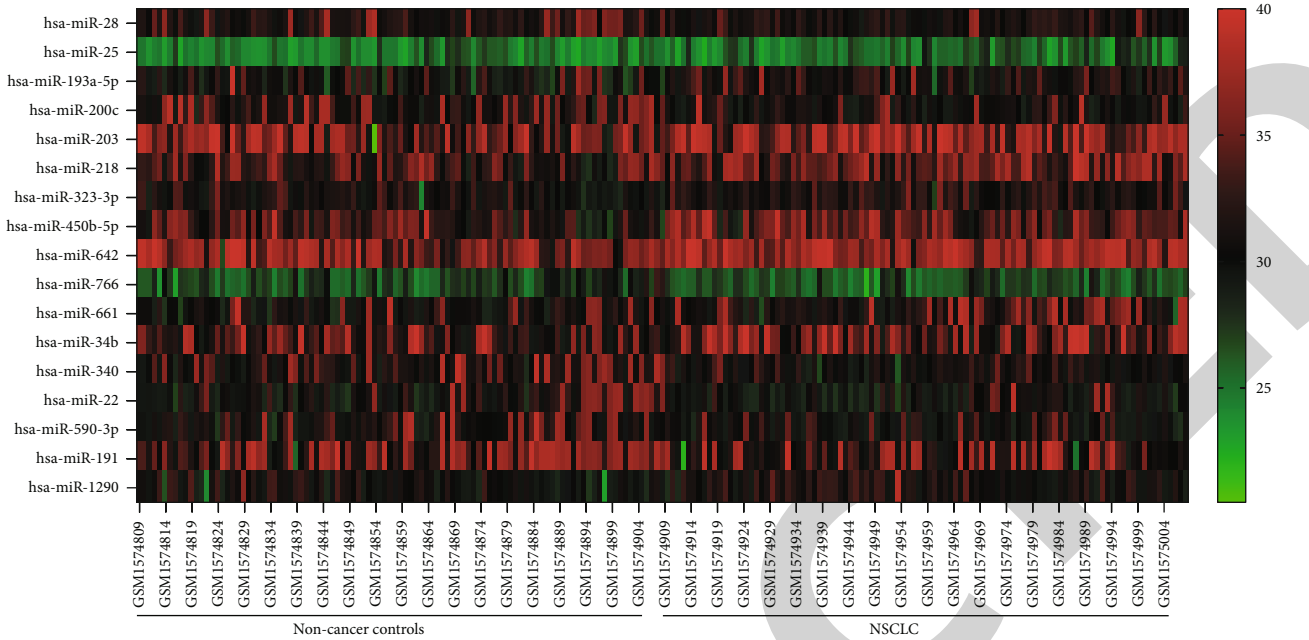


Figure 1: MicroRNA profiles showed significant miRNAs in plasma from NSCLC patients according to GSE64591 dataset. Note: A total of 17 miRNAs in plasma showed significant correlation with the occurrence of NSCLC, including miR-28, miR-25, miR-193a-5p, miR-200c, miR-203, miR-218, miR-323-3p, miR-450b-5p, miR-642, miR-766, miR-661, miR-34b, miR-340, miR-22, miR-590-3p, miR-191, and miR-1290.

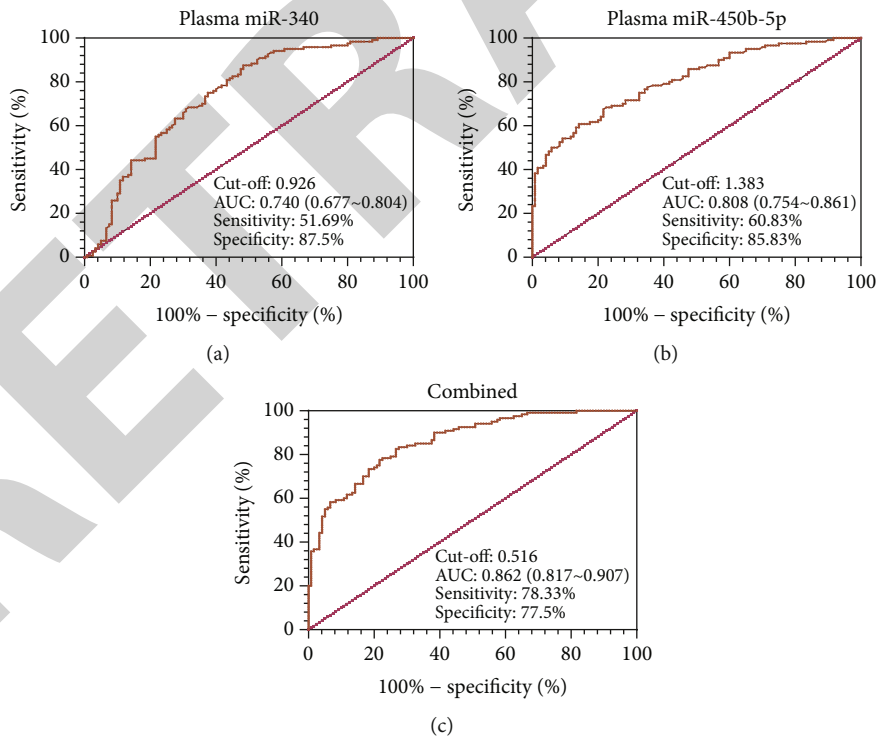


Figure 2: The diagnostic power of circulating miR-340 and miR-450b-5p in NSCLC. Note: A-C: ROC curve analysis of plasma miR-340 (a), plasma miR-450b-5p (b), and the combination miR-340 and miR-450b-5p (c) for NSCLC diagnostics.

and p-PI3K/AKT in human bladder cancer [28]. In the researches of NSCLC, miR-340 was reported to express lower level in NSCLC tissues compared to paracarcinoma tissues and inhibited cell proliferation by downregulating CDK4 expression [29]. miR-340 induced cell growth arrest of NSCLC by targeting three key negative regulators of p27, and its expression was negatively related to clinical four stages [16]. miR-450b-5p was downregulated in in lipopolysaccharide-

Table 2: Correlation of plasma levels of miR-340 and miR-450b-5p with clinical and pathological characteristics of NSCLC patients.

| | *N* | Plasma miR-340 | Plasma miR-450b-5p |
|---|---|---|---|
| Age | | | |
| ≤60 | 28 | 0.654 ± 0.273 | 1.348 ± 0.503 |
| >60 | 92 | 0.633 ± 0.283 | 1.337 ± 0.457 |
| *P* | | 0.731 | 0.915 |
| Gender | | | |
| Female | 28 | 0.665 ± 0.304 | 1.248 ± 0.485 |
| Male | 92 | 0.630 ± 0.273 | 1.368 ± 0.459 |
| *P* | | 0.567 | 0.233 |
| Histotype | | | |
| Squamous cell carcinoma | 36 | 0.631 ± 0.309 | 1.332 ± 0.424 |
| Adenocarcinoma | 84 | 0.641 ± 0.268 | 1.343 ± 0.485 |
| *P* | | 0.852 | 0.906 |
| Adjuvant chemotherapy | | | |
| No | 84 | 0.620 ± 0.270 | 1.394 ± 0.445 |
| Yes | 36 | 0.679 ± 0.301 | 1.215 ± 0.495 |
| *P* | | 0.293 | 0.053 |
| Radiotherapy | | | |
| No | 112 | 0.650 ± 0.279 | 1.321 ± 0.461 |
| Yes | 8 | 0.470 ± 0.253 | 1.612 ± 0.480 |
| *P* | | 0.079 | 0.087 |
| Smoke habits | | | |
| Never smoker | 9 | 0.658 ± 0.382 | 1.226 ± 0.722 |
| Former smoker | 59 | 0.626 ± 0.269 | 1.330 ± 0.450 |
| Smoker | 52 | 0.648 ± 0.277 | 1.371 ± 0.437 |
| *P* | | 0.895 | 0.673 |
| T stage | | | |
| T1 | 43 | 0.834 ± 0.256 | 1.000 ± 0.456 |
| T2 | 60 | 0.542 ± 0.239 | 1.490 ± 0.369 |
| T3 | 17 | 0.482 ± 0.187 | 1.671 ± 0.236 |
| *P* | | < 0.001 | < 0.001 |
| N stage | | | |
| N0 | 82 | 0.730 ± 0.271 | 1.162 ± 0.411 |
| N1 | 27 | 0.442 ± 0.163 | 1.705 ± 0.302 |
| N2 | 11 | 0.431 ± 0.212 | 1.772 ± 0.395 |
| *P* | | < 0.001 | < 0.001 |
| TNM stage | | | |
| Stage I (A + B) | 50 | 0.858 ± 0.238 | 0.923 ± 0.296 |
| Stage II (A + B) | 59 | 0.490 ± 0.182 | 1.612 ± 0.290 |
| Stage III A | 11 | 0.431 ± 0.212 | 1.772 ± 0.395 |
| *P* | | < 0.001 | < 0.001 |
| Tumor grade | | | |
| G1 | 15 | 0.757 ± 0.274 | 1.240 ± 0.466 |
| G2 | 73 | 0.657 ± 0.258 | 1.296 ± 0.465 |
| G3 | 32 | 0.538 ± 0.307 | 1.487 ± 0.450 |
| *P* | | 0.027 | 0.104 |

Note: Smokers (smoking history: at least 5 years, smoking exposure: about more than 20 packs/year); never-smokers (subjects with no history of past and present smoking, neither active nor passive); former smokers (those who have quit smoking).

induced acute lung injury [30], and miR-450b-5p inhibitor promoted cervical cancer progression [31]. In our retrospective analysis, the result also showed plasma miR-340 was decreased in the NSCLC patients when compared with the healthy controls, while the plasma miR-450b-5p was increased, suggesting the important role of miR-450b-5p and miR-340 in early-stage NSCLC.

Furthermore, miR-340 can be regarded as diagnostic biomarker of NSCLC, with 0.740 AUC (95% CI: 0.677~0.804) and 87.5% specificity. This study also confirmed that decreased miR-340 plasma level was observed in the patients with advanced T stage, N stage, and TNM stage, and the tumor grade was adversely correlated with miR-340 expression. As demonstrated by Li et al., miR-340 level was significantly correlated with tumor differentiation and tumor size in cervical squamous cell carcinoma. The AUC and specificity of miR-340 in high-grade squamous intraepithelial lesion diagnosis was 0.764 and 48.6%, respectively [32]. Our study performed the correlation analysis between miR-340 expression and 5-year OS. The results showed that the patients with miR-340 high class presented remarkably longer OS than those with miR-340 low class. Besides, OS was significantly associated with T stage and miR-340 plasma level in multivariate model.

However, the findings in our study revealed the increased expression of miR-450b-5p was found in the patients with advanced T stage, N stage, and TNM stage, being similar with a previous study, suggesting that miR-450b-5p was elevated in colorectal cancer and expression level of miR-450b-5p was positively associated with advanced TNM classification and negatively related to prognosis [33]. Regarding the diagnostic value of miR-450b-5p in NSCLC, miR-450b-5p was reported to show 0.808 AUC and 85.83% specificity. In a study of hepatocellular carcinoma, Li et al. [34] revealed that miR-450b-5p suppressed cell viability and invasion ability through reversely regulating KIF26B, and overexpression of KIF26B contributed to poor OS. We analyzed the impacts of miR-450b-5p on 5-year OS, and significantly longer OS was discovered in the patients with miR-450b-5p low class compared to those with miR-450b-5p high class. Furthermore, according to the results of multivariate Cox regression, a significant link was also found between OS and T stage and miR-450b-5p level.

In conclusion, dysregulated plasma miR-340 and miR-450b-5p in NSCLC were identified in our study, and both levels were associated with prognosis. This study is the first

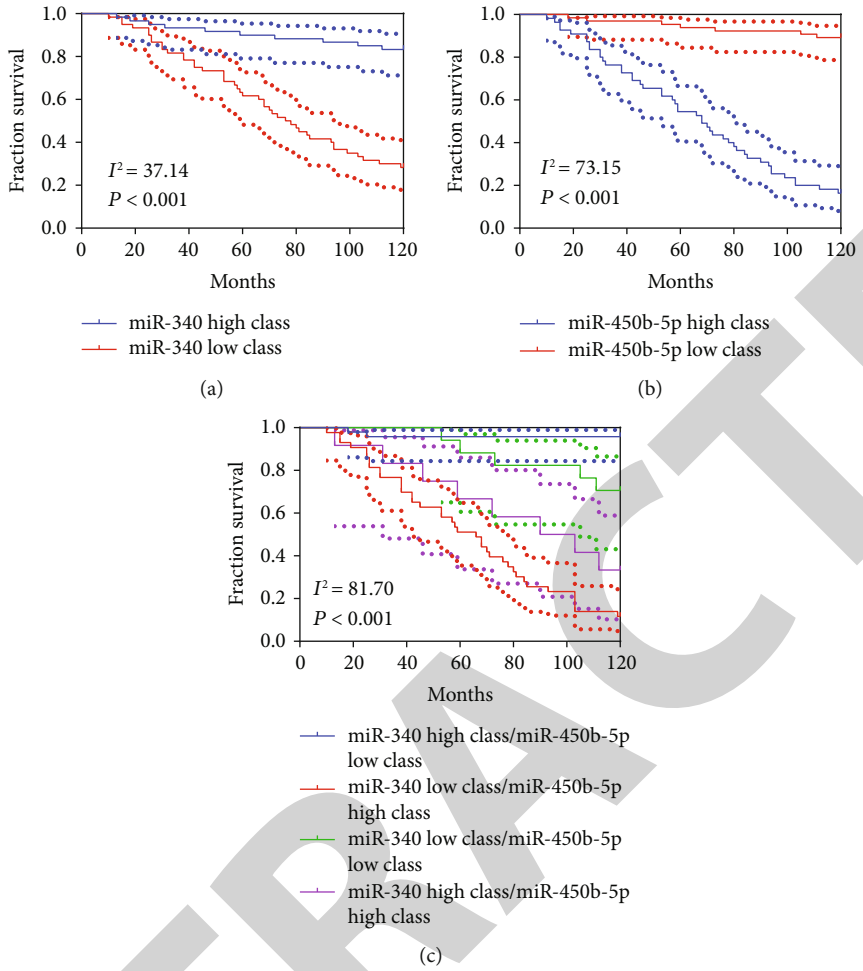


Figure 3: Kaplan-Meier curves obtained by stratifying 120 NSCLC patients according to the median plasma levels miR-340 (a) and miR-450b-5p (b), as well as plasma miR-340 combined with plasma miR-450b-5p (c).

Table 3: Univariate and multivariate Cox regression analyses of the NSCLC patients.

| | Univariate Cox regression | | | Multivariable Cox regression | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | $P$ | HR | 95% CI | $P$ |
| Age | 1.013 | 0.532~1.928 | 0.968 | | | |
| Gender | 1.101 | 0.567~2.140 | 0.776 | | | |
| Histotype | 0.690 | 0.369~1.290 | 0.245 | | | |
| Adjuvant chemotherapy | 0.613 | 0.322~1.168 | 0.137 | | | |
| Radiotherapy | 2.136 | 0.911~5.01 | 0.081 | | | |
| Smoke habits | 1.074 | 0.683~1.689 | 0.758 | | | |
| T stage | 3.465 | 2.250~5.337 | < 0.001 | 2.370 | 1.049~5.355 | 0.038 |
| N stage | 3.298 | 2.354~4.620 | < 0.001 | 1.151 | 0.467~2.838 | 0.760 |
| TNM stage | 5.680 | 3.728~8.654 | < 0.001 | 2.276 | 0.778~6.662 | 0.133 |
| Tumor grade | 2.076 | 1.299~3.318 | 0.002 | 1.237 | 0.723~2.116 | 0.437 |
| Plasma miR-340 | 0.009 | 0.002~0.036 | < 0.001 | 0.099 | 0.018~0.540 | 0.008 |
| Plasma miR-450b-5p | 16.460 | 8.796~30.802 | < 0.001 | 5.725 | 2.405~13.627 | < 0.001 |

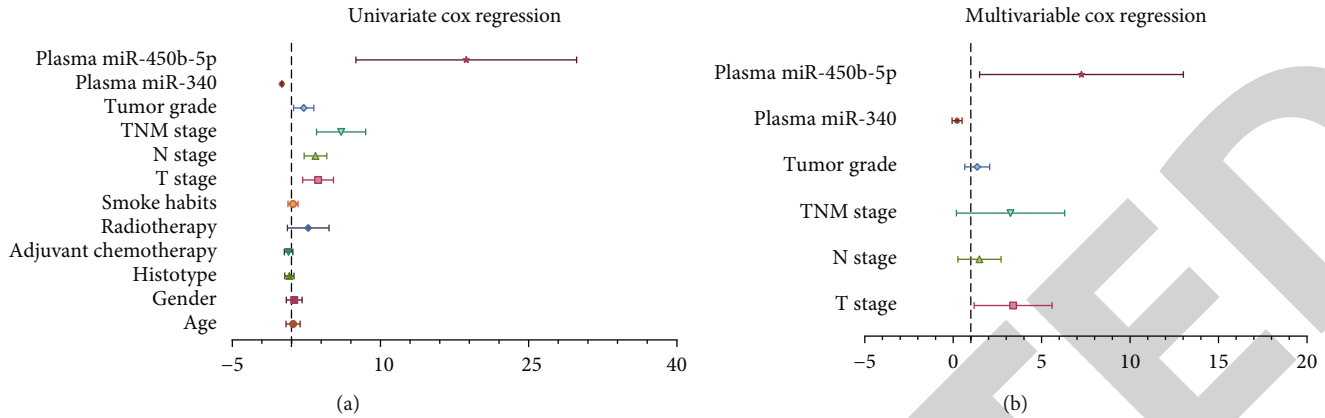


Figure 4: Forest plots of univariate and multivariate Cox regression analyses of OS. Note: (a) Univariate Cox regression analysis for OS. (b) Multivariate Cox regression analysis for OS.

to demonstrate that circulating miR-202 and miR-26a could potentially be used as diagnostic and prognostic marker for NSCLC, thus being a potential therapeutic target in NSCLC management. However, confirmatory results in larger and prospective studies composed of patients with different NSCLC histological cancer subtypes and at advanced stages of the disease are needed to help translate this biomarker in clinical practice, which is the main limitation of our study. Moreover, further studies are needed to fully investigate the mechanism of miR-340 and miR-450b-5p influencing the NSCLC cell characteristics *in vitro* and the tumor growth *in vivo*.

## Data Availability

The data supporting the results were included in article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Yanmin Wu and Hui Jing contributed equally to this work.

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*Retraction*

# Retracted: Effects of Modified Duhuo Jisheng Decoction Combined with Arthroscopic Surgery on Bone Metabolism, Oxidative Stress, and Serum TLR4 and TGF-$\beta$1 in Patients with Knee Osteoarthritis

**Journal of Environmental and Public Health**

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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] X. Zeng, S. Lin, and Y. Li, "Effects of Modified Duhuo Jisheng Decoction Combined with Arthroscopic Surgery on Bone Metabolism, Oxidative Stress, and Serum TLR4 and TGF-$\beta$1 in Patients with Knee Osteoarthritis," *Journal of Environmental and Public Health*, vol. 2022, Article ID 1933504, 6 pages, 2022.

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*Research Article*

# Effects of Modified Duhuo Jisheng Decoction Combined with Arthroscopic Surgery on Bone Metabolism, Oxidative Stress, and Serum TLR4 and TGF-$\beta$1 in Patients with Knee Osteoarthritis

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*Objective*. To analyze the effects of modified Duhuo Jisheng Decoction combined with arthroscopic surgery on bone metabolism, oxidative stress, and serum TLR4 and TGF-$\beta$1 in patients with knee osteoarthritis (KOA). *Methods*. Prospectively select 82 patients with KOA from January 2020 to January 2022 in our hospital and divide them into the control group and observation group according to the random number table method, with 41 patients in each group. The control group was treated with arthroscopic surgery alone and routine anti-infection after operation. The observation group was treated with Duhuo Jisheng Decoction on the basis of the treatment of the control group. The patients in the two groups were treated continuously for 4 weeks. The improvement of patients' symptoms was evaluated by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Before treatment and 4 weeks after treatment, the scores of traditional Chinese medicine (TCM) symptoms, bone metabolism indicators (cartilage oligomeric matrix protein (COMP), collagen type II carboxy terminal peptide (ctx-II), and matrix metalloproteinase-3 (MMP-3)), oxidative stress indicators (superoxide dismutase (SOD), glutathione peroxidase (GSHPx), malondialdehyde (MDA), nitric oxide (NO)), serum Toll-like receptor 4 (TLR4), and transforming growth factor $\beta$ (TGF-$\beta$) level were compared between the two groups. *Results*. After treatment, the WOMAC score of the two groups decreased ($42.45 \pm 10.83$) in the observation group and ($67.81 \pm 14.63$) in the control group. The WOMAC score of the observation group was lower than that of the control group ($P < 0.05$). After treatment, the levels of COMP, CTX-II, and MMP-3 in the two groups decreased, and the levels of COMP, CTX-II, and MMP-3 in the observation group were lower than those in the control group ($P < 0.05$). After treatment, the levels of SOD and GSHPx increased, while the levels of MDA and NO decreased in the two groups. The levels of SOD and GSHPx in the observation group were higher than those in the control group, while the levels of MDA and NO were lower than those in the control group ($P < 0.05$). After treatment, the TLR4 level in the observation group was lower than that of the control group, and the level of TGF-$\beta$ in the observation group was higher than that of the control group ($P < 0.05$). *Conclusion*. Compared with arthroscopic surgery alone, combined with modified Duhuo Jisheng Decoction can better alleviate the clinical symptoms of patients with KOA, improve their bone metabolism, oxidative stress indicators, and serum TLR4 and TGF-$\beta$ 1 level, and reduce the inflammatory injury of knee joint.

## 1. Introduction

Knee osteoarthritis (KOA) is also known as knee joint degenerative osteoarthritis; specifically, it refers to the chronic inflammation caused by a variety of factors, the symptoms of which are centered on the degenerative changes of articular cartilage and involve the pathological changes of multiple structures such as bone, synovial membrane, and joint capsule [1, 2]. KOA is a common knee joint disease in clinical practice. In the early stage, the patient with KOA only showed mild soreness or dull pain in the joints. As the disease progressed, the joint movement became

unfavorable, pain increased, localized stiffness, joint swelling, etc., which had a great impact on daily life. Relevant data showed that the disability rate of KOA was only less than cardiovascular disease [3, 4]. In recent years, with the increasing aging trend in my country, the incidence of KOA has been increasing, and the clinical treatment of KOA is mostly drug therapy and surgery [5]. Arthroscopic debridement of knee joint is a minimally invasive treatment with short treatment time, which has the characteristics of less trauma and remarkable effect. With the development of minimally invasive technology, the frequency of knee arthroscopy is gradually increased. However, some patients may have sequelae such as nausea, dizziness, and knee swelling after knee arthroscopy [6]. Duhuo Jisheng Decoction is a classic TCM formula for treating KOA. Based on this, this study intends to combine the modified Duhuo Jisheng Decoction with arthroscopic surgery to improve the therapeutic effect of KOA. The results were reported below.

## 2. Materials and Methods

*2.1. General Information.* A total of 82 KOA patients who were admitted to our hospital from January 2020 to January 2022 were prospectively selected and divided into the control group and observation group according to the random number table method, with 41 cases in each group. In the observation group, there were 16 males and 25 females; the age ranged from 48 to 80 years, with an average of $(61.44 \pm 7.38)$ years; the course of KOA was 4 to 73 months, with an average of $(52.63 \pm 13.15)$ months; Kellgren-Lawrence classification grades II and III were 24 cases and 17 cases, respectively. In the control group, there were 17 males and 24 females; the age ranged from 43 to 75 years, with an average of $(62.41 \pm 7.36)$ years; the course of KOA was 5 to 73 months, with an average of $(52.54 \pm 12.47)$ months; Kellgren-Lawrence classification grades II and III were 26 cases and 15 cases, respectively. There were no significant differences in gender, age, disease course, and Kellgren-Lawrence classification between the two groups ($P > 0.05$), which were comparable. This study complies with the Declaration of Helsinki.

*2.2. Diagnostic Criteria.* Based on the "Guidelines for the Diagnosis and Treatment of Osteoarthritis (2018 Edition)" formulated by the Joint Surgery Group of the Orthopaedic Branch of the Chinese Medical Association, the diagnostic criteria for KOA were formulated: ① signs include joint pain, swelling, stiffness, deformity, a sense of snapping or friction, limited joint movement, and difficulty in walking or squatting [7]; ② recurrent joint pain within 1 month; ③ knee X-ray examination showed asymmetric joint space narrowing, subchondral bone sclerosis or cystic lesions, and osteophyte formation at the joint edge; and ④ magnetic resonance examination showed the thickness of knee articular cartilage thinning, defect, bone marrow edema, cystic changes, and some joint effusion or popliteal cyst.

*2.3. Inclusion and Exclusion Criteria.* Inclusion criteria were as follows: ① patients who met the diagnostic criteria of KOA had the corresponding symptoms and were confirmed by knee joint X-ray examination after admission; ② age of patients over 18 years old; ③ patients with Kellgren-Lawrence's classification is grade II or III; ④ patients meeting indications for arthroscopic surgery; ⑤ patients who are not allergic to the drugs used in this study; ⑥ patients who have not received other KOA treatment drugs in the past 1 month; and ⑦ patients and their families understand the research content, know the pros and cons, and have signed the informed consent. Exclusion criteria were as follows: ① combined with rheumatoid arthritis or other types of arthritis; ② patients with contraindications to surgery; ③ combined with bone tumor or other malignant tumor bone metastasis; ④ patients had severe joint space stenosis and required joint replacement; ⑤ patients with bilateral KOA; ⑥ and patients with knee joint skin injury or knee joint local infection.

*2.4. Methods.* Both groups of patients underwent knee arthroscopy. The operation steps were as follows: take the patient in a supine position, perform epidural anesthesia, fix the balloon tourniquet on the thigh root of the affected limb, keep the knee joint flexed at 90°, and keep the affected limb at 90°. In a normal drooping state, inflate the airbag after disinfection and towel laying operation. Select the joint approach of anteromedial and anterolateral knee joint, anterolateral approach for arthroscopy, and anteromedial approach for surgical operations. After the approach, the joints were washed with a large amount of normal saline, and the inspections were carried out in order. Surgical operations include cleaning up floating debris, excision of hyperplastic synovium, trimming of meniscus, grinding of osteophytes, etc., removal of loose bodies, and subsequent grinding of cartilage shedding and bone surface. Players drill microholes on the surface of cartilage and rinse the joint with a large amount of normal saline. After operation, check whether the range of motion of the joints is normal, confirm that there is no abnormal compression and snapping, then suture the wound, and use an elastic bandage for pressure dressing for 48 hours to avoid massive bleeding. After the operation, a drainage tube was set in the affected area for 24 hours, antibiotics were used for 4-5 days, and the quadriceps muscle rehabilitation training was performed after the drainage tube was removed. On this basis, the patients in the observation group were treated with Duhuo Jisheng Decoction orally. The prescriptions were as follows: Duhuo 15 g, Asarum 6 g, Angelica sinensis 10 g, Licorice 10 g, Cinnamon Heart 10 g, Eucommia 10 g, Qinji 10 g, Achyranthes 10 g, Fangfeng 10 g, Shaoyao 10 g, Rehmannia glutinosa 10 g, Chuanxiong 10 g, Mulberry parasitic 10 g, and Poria 10 g. For those with severe pain, add Fuzi 5 g, for those with severe limbs, add Atractylodes 6 g and Papaya 9 g, if the congestion persists, add 9 g of Salvia miltiorrhiza and 12 g of Chickweed, and for those with a longer course of disease, add 9 g of Dilong and a centipede. Add 600 ml of water to decoct, remove the residue, take 300 ml of juice, take one dose a day, warm twice in the morning and evening, and take it continuously for 4 weeks.

*2.5. Observation Indicators.* ① The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was as follows: the WOMAC score was evaluated before

treatment and after 4 weeks of treatment. The scale contains three dimensions, namely, pain (5 items), stiffness (2 items), and difficulty in performing daily activities (17 items); with a total of 24 items, each item is 0-9 points, and the higher the total score, the more severe the symptoms. ② In bone metabolism index, 5 ml of fasting venous blood was collected from patients before treatment and after 4 weeks of treatment, 3000 r/min centrifugation for 10 min, and the upper serum was taken and stored at -70°C for testing. The levels of cartilage oligomeric matrix protein (COMP), collagen type II carboxy-terminal peptide (CTX-II), and matrix metalloproteinase-3 (MMP-3) were detected by enzyme-linked immunosorbent assay. The kits were selected from Beijing Rongzhi Haida Biotechnology Co., Ltd. ③ In oxidative stress indicators, before treatment and after 4 weeks of treatment, the synovial fluid of the patient was collected, centrifuged at 2500 r/min for 5 min, and the supernatant was collected by enzyme-linked immunosorbent assay to detect superoxide dismutase (SOD), glutathione peroxidase (GSHPx), malondialdehyde (MDA), and nitric oxide (NO) levels, and the kits were selected from Shanghai Enzyme Link Biopharmaceutical Co., Ltd.; ④ serum Toll-like receptor 4 (TLR4), transforming growth factor $\beta$ (TGF-$\beta$) levels, and serum samples were taken from patients before treatment and after 4 weeks of treatment (the operation method is the same as ②), the enzyme-linked immunosorbent assay was used to detect TLR4 and TGF-$\beta$, and the kit was selected from Nanjing Jinyibai Biotechnology Co., Ltd.

*2.6. Statistical Processing.* The statistical software SPSS22.0 was used to process the data, the count data were expressed as ($n$, %), and the $\chi^2$ test was performed. The measurement data (such as WOMAC score, bone metabolism index, oxidative stress index, and serum TLR4 and TGF-$\beta$ levels) was expressed as the mean ± standard deviation ($\bar{x} \pm s$). Graphing was done with GraphPad Prism 8 software.

## 3. Results

*3.1. Comparison of WOMAC Scores between the Two Groups.* Before treatment, the WOMAC score of the observation group was (106.74 ± 20.14) points, and that of the control group was (108.02 ± 19.45) points. After treatment, the WOMAC scores of both groups decreased, the observation group was (42.45 ± 10.83) points, and the control group was (67.81 ± 14.63) points; the WOMAC score of the observation group was lower than that of the control group, and the difference was statistically significant ($t = -8.948$, $P < 0.05$), as shown in Figure 1.

*3.2. Comparison of Bone Metabolism Indexes between the Two Groups.* Before treatment, there was no statistical difference in three bone metabolism indexes between the two groups ($P > 0.05$). After treatment, the levels of COMP, CTX-II, and MMP-3 in the two groups were decreased, the levels of COMP, CTX-II, and MMP-3 in the observation group were lower than those in the control group, and the difference was statistically significant ($P < 0.05$), as shown in Table 1.

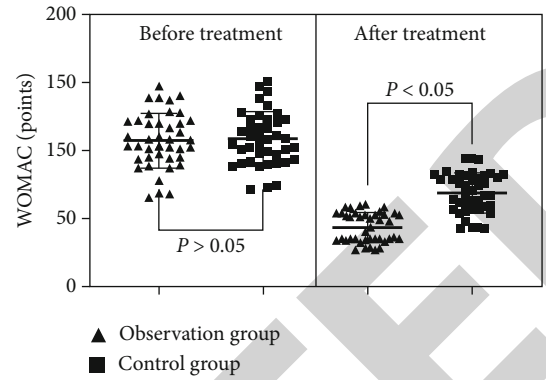


Figure 1: Comparison of WOMAC scores between the two groups.

*3.3. Comparison of Oxidative Stress Indicators between the Two Groups.* Before treatment, there was no significant difference in the four oxidative stress indicators between the two groups ($P > 0.05$). After treatment, the levels of SOD and GSHPx in the two groups were increased, while the levels of MDA and NO were decreased, the levels of SOD and GSHPx in the observation group were higher than those in the control group, and the levels of MDA and NO were lower than those in the control group, with statistical significance ($P < 0.05$), as shown in Table 2.

*3.4. Comparison of TLR4 and TGF-β Levels between the Two Groups.* Before treatment, the levels of TLR4 and TGF-$\beta$ in the observation group were (18.05 ± 1.20) ng/ml and (20.12 ± 4.34) $\mu$g/ml, and those in the control group were (18.07 ± 1.21) ng/ml and (20.07 ± 4.39) $\mu$g/ml; after treatment, the levels of TLR4 in both groups decreased, while the levels of TGF-$\beta$ increased. The levels of TLR4 and TGF-$\beta$ in the observation group were (10.45 ± 1.32) ng/ml and (28.45 ± 5.36) $\mu$g/ml, respectively, and the control group was (14.45 ± 1.40) ng/ml and (24.64 ± 5.07) $\mu$g/ml; the level of TLR4 in the observation group was lower than that in the control group, but the level of TGF-$\beta$1 was higher than that in the control group, and the differences were statistically significant ($t = -13.308$, 3.307, $P < 0.001$), as shown in Figure 2.

## 4. Discussions

KOA is a common orthopedic disease in the elderly, and its incidence is closely related to knee strain and body trauma. Some scholars have found that most patients with KOA are caused by the reduction of endogenous sodium hyaluronate in synovial fluid and cartilage or the imbalance of synthetic degradation [8, 9]. There is currently no targeted radical cure for KOA in clinical treatment. Most of them focus on relieving knee joint degeneration, improving pain, preventing disease progression, and ensuring a high quality of life for patients [10]. In past clinical experience, intra-articular injection of sodium hyaluronate can form a protective film on the knee joint surface to avoid tissue adhesion, thereby improving joint mobility [11]. However, some patients have a high recurrence rate after receiving

Table 1: Comparison of bone metabolism indexes between the two groups ($\bar{x} \pm s$).

| Group | Time | COMP (ng/l) | CTX-II (ng/l) | MMP-3 (ng/l) |
|---|---|---|---|---|
| Observation group ($n = 41$) | Before treatment | 4.01 ± 0.52 | 560.37 ± 100.28 | 3.78 ± 0.40 |
| | After treatment | 2.94 ± 0.35 | 430.16 ± 82.45 | 2.60 ± 0.30 |
| | $t$ | 19.318 | 10.895 | 16.866 |
| | $P$ | <0.001 | <0.001 | <0.001 |
| Control group ($n = 41$) | Before treatment | 4.03 ± 0.49 | 570.14 ± 108.65 | 3.80 ± 0.37 |
| | After treatment | 3.32 ± 0.37 | 483.54 ± 90.45 | 3.31 ± 0.29 |
| | $t$ | 12.346 | 5.547 | 10.063 |
| | $P$ | <0.001 | <0.001 | <0.001 |
| Before treatment between groups | $t$ | -0.179 | -0.423 | -0.235 |
| | $P$ | 0.858 | 0.673 | 0.815 |
| After treatment between groups | $t$ | -4.774 | -2.793 | -10.894 |
| | $P$ | <0.001 | 0.007 | <0.001 |

Table 2: Comparison of oxidative stress indicators between the two groups ($\bar{x} \pm s$).

| Group | Time | SOD (nU/ml) | GSHPx (U/l) | MDA (nmol/ml) | NO ($\mu$mol/l) |
|---|---|---|---|---|---|
| Observation group ($n = 41$) | Before treatment | 80.14 ± 7.90 | 83.12 ± 6.68 | 7.54 ± 1.30 | 24.15 ± 2.70 |
| | After treatment | 118.45 ± 10.38 | 116.64 ± 10.45 | 3.72 ± 0.60 | 16.34 ± 1.57 |
| | $t$ | -30.193 | -23.082 | 17.966 | 23.398 |
| | $P$ | <0.001 | <0.001 | <0.001 | <0.001 |
| Control group ($n = 41$) | Before treatment | 81.50 ± 7.42 | 84.00 ± 6.48 | 7.59 ± 1.25 | 24.20 ± 2.62 |
| | After treatment | 99.67 ± 8.45 | 102.45 ± 8.37 | 5.12 ± 0.80 | 19.31 ± 1.98 |
| | $t$ | -16.824 | -17.253 | 15.355 | 13.314 |
| | $P$ | <0.001 | <0.001 | <0.001 | <0.001 |
| Before treatment between groups | $t$ | -0.803 | -0.606 | -0.177 | -0.085 |
| | $P$ | 0.424 | 0.547 | 0.860 | 0.932 |
| After treatment between groups | $t$ | 8.984 | 6.787 | -8.963 | -7.526 |
| | $P$ | <0.001 | <0.001 | <0.001 | <0.001 |

treatment, and the effect on improving the quality of life is limited. In recent years, with the continuous updating of medical concepts, TCM treatment for KOA patients has been recognized clinically in China on the basis of modern medical treatment [12].

Knee arthroscopy is a commonly used minimally invasive cleaning method in orthopaedics. It has obvious effects on improving joint wear and meniscus damage, removing abnormal knee joint debris and proliferative tissue, and improving joint mobility. After knee arthroscopy, most patients can effectively control the development of the disease and avoid the need for knee replacement [13, 14]. In this study, the WOMAC scores of 41 control patients were significantly reduced after arthroscopic surgery, and the bone metabolism indexes and oxidative stress indexes were well improved, indicating that arthroscopic surgery does have a certain therapeutic effect on KOA patients. This is because in the process of arthroscopic surgery, continuous irrigation can effectively remove necrotic tissue, improve the internal environment of the body, and speed up recovery. However, from the analysis of clinical data in recent years, due to the different pathogenic factors and constitutions of patients, the effective rate of surgery has been significantly decreased in some patients. Therefore, selecting certain combined treatment according to the situation of patients after knee arthroscopy can improve the overall treatment effect of KOA [15].

There is no separate definition of KOA in traditional Chinese medicine, but it can be attributed to the field of "arthromyodynia." The theory of TCM believes that KOA is related to the six exogenous pathogens caused by aging and physical insufficiency, lack of righteousness, and deficiency of the body. Dampness and cold are their causes; so, TCM treatment of KOA should focus on nourishing the

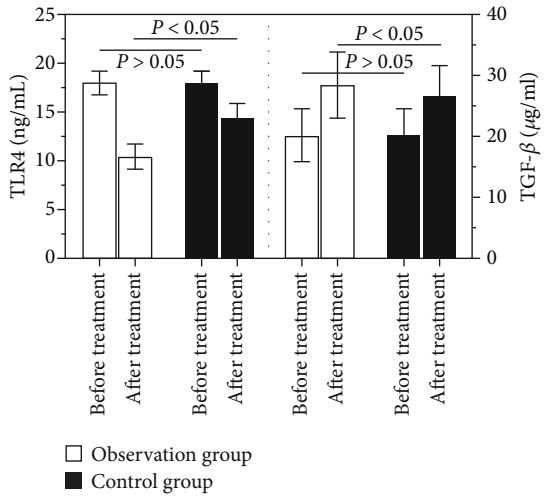


Figure 2: Comparison of TLR4 and TGF-$\beta$ levels between the two groups.

liver and kidney, dispelling rheumatism, relieving pain, and dredging meridians [16–19]. Duhuo Jisheng Decoction is a TCM decoction made by Sun Simiao, a famous Chinese medical scientist. The results of this study showed that after treatment, the WOMAC score of the observation group was significantly lower than that of the control group, and its bone metabolism indexes and oxidative stress indexes improved more obviously. This shows that the Duhuo Jisheng Decoction combined with arthroscopic surgery can significantly improve the efficiency of symptom recovery and knee joint activity. In addition, by detecting the levels of TLR4 and TGF-$\beta$, it was found that the level of TLR4 in the observation group was lower than that of the control group, and the level of TGF-$\beta$ was higher than that of the control group. TLR4 mainly mediates innate immunity and inflammatory response, and TGF-$\beta$ can decompose chondrocytes. Proteoglycan produced a reversal effect, which further indicated that the modified application of Duhuo Jijitang could improve cartilage metabolism and internal environment inflammation to some extent. It is speculated that the reason is that Duhuo Jisheng Decoction uses Duhuo as the monarch medicine, which can control the wind and eliminate the pathogens of wind, cold, and dampness between the "lower energizer" and the muscles and bones. Asarum can disperse the wind-cold in the yin meridian and has analgesic effect. Ginseng can invigorate Qi and spleen; Angelica can activate blood and nourish Qi. Combination of various drugs can treat arthralgia caused by deficiency of the liver and kidney and deficiency of Qi and blood. In addition, we also modified the original prescription of Duhuo Jisheng decoction according to different constitutions of patients: for patients with severe pain, add Fuzi 5 g, for those with severe limbs, add Atractylodes 6 g and Papaya 9 g, if the congestion persists, add 9 g of Salvia miltiorrhiza and 12 g of Chickweed, and for those with a longer course of disease, add 9 g of Dilong and a centipede. We have summarized in the previous clinical practice that when the original recipe of Duhuo Jisheng Decoction was modified with the above chemotherapy drugs according to the characteristics of patients' conditions, the efficacy of the drugs could be significantly improved. At the same time, the modified application of Duhuo Jisheng Decoction can also improve the symptoms of patients according to different conditions, regulate the body's inflammatory factors and oxidative stress with multiple targets and multiple pathways, and inhibit the degradation of extracellular matrix.

In conclusion, compared with arthroscopic surgery alone, combined with modified Duhuo Jisheng Decoction therapy can better relieve the clinical symptoms of KOA patients and improve their bone metabolism, oxidative stress indexes and serum TLR4, and TGF-$\beta$1 levels, so as to reduce knee joint inflammation injury.

## Data Availability

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

## Conflicts of Interest

The authors declare no conflict of interest, financial, or otherwise.

## Authors' Contributions

Xiangjing Zeng and Shaoru Lin are co-first authors.

## Acknowledgments

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*Retraction*

# Retracted: Clinical Effect of Open Reduction and Internal Fixation for Femoral Neck Fracture in Young Adults and Related Factors of Femoral Head Necrosis

**Journal of Environmental and Public Health**

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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:

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(2) Discrepancies in the description of the research reported
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(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. Lin, D. Yang, and W. Sui, "Clinical Effect of Open Reduction and Internal Fixation for Femoral Neck Fracture in Young Adults and Related Factors of Femoral Head Necrosis," *Journal of Environmental and Public Health*, vol. 2022, Article ID 2974830, 5 pages, 2022.

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*Research Article*

# Clinical Effect of Open Reduction and Internal Fixation for Femoral Neck Fracture in Young Adults and Related Factors of Femoral Head Necrosis

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*Objective*. The purpose of this article is to analyze the clinical effect of open reduction and internal fixation on femoral neck fracture in young adults and to explore the related factors of femoral head necrosis. *Methods*. The subjects were young and middle-aged femoral neck fracture patients admitted to our hospital from July 2019 to July 2021. 90 patients were randomly divided into two groups according to different treatment methods. The control group ($n = 45$) was treated with open reduction and internal fixation with hollow nails, while the observation group ($n = 45$) was treated with closed reduction and internal fixation with hollow nails. The clinical effects and adverse reactions of the two groups and the risk factors of avascular necrosis of femoral head were analyzed. *Results*. Compared with the control group, the operation time of the observation group was significantly shortened ($P < 0.05$), the amount of bleeding during the operation was significantly reduced ($P < 0.05$), and the incidence of total adverse reactions was significantly reduced ($P < 0.05$). The HSS score and Harris score of the two groups were significantly decreased after treatment ($P < 0.05$), but there was no significant difference in the above scores between the two groups before and after treatment ($P > 0.05$). The related risk factors of necrosis included gender, Garden classification, time from injury to operation, and time of weight bearing after operation ($P < 0.05$) but not related to age and cause of injury ($P > 0.05$). *Conclusion*. Open and closed reduction and internal fixation can effectively treat femoral neck fracture in young adults. The risk factors of adverse reactions of osteonecrosis include gender, Garden classification, time from injury to operation, and weight-bearing time after operation.

## 1. Introduction

Femoral neck fractures are common hip traumas caused by transmitted or twisting violence and are primarily fractures caused by rotational and angling stresses from top-down forces acting on the femoral head and neck [1, 2]. The quality of reduction, more than time to surgery, has the most impact on optimizing outcomes and function. There is no consensus in the best fixation construct for these fractures. Neck shortening and varus collapse are the most common challenges of the current fixation options. Use of newer implants is being reported with cautious optimism, and further studies are needed. Young adults are a common population of femoral neck fractures, and the incidence is increasing year by year [3]. At the same time, patients with femoral neck fracture are prone to unhealed fractures and femoral head necrosis, which seriously affects the prognosis of patients [4]. Manipulative reduction and internal fixation are a common clinical treatment for femoral neck fractures, such as open reduction and internal fixation and closed reduction and internal fixation [5]. Fracture internal fixation is aimed at achieving the reduction of the patient's anatomy, restoring the blood supply inside the femoral head, and protecting the femoral head. Especially in young and middle-aged patients, internal fixation has a positive effect on preventing long-term complications such as femoral head necrosis and bone nonunion after fracture surgery [6]. This study analyzed the clinical effect of reduction and internal

fixation on the treatment of femoral neck fractures, explored the related factors of femoral head necrosis, and provided reference for clinical treatment.

## 2. Materials and Methods

*2.1. Research Objects.* The research subjects were young and middle-aged patients with femoral neck fractures admitted to our hospital from July 2019 to July 2021. Inclusion criteria were as follows: age 25–50 years and have typical femoral fracture manifestations. Femoral fractures were diagnosed by CT plain scan combined with three-dimensional reconstruction or magnetic resonance imaging. The clinical data were complete, the patients agreed to this study, and the patients were followed up for more than 6 months. Exclusion criteria were as follows: patients with severe cardiac and renal organic lesions or dysfunction, female patient in pregnancy, patients with severe metabolic system diseases or neurological dysfunction, patients with concurrent malignant tumors, patients complicated with fractures in other parts, and clinical data being incomplete or the subjects dropping out of the study. Ninety patients were randomly divided into two groups according to the treatment method: the control group ($n = 45$) patients were treated with open reduction cannulated screw internal fixation, and the observation group ($n = 45$) patients were treated with closed reduction cannulated screw internal fixation. There were no significant differences in general data such as the gender ratio, age distribution, injury cause, Garden classification, and postoperative weight-bearing time between the two groups ($P > 0.05$). All research subjects were informed and consented, and this study complied with the requirements of the Ethics Committee of Qionghai People's Hospital.

*2.2. Methods.* 90 patients were randomly divided into two groups according to the treatment method: control group ($n = 45$) patients were treated with open reduction cannulated screw internal fixation: supine position, routine disinfection and drape after anesthesia, and Watson-Jones (WJ). A 10 cm longitudinal incision was made through the approach to separate the patient's sartorius muscle and tensor fascia lata muscle space, and the joint capsule of the study object was incised (in a T-shaped manner), and components such as hematoma and loose bodies were removed. The synovium was swollen, and the lateral cortical bone of the upper segment of the femur was exposed, the surrounding contractile muscles were cut off, the fracture site was exposed, the limb was distracted, and the rotation and abduction reduction were performed. After confirming the reduction of the fracture by X-ray fluoroscopy, the guide pin is drilled through the fracture line and then enters the femoral neck. The hollow screw core is used to fix the perspective shot position and the lateral position. First stop bleeding, then wash the joint cavity, suture the joint capsule of the patient, repair the ligament tissue around the joint at the operation site, and finally conduct layered incision. The patients in the observation group ($n = 45$) were fixed with closed reduction cannulated screws: supine position, routine disinfection and drape after anesthesia, traction using a traction bed under "G-arm" fluoroscopy, closed reduction, and "G-arm" fluoroscopy for confirmation; under the reduction and traction to maintain satisfactory reduction, make a small incision on the side of the greater trochanter and drill into the guide needle and take "G-arm" positive and lateral X-ray films and suture the patient's incision after hemostasis.

*2.3. Observation Indicators.* In this study, the clinical effects of the two groups of patients were analyzed, mainly including the operation time, intraoperative blood loss, and hospitalization time. The recovery of the joints of the patients was analyzed, and the changes of the HSS score (HSS knee joint scale) and Harris score (Harris hip function scale) were mainly investigated. This article also analyzes the clinically relevant risk factors for femoral head necrosis, including gender, Garden classification, postoperative weight-bearing time, age, and causes of injury. The Garden classification consists of four grades: type I incomplete stable fracture with impaction in valgus, type II complete but nondisplaced with two groups of trabeculle in line, type III partially displaced with varus with all three trabeculle disturb, and type IV completely displaced with no contact between the fracture fragments.

*2.4. Statistical Analysis.* SPSS 21.0 software was used for data analysis. The comparison of measurement data between the two groups was carried out first by normality and homogeneity of variance the test, and the comparison of eligible data was analyzed by independent sample $t$-test, and the results were expressed as mean ± standard deviation ($\bar{x} \pm S$). The count data between the two groups were expressed as percentages, and the comparison was performed using the chi-square test. $P < 0.05$ means that there is a statistical difference in the difference.

## 3. Results

*3.1. Analysis of the Surgical Conditions of the Two Groups of Patients.* The study found that compared with the control group, the operation time of the observation group was significantly shortened ($P < 0.05$) and the intraoperative blood loss was significantly reduced ($P < 0.05$), while there was no significant difference in the hospitalization time between the two groups ($P > 0.05$), as shown in Table 1.

*3.2. Comparison of Postoperative Pain Scores and Hip Joint Function Analysis between the Two Groups of Subjects.* The study found that the HSS score and Harris score of the two groups of patients were significantly decreased after treatment ($P < 0.05$), However, there was no significant difference in the scores of the above indicators between the two groups before and after treatment ($P > 0.05$), as shown in Table 2.

*3.3. Complications.* The results showed that the complications of the two groups of subjects mainly included bone nonunion and avascular necrosis of the femoral head and the incidence of total adverse reactions in the control group was significantly higher than that in the observation group ($P < 0.05$), as shown in Table 3.

Table 1: Analysis of the surgical conditions of the two groups of patients.

| Group | | Operation time (min) | Intraoperative bleeding (ml) | Length of hospital stay (d) |
|---|---|---|---|---|
| Test group | Number of cases (45) | 107.53 ± 11.43 | 54.65 ± 7.86 | 10.04 ± 2.09 |
| Control group | Number of cases (45) | 150.54 ± 12.65 | 124.56 ± 11.54 | 11.08 ± 2.15 |
| $t$ | | 4.365 | 3.980 | 5.637 |
| $P$ | | <0.05 | <0.05 | >0.05 |

Table 2: Comparison of postoperative pain scores and hip joint function of the two groups of subjects.

| Group | | HSS score | Harris score |
|---|---|---|---|
| Control group (45) | Before treatment | 65.87 ± 7.09 | 45.47 ± 8.43 |
| | After treatment | 88.87 ± 9.33 | 70.54 ± 6.71 |
| $t$ | | 3.895 | 4.901 |
| $P$ | | <0.05 | <0.05 |
| Test group (45) | Before treatment | 66.08 ± 6.71 | 45.98 ± 8.23 |
| | After treatment | 90.54 ± 8.32 | 72.43 ± 9.06 |
| $t$ | | 5.784 | 4.413 |
| $P$ | | <0.05 | <0.05 |

Table 3: Analysis of the occurrence of complications.

| Group | | Does not heal of the bone (%) | Avascular necrosis of the femoral head (%) | Total adverse reaction rate (%) |
|---|---|---|---|---|
| Control group | Number of cases (45) | 11 (12.4%) | 2 (2.2%) | 13 (14.6%) |
| Test group | Number of cases (45) | 4 (4.4%) | 5 (5.5%) | 9 (9.9%) |
| $x^2$ | | 2.359 | 4.385 | 6.995 |
| $P$ | | <0.05 | <0.05 | <0.05 |

*3.4. Analysis of Risk Factors for Femoral Head Necrosis.* The study found that the related risk factors of femoral head necrosis included gender, Garden classification, and postoperative weight-bearing time ($P < 0.05$) but were not related to age and cause of injury ($P > 0.05$), as shown in Table 4.

## 4. Discussion

Patients with femoral neck fractures are prone to complications such as nonunion and femoral head ischemia, which have a significant impact on the quality of life of patients. The goal for surgical treatment of femoral neck fractures in young patients is achieving union through an anatomic reduction and stable fixation while avoiding osteonecrosis. The time to surgery remains controversial. At present, manual reduction and internal fixation are usually used in clinical treatment of femoral neck fractures. Manual reduction and internal fixation can effectively achieve the reduction of the anatomical structure, restore the blood supply of the patient's femoral head, and effectively prevent the occurrence of complications. The most descriptive classification used for femoral neck fractures in young patients is the Pauwels classification. As the degree of the femoral neck fracture line relative to the horizontal plane increases, the types differ (<30 degrees type I, between 30 degrees and 50 degrees type II, and >50 degrees type III), Type III fractures are associated with increasing risks of fixation failure, osteonecrosis, and malunion or nonunions. This study found that the operation time, intraoperative blood loss, and incidence of total adverse reactions in the observation group were significantly reduced. The HSS score and Harris score of the two groups of patients were significantly decreased after treatment, but there was no significant difference in the above scores between the two groups before and after treatment. The related risk factors of osteonecrosis included gender, Garden classification, and postoperative weight-bearing time but were not related to age and the cause of injury.

Fracture internal fixation can achieve the reduction of the anatomical structure of fracture patients and has a positive effect on restoring the normal maintenance of blood in the patient's femoral head. In an analysis of the comparative study of minimally invasive plate fixation reduction surgery

Table 4: Clinical risk factors for necrosis of the femoral head.

| Indexes | | Avascular necrosis of the femoral head | Number of cases (35) | Nonavascular necrosis of the femoral head | Number of cases (35) | $x^2$ | $P$ |
|---|---|---|---|---|---|---|---|
| Gender | Male | 25 | | 75 | | 3.524 | <0.05 |
| | Female | 10 | | 70 | | | |
| Age | <40 years | 15 | | 68 | | 0.458 | >0.05 |
| | ≥40 years | 20 | | 77 | | | |
| Cause of injury | Hit | 20 | | 76 | | 0.771 | >0.05 |
| | Fall | 15 | | 69 | | | |
| Garden type | I/II | 10 | | 67 | | 3.452 | <0.05 |
| | III/IV | 25 | | 78 | | | |
| Postoperative weight-bearing time | <3 months | 25 | | 55 | | 3.123 | <0.05 |
| | ≥3 months | 10 | | 90 | | | |

with fractures, it was found that the effect of minimally invasive plate fixation reduction surgery was better than that of open reduction and internal fixation and the incidence of complications was lower [7]. The treatment effect of minimally invasive internal fixation on patients with distal tibia fractures is better than that of open reduction and internal fixation with a plate [8], and closed reduction and internal fixation for supracondylar fractures of the humerus have a good surgical effect and can significantly reduce the number of children with family burden [9]. The tibia plateau is an important loading structure of the knee joint, and its fractures are mostly caused by violence directly or indirectly. Tibia plateau fracture is a high-energy trauma, which will have a certain impact on the stability and function of the patient's knee joint, so its treatment has always been a difficult point in clinical treatment. The clinical indicators of the closed reduction group after treatment are better than those of the open reduction group [10], and compared with open reduction, closed reduction and internal fixation can speed up the healing of fractures and promote the recovery of normal physiological function of the knee joint [11]. Previous studies have also confirmed that closed reduction has a very significant effect on the treatment of lower tibial fractures and has a significant effect on the healing rate of fractures with good joint mobility [12] and internal fixation for ankle fractures after treatment has fewer complications and can be significantly improved. For ankle joint function, the effect is significant [13]. This study also found that the operation time of the observation group (closed reduction and internal fixation) was significantly shortened, the intraoperative blood loss was significantly reduced, and the incidence of total adverse reactions was significantly reduced. The HSS scores and Harris scores of the two groups of patients were significantly decreased after treatment, but there was no significant difference in the above scores between the two groups before and after treatment, indicating that open and closed reduction and internal fixation can effectively treat femoral neck fractures in young adults.

Most intracapsular femoral neck fractures occur in the elderly population. Femoral neck fractures in young patients are much less common and typically a result of a high-energy mechanism. However, femoral head necrosis is a common complication after reduction and internal fixation and its occurrence is related to a variety of internal and external factors [14, 15]. When analyzing the risk factors of femoral head necrosis after internal fixation in elderly patients with femoral neck fracture, it was also found that the time from injury to operation was longer, whether the internal fixator was taken out and the time to take out. The anatomical displacement of the fracture and the effect of reduction after displacement are the clinical risk factors for the occurrence of femoral head necrosis [16]. This study found that the complications of the two groups of subjects mainly included bone nonunion and avascular necrosis of the femoral head and related risk factors for adverse reactions of osteonecrosis included gender, Garden classification, and postoperative weight-bearing time. In future research, we will further carry out the research on the correlation between related risk factors and complications of femoral head necrosis and analyze the correlation coefficient of each factor, so as to provide reference for more reasonable clinical treatment and improvement of patient prognosis.

Therefore, both open and closed reduction and internal fixation can effectively treat femoral neck fractures in young adults and the disease-related risk factors for adverse reactions of osteonecrosis include gender, Garden classification, and postoperative weight-bearing time.

## Data Availability

The raw data supporting the conclusion of this article will be available from the authors without undue reservation.

## Conflicts of Interest

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

## Authors' Contributions

Guanghui Lin and Dongliang Yang are co-first authors.

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*Retraction*

# Retracted: Retrospective Case Analysis of 104 Cases of Talipes Equinus

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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:

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(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

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(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

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

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

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## References

[1] Q. Tan, G. Yang, Y. Liu et al., "Retrospective Case Analysis of 104 Cases of Talipes Equinus," *Journal of Environmental and Public Health*, vol. 2022, Article ID 9769092, 6 pages, 2022.

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*Research Article*

# Retrospective Case Analysis of 104 Cases of Talipes Equinus

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A retrospective study of 104 patients (81 male and 23 females, the age range from 2 to 288days) with talipes equinus was conducted to explore the case factors associated with it. We analyzed and discussed the correlation of plaster correction times, age of first visit, gender, and birthplace of patients in the department and understood their correlation and causality. The data were analyzed using frequency analysis, normality test, chi-square goodness-of-fit test, chi-square test, and PLS regression. The findings are set out below. All the distributions of the number of plaster casts in the samples did not have normality. Therefore, we used the nonparametric test and partial least squares regression (PLS regression) and found that the number of plaster casts was more closely related to the age at first visit, gender, and birthplace and had a strong positive correlation. There was a negative correlation between the times of plaster correction and the compliance of braces. The lower the compliance of patients with braces, the more times the plaster correction will be conducted.

## 1. Introduction

Talipes equinus is a common congenital deformity of the foot [1], mostly caused by cerebral hypoplasia [2]. During development, the tendons and ligaments of the foot fail to keep pace with the development of other tendons and ligaments of the foot, leaving each bone in an abnormal position [3]. This results in varus, stiff feet, and inability to return to the normal position [4]. It is estimated that one in every 1000 live births is affected by talipes equinus [5].

In contrast to successfully treated talipes equinovarus, knowledge of the kinematic characteristics of recurrent talipes equinovarus facilitates early recognition of recurrence and improves treatment planning [6]. Supportive noncompliance is considered to be the major cause of treatment failure [7]. The assessment of talar dysplasia was a prognostic factor for the efficacy of Ponseti's technique in the treatment of talipes equinovarus [8]. Because some patients are too young to fit or have a cast, the Ponseti method has the potential to recur with frequent complications [9]. The Ilizarov ring fixator is an effective and reliable method for the treatment of difficult and challenging talipes equinovarus [10] using the new unconstrained Ilizarov framework system technique to safely and progressively correct horse deformity without subluxation of the talus [11]. JESS is a useful technique for treating neglected, resistant, and relapsed cases of CTEV [12]. Mathematic tools have been widely used in medical analysis [13, 14].

Retrospective analysis has been extensively used in studies in which talipes equinus was associated with its treatment [15–17]. The general treatment of talipes equinus is correction, performed more than once, with a cast and mold support [18]. The Ponseti method is the gold standard for the treatment of talipes equinus [19–21]. The Ponseti method has a more pronounced correction rate in the treatment of talipes equinovarus than the Kite method [22]. Biomechanical function and long-term results in children treated with the Ponseti method in the middle childhood were closer to those in healthy individuals than in children treated with surgery alone [23]. An important aspect of the Ponseti™ casting technique is Achilles tendon amputation (AT) [24–26] to obtain a flexible foot rather than a fully corrected foot [27]. We analyzed and discussed the correlation of plaster correction times, age of first visit, gender, and birthplace of patients in the department and understood their correlation and causality.

## 2. Objective and Methods

Inclusion criteria: 104 (81 male and 23 females) patients with talipes equinus, Age: 2 to 288 (days) in our hospital.

Exclusion criteria: unable to collect data.

Statistical analysis was performed on all data using SPSS 23.0 software. Frequency analysis, normality test analysis, chi-square goodness-of-fit test, chi-square test analysis, and PLS regression were used.

Operation instructions: the talipes equinus operation was divided into two parts: in the first stage, the external fixator was used to allow the heel to fall to the ground and the instep to be flat, which would take about three to six months. Further treatment is required according to the patient's recovery. In some patients, recovery is good, and treatment ends there. The external frame can be removed. However, more than half of the patients still feel uncomfortable in their feet after removing the external frame and even have a tendency of relapse. Some patients require a second procedure, arthrodesis, after a second evaluation by the doctor. Generally, the first stage of arthrodesis is not considered.

## 3. Results and Discussion

Table 1 shows that there are 104 sample cases in total. From the perspective of gender, more than 70% of the samples are "male", and three become "female". More than 40% of samples in birthplace chose "rural area." The proportion of patients with affected side who chose the "right" side of the sample was 49.04% and the proportion of affected side who were bilateral was 34.62%. The majority of the plaster casts in the samples were corrected four times in 39.42%.

Table 1: Frequency analysis results.

| Name | Option | Frequency | Percentage (%) |
|---|---|---|---|
| Gender | Female | 23 | 22.12 |
| | Male | 81 | 77.88 |
| Birthplace | Rural area | 50 | 48.08 |
| | Country town | 17 | 16.35 |
| | Urban area | 37 | 35.58 |
| Affected side | Bilateral | 36 | 34.62 |
| | Right | 51 | 49.04 |
| | Left | 17 | 16.35 |
| Gypsum correction times | 2.0 | 4 | 3.85 |
| | 3.0 | 29 | 27.88 |
| | 4.0 | 41 | 39.42 |
| | 5.0 | 17 | 16.35 |
| | 6.0 | 8 | 7.69 |
| | 7.0 | 4 | 3.85 |
| | 8.0 | 1 | 0.96 |
| Add up to | | 104 | 100.0 |

As shown in Table 2, Jarque-Bera test results based on the data showed that all the gypsum correction times presented significant differences ($p < 0.05$), which meant that the original hypothesis was rejected, and the distribution of gypsum correction times in the samples all did not have normal characteristics. Therefore, the nonparametric test is used. For those who can use parametric test, parametric test is preferred, and for those who cannot meet the conditions, nonparametric test is selected.

Parameters generally include $t$-test, analysis of variance (requirements: homogeneity and normal distribution of variance), which are generally used to measure data. Nonparametric tests are selected as follows: (1) the overall distribution is not easy to determine (that is, I do not know whether it is normal or not); (2) the distribution is nonnormal and there is no appropriate data conversion method; (3) grade data; and (4) there is no certain data in one or two sections (for example, the data in one section is >50, which is an open interval).

(1) Parametric test is an assumption for parameters, while nonparametric test is an assumption for overall distribution, which is an important feature to distinguish parametric test from nonparametric test

(2) The fundamental difference between the two is that the parameter test should make use of the general information (general distribution, some general parameter characteristics such as variance) and infer the general parameters with the general distribution and sample information; nonparametric test does not need to use the information of the population (population distribution, some parameter characteristics of the population such as variance) and infer the population distribution with the sample information

(3) Parameter inspection can only be used for equidistant data and proportional data, while nonparametric inspection is mainly used for counting data. It can also be used for equidistant and proportional data, but the accuracy will be reduced

The chi-square goodness-of-fit test is a nonparametric test that tests whether a sample's overall distribution is equal to some given theoretical distribution based on its frequency distribution. A chi-square goodness-of-fit test was performed for gender, birthplace, and number of plaster casts to see if the data were distributed as expected. As shown in Table 3, gender, birthplace, and the number of gypsum correction all showed significant ($p < 0.05$). This meant that the original hypothesis (original hypothesis: the actual distribution ratio was consistent with the expected ratio) that the data were not distributed as expected was rejected, indicating that the various types of data for subjects were not distributed equally. Thus, in the correlation analysis, each category item cannot show the relationship between the data items, as shown in Table 4.

As shown in Table 4, the chi-square test (cross-analysis) was used to study the difference relationship of the number

Table 2: Analysis results of normality test.

| Name | Sample size | Average value | Standard deviation | Skewness | Kurtosis | Kolmogorov-Smirnov test | | Shapiro-Wilk test | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Statistics $d$ value | $p$ | Statistic $w$ value | $p$ |
| Gypsum correction times | 109 | 4.147 | 1.208 | 0.707 | 0.452 | 0.236 | ≤0.001 | 0.907 | ≤0.001 |

Table 3: Chi-square goodness of fit test.

| Name | Item | Actual frequency | Expected frequency | Residual | Actual proportion | Desired proportion | $\chi^2$ | $p$ |
|---|---|---|---|---|---|---|---|---|
| Gender | Female | 23.000 | 52.000 | -29.000 | 22.12% | 50.00% | 32.346 | ≤0.001 |
| | Male | 81.000 | 52.000 | 29.000 | 77.88% | 50.00% | | |
| Birthplace | Rural area | 5 ≤ 0.001 | 34.667 | 15.333 | 48.08% | 33.33% | 15.942 | ≤0.001 |
| | Country town | 17.000 | 34.667 | -17.667 | 16.35% | 33.33% | | |
| | Urban area | 37.000 | 34.667 | 2.333 | 35.58% | 33.33% | | |
| Gypsum correction times | 2.0 | 4.000 | 14.857 | -10.857 | 3.85% | 14.29% | 91.731 | ≤0.001 |
| | 3.0 | 29.000 | 14.857 | 14.143 | 27.88% | 14.29% | | |
| | 4.0 | 41.000 | 14.857 | 26.143 | 39.42% | 14.29% | | |
| | 5.0 | 17.000 | 14.857 | 2.143 | 16.35% | 14.29% | | |
| | 6.0 | 8.000 | 14.857 | -6.857 | 7.69% | 14.29% | | |
| | 7.0 | 4.000 | 14.857 | -10.857 | 3.85% | 14.29% | | |
| | 8.0 | 1.000 | 14.857 | -13.857 | 0.96% | 14.29% | | |

Table 4: Chi-square test analysis.

| Subject | Name | Gypsum correction times | | | | | | | Amount to | $\chi^2$ | $p$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2.0 | 3.0 | 4.0 | 5.0 | 6.0 | 7.0 | 8.0 | | | |
| Birthplace | Rural area | 0.00% | 55.17% | 41.46% | 52.94% | 50.00% | 100.00% | 0.00% | 48.08% | 18.069 | 0.114 |
| | Country town | 0.00% | 17.24% | 19.51% | 23.53% | 0.00% | 0.00% | 0.00% | 16.35% | | |
| | Urban area | 100.00% | 27.59% | 39.02% | 23.53% | 50.00% | 0.00% | 100.00% | 35.58% | | |
| Amount to | | 4 | 29 | 41 | 17 | 8 | 4 | 1 | 104 | | |
| Brace compliance | Not in details | 0.00% | 3.45% | 2.44% | 5.88% | 0.00% | 0.00% | 0.00% | 2.88% | 4.532 | 0.972 |
| | Noncooperative | 0.00% | 3.45% | 2.44% | 0.00% | 12.50% | 0.00% | 0.00% | 2.88% | | |
| | Cooperative | 100.00% | 93.10% | 95.12% | 94.12% | 87.50% | 100.00% | 100.00% | 94.23% | | |
| Amount to | | 4 | 29 | 41 | 17 | 8 | 4 | 1 | 104 | | |
| Gender | Female | 50.00% | 17.24% | 14.63% | 29.41% | 50.00% | 25.00% | 0.00% | 22.12% | 7.978 | 0.240 |
| | Male | 50.00% | 82.76% | 85.37% | 70.59% | 50.00% | 75.00% | 100.00% | 77.88% | | |
| Amount to | | 4 | 29 | 41 | 17 | 8 | 4 | 1 | 104 | | |

of gypsum corrections to birthplace, compliance with braces, and gender in total. From the above table, it can be seen that for birthplace, samples with different number of gypsum corrections to comply with braces, and gender in total did not show significant difference ($p > 0.05$), meaning that samples with different number of gypsum corrections to comply with birthplace, and gender in total showed consistent with each other and had no difference.

This may be due to the small sample size. We selected a nonparametric test, partial least squares regression (PLS regression), for our study. In order to deal with complex problems lacking theoretical knowledge, PLS adopts a "soft"

Table 5: Mathematical relationship expression between principal components of PLS regression and study items.

| | Principal component $U1$ |
|---|---|
| Brace compliance | -0.005 |
| Age at first visit | 0.648 |
| Gender | 0.485 |
| Birthplace | 0.587 |
| | Principal component $V1$ |
| Gypsum correction times | 1.000 |

Table 6: PLS regression principal components and study items (loading values).

| | Principal component $U1$ |
|---|---|
| Brace compliance | -0.088 |
| Age at first visit | 0.692 |
| Gender | 0.480 |
| Birthplace | 0.543 |
| | Principal component $V1$ |
| Gypsum correction times | -0.203 |

Table 7: Regression coefficients of the relationship between dependent variable $y$ and independent variable $x$ of PLS regression.

| | Gypsum correction times | Gypsum correction times (standardized) |
|---|---|---|
| Constant | 4.832 | ≤0.001 |
| Brace compliance | 0.003 | 0.001 |
| Age (number) at first visit | -0.004 | -0.131 |
| Gender | -0.279 | -0.098 |
| Birthplace | -0.155 | -0.119 |

method. No matter the size of the model, PLS method can get "instant estimation" and get gradual and correct estimation. PLS estimation is consistent and basically consistent (consistency at large) when the sample size is large and the explicit variables of each hidden variables are large. Methods cross-validation method of Parvandeh (Parvandeh, Yeh, Paulus, & McKinney, 2020) was used to examine the causal prediction relationship. We mainly examined the relationship between birthplace, fixture compliance, gender, and the age of initial visit ($x$) and the number of times of cast correction ($y$). PLS regression is generally used for regression analysis with less than 100 samples and possible collinearity problem. It is a combination of typical correlation, principal component analysis, and multivariate linear regression. In PLS regression, the independent variable x and dependent variable $y$ were first condensed and expressed by principal component $U$ and principal component $V$, respectively, and then the principal component $U$ and principal component $V$ were used as the bridges for research. The number of principal components was paired, and it usually needed to be judged by combining cross-validation with VIF index.

Table 5 shows the mathematical relationship expressions between principal component and study item, including the relationship expression between principal component $U$ and independent variable $x$, and the relationship expression between principal component $V$ and dependent variable $y$, respectively, as follows:

$$\begin{aligned}\text{Principal component } U1 = {} & -0.005^{*}\text{brace compliance} \\ & + 0.648^{*}\text{age at first visit} \\ & + 0.485^{*}\text{gender} \\ & + 0.587^{*}\text{birthplace}.\end{aligned}$$

$$\begin{aligned}\text{Principal component } V1 = {} & \\ & 1.000^{*} \\ & \text{gypsum correction times}.\end{aligned} \tag{1}$$

Table 6 is used to analyze the correlation between principal components and analysis items. Loading values refer to the factor loading values between the principal components and the study items. As shown in the above table, the factor load coefficient values of principal component $U$ 1 with respect to support compliance, first visit age, gender, and birthplace were -0.088, 0.692, 0.480, and 0.543, respectively, indicating that the number of plaster casts was more closely related to the first visit age, gender, and birthplace and had a strong positive correlation. Principal component $U1$ had a negative correlation with brace compliance. The lower the compliance of patients with braces, the more times the plaster correction will be conducted.

Table 7 shows the regression relationship expression between dependent variable $y$ and independent variable $x$, including the relationship expression between each dependent variable y and all independent variables, as follows:

$$\begin{aligned}\text{Number of plasters corrected} = {} & 0.001^{*}\text{support compliance} \\ & -0.131^{*}\text{Age at First Visit} \\ & -0.098^{*}\text{gender} \\ & -0.119^{*}\text{birthplace}.\end{aligned} \tag{2}$$

## 4. Conclusions

More than 70% of the samples were "male" and three were "female". More than 40% of samples in birthplace chose "rural area." The majority of the plaster casts in the samples were corrected four times in 39.42%.

All the distributions of the number of plaster casts in the samples did not have normal characteristics. Therefore, using the nonparametric test, partial least squares regression (PLS regression), we found that the number of plaster casts was more closely related to the age at first visit, gender, and birthplace and had a strong positive correlation. There

was a negative correlation between the times of plaster correction and the compliance of braces. The lower the compliance of patients with braces, the more times the plaster correction will be conducted.

## Data Availability

All data used to support the findings of this study are included within the article and in the supplementary information file (available here).

## Ethical Approval

Ethical approval for this work was obtained from the ethical review committee of Hunan Children's Hospital, China.

## Conflicts of Interest

The authors declare no conflict of interest.

## Acknowledgments

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## Supplementary Materials

Raw data for the analysis. *(Supplementary Materials)*

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*Retraction*

# Retracted: The Diagnostic Accuracy of Transabdominal and Transvaginal Color Doppler Ultrasound for Pregnant Women with Vasa Previa and Velamentous Cord Insertion

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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.

## References

[1] Q. Liu, Q. Zhang, and P. Liu, "The Diagnostic Accuracy of Transabdominal and Transvaginal Color Doppler Ultrasound for Pregnant Women with Vasa Previa and Velamentous Cord Insertion," *Journal of Environmental and Public Health*, vol. 2022, Article ID 1685783, 7 pages, 2022.

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*Research Article*

# The Diagnostic Accuracy of Transabdominal and Transvaginal Color Doppler Ultrasound for Pregnant Women with Vasa Previa and Velamentous Cord Insertion

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*Objective*. The objective of this study is to evaluate feasibility and accuracy of transabdominal color Doppler ultrasound (TA-CDUS) and transvaginal color Doppler ultrasound (TV-CDUS) as screening methods for pregnant women with vasa previa (VP) and velamentous cord insertion (VCI). *Methods*. A retrospective diagnostic accuracy study was performed on 5,434 pregnant women from 2018 to 2021, who underwent both TA-CDUS and TV-CDUS. Diagnostic performance of TA-CDUS and TV-CDUS was determined using specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and positive and negative likelihood ratios ($LR^+$ and $LR^-$), using the delivery information (gross examination) as the "Gold-standard". Patient records were reviewed for demographics and diagnosis. *Results*. The combination of VP and VCI was diagnosed in 37/5434 (0.68%) women at delivery. The sensitivity, specificity, PPV, NPV, and overall test accuracy of TA-CDUS were 72.97%, 99.85%, 77.14%, 99.81%, and 99.67%, respectively, for diagnosing VP with VCI. The corresponding values for TV-CDUS were 89.19%, 99.87%, 82.50%, 99.93%, and 99.80%, respectively. Moreover, the sensitivity of combination of TA-CDUS and TA-CDUS in determining VP with VCI was 97.30%, specificity 99.98%, PPV 97.30%, NPV 99.98%, and accuracy 99.96%. No significant difference in the misdiagnosis and missed diagnosis was found between the examination by TA-CDUS and TV-CDUS. *Conclusions*. Both TA-CDUS and TV-CDUS can be acceptable diagnostic tools for assessment of pregnant women with VP and VCI, with a better application of TV-CDUS with higher accuracy. The combination of TA-CDUS and TV-CDUS could provide an objective imaging basis for choosing clinical treatment strategies and predicting prognosis.

## 1. Introduction

Vasa previa (VP) are the umbilical vessels that is a complication of pregnancy in which fetal blood vessels lie outside the chorionic plate, in close proximity to the internal cervical os [1], which has been usually classified into (1) vessels connect a velamentous cord insertion (VCI) to the placenta and (2) vessels connect the lobes of a bilobed placenta or the placenta to a succenturiate lobe [2]. In VP cases, the protection of the umbilical cord by placental tissue or Wharton's jelly is absent, and the compression of the umbilical vessels may result in fetal heart decelerations and blood loss, as well as fetal mortality [3, 4]. It was reported that VP has an incidence of 0.0004~0.08% with a high fetal mortality due to fetal exsanguination [5, 6], which was commonly caused by second trimester low-lying placenta/placenta previa, bilobed/succenturiate lobe placenta, assisted reproductive technologies, vaginal bleeding, multiple gestation, and first trimester umbilical cord insertion in the lower 1/3 of the uterus [7].

VCI as a rare placental abnormality had an incidence of 0.23~1% and 15% in singleton gestation and monochorionic twin pregnancies, respectively [8, 9]. The associated pathology for VP is mainly fetal heart abnormalities, and the risk factors are assisted reproduction, low-lying placenta, placenta previa, accessory lobe/bilobated placenta, and multiple pregnancy [6]. VP prenatally with VCI may be associated with several pregnancy outcomes, such as preterm delivery

and postpartum hemorrhage [6, 10, 11]. The antenatal diagnosis increases the neonatal survival from 44% to 97% and improves the neonatal outcome [12]. Therefore, the correct diagnosis of the general classification of umbilical cord anomalies, namely, VP and VCI, is clinically important, while it still remains a challenge recently in the obstetrical practice.

Color Doppler ultrasound is a noninvasive diagnostic method for clinical diagnosis of obstetrics and gynecology diseases, which can be used to detect blood flow signals and highlight the umbilical vessel pathway [9, 13], which have proven to be valuable antepartum diagnostic tools for the early recognition of VP [14]. Moreover, ultrasound used color Doppler had a 74.1% sensitivity for the diagnosis of VCI with a positive predictive value (PPV) of 90.9% [15, 16], which was reported to have increased sensitivity to 100% with a lower PPV (85.7%) after the limited analysis by Rodriguez D et al. [17]. Currently, transabdominal color Doppler ultrasonography (TA-CDUS) and transvaginal color Doppler ultrasonography (TV-CDUS) are both used in the clinical diagnosis of several diseases, such as uterine adenomyoma and uterine fibroids [18], endometrial polyps [19], and ventriculo-coronary communications [20]. However, both of which have their own advantages and limitations [18]. Transabdominal ultrasound (TAS) and transvaginal ultrasound (TVS) examinations performed during the mid-trimester are a valuable tool in terms of achieving a timely and accurate diagnosis of VP [21] or VCI [22], especially with the color Doppler, which could increase its diagnostic accuracy [19].

At present, we determined the value and the comparison of TA-CDUS and TV-CDUS in distinguishing the patients with VP and VCI. Moreover, we also showed the combined value in the diagnosis of the included pregnant women.

## 2. Methods and Materials

*2.1. Participants.* We retrospectively reviewed the clinical data of 5,434 women from 2018 to 2021, who received cesarean delivery in our hospital. All participants at 22~36 weeks' gestation underwent both TA-CDUS and TV-CDUS Doppler ultrasound. Inclusion criteria are as follows: (1) older than 18 years and (2) of singleton pregnancy. Exclusion criteria are as follows: (1) patients with coagulation dysfunction; (2) women with incomplete data; (3) women with multiple pregnancies; and (4) patients were complicated with reproductive system malignancies.

*2.2. Ultrasound Examinations with TA-CDUS and TV-CDUS.* All patients were allotted approximately 20 min for TA-CDUS in the second trimester and TV-CDUS in the third trimester using Mindray Resona 7 (Shenzhen, China) and Voluson E10 GE ultrasound machine with an RM6C transducer (GE Medical Systems, Zipf, Austria) equipped with a transabdominal 1~5 MHz convex probe and with a 5~9 MHz convex vaginal transducer. After the bladder was emptied, the patient lays on the gynecologic examination table in the lithotomy position for TV-CDUS examination. After the coupling agent was applied on the surface of the probe, which was slowly sent to the vagina of the subject followed by placing in the external cervical opening of the vagina, for TA-CDUS examination, the patient was in a supine position on full bladder. A coupling agent was applied to the lower abdomen of the patient. The examiners were obstetricians/gynecologists, who had 3 to 5 years of experience.

*2.3. Diagnostic Criteria for VP and VCI.* The diagnosis of VP was made when the umbilical vessels located 2 cm proximal to the cervical os. The VCI was diagnosed by (1) umbilical vessels entering the placenta margin parallel to the uterine wall and connecting to superficial placental vessels; (2) the cord insertion was immobile, even when the uterus was shaken; and (3) the umbilical vessels diverged as they traversed the membrane. The representative image of patients with VP and VCI is illustrated in Figure 1.

*2.4. Observation Index.* Taking the delivery information (Figure 2) as the gold standard, the number of true positives, false positives, true negatives, and false negatives was determined and presented in a $2 \times 2$ contingency table. The diagnostic efficacy of TA-CDUS, TV-CDUS, and these combinations was compared by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, as well as the positive and negative likelihood ratios ($LR^+$ and $LR^-$).

*2.5. Statistical Analysis.* The sample is described in its clinical and demographic characteristics using quantitative variables, which are summarized with mean and standard deviation (SD). The categorical data of misdiagnosis and missed diagnosis using TA-CDUS and TV-CDUS are expressed as frequencies and percentages, which were evaluated and compared using $\chi^2$ test in SPSS 22.0 software for Windows (SPSS Inc., Chicago, IL, USA). The data were considered no statistically significant at two-sided $P \geq 0.05$.

## 3. Result

*3.1. Patient Demographics.* A total of 37 patients (0.68%) of 5434 pregnant mothers at delivery were clinically extraordinarily positive as VP prenatally with VCI and 5,397 patients (99.32%) were negative. The identification using TA-CDUS and TV-CDUS showed a total of 35 and 40 patients combined with VP and VCI, respectively. The demographics findings in 51 cases who were diagnosed as VP with VCI by delivery information, TA-CDUS, or TV-CDUS are shown in Table 1. The maternal age of participants was 28.65 (SD = 4.86) years with the body mass index (BMI) of $23.84 \pm 3.54\ kg/m^2$. The gravidity and parity of women were $2.59 \pm 1.08$ (range = 1~5) and $0.65 \pm 0.59$ (range = 0~2), respectively, with the gestational age at delivery of $35.43 \pm 1.15$ weeks and neonatal birth weight of $2653.86 \pm 233.71$ g. Moreover, smoking during pregnancy (>5 cigarettes/day) was seen in 3 (5.88%) cases. No pregnant woman had alcohol consumption during pregnancy.

*3.2. Diagnostic Accuracy of TA-CDUS and TV-CDUS in Pregnant Women with VP and VCI.* In order to show the

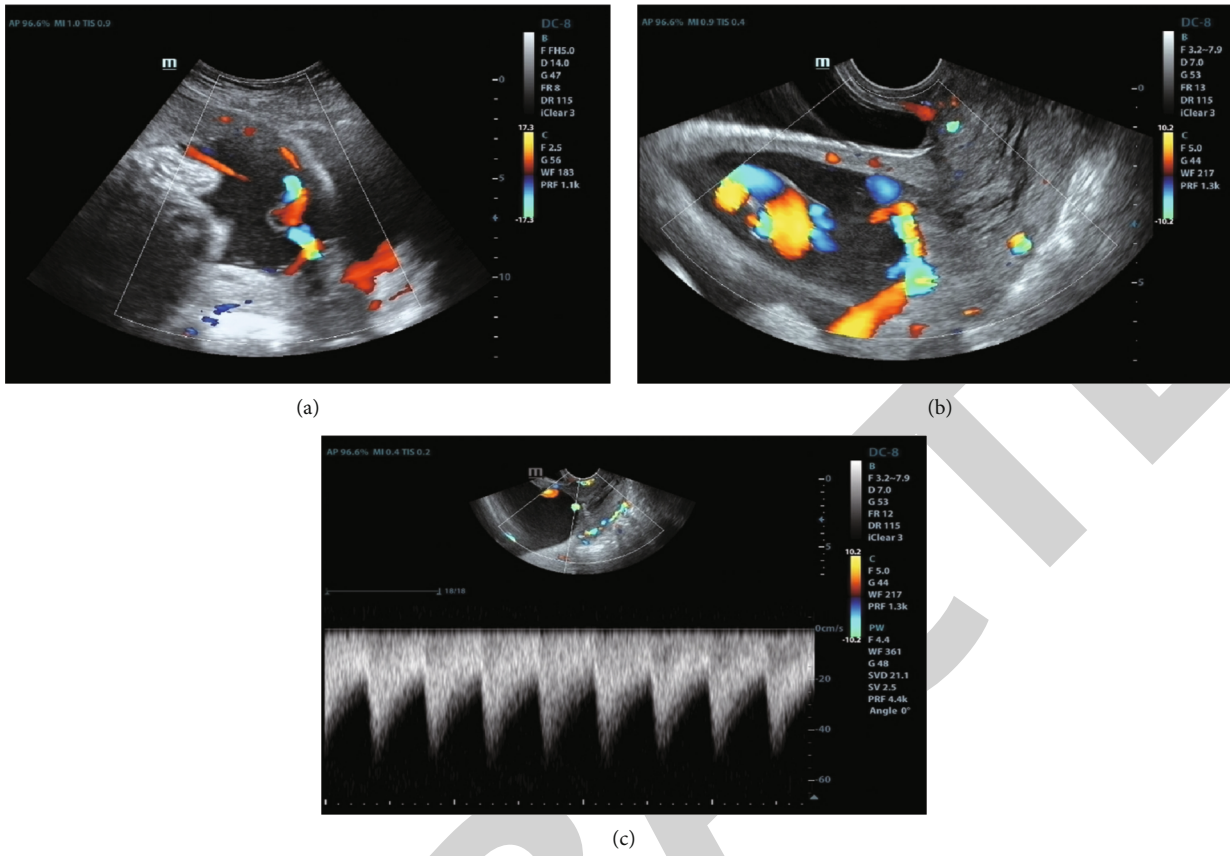


Figure 1: Color Doppler ultrasonography indicated the patients with VP + VCI (gestational week: 34+ 4 weeks; age: 31 years). Note: (a) TA-CDUS: the placenta was located on the posterior wall of the uterus near the internal os. (b) TV-CDUS: The umbilical vessel was fixed at the internal os with the adherence of the placenta to the posterior region. (c) The Doppler spectrum of the blood vessels above the internal os was consistent with the umbilical artery spectrum.

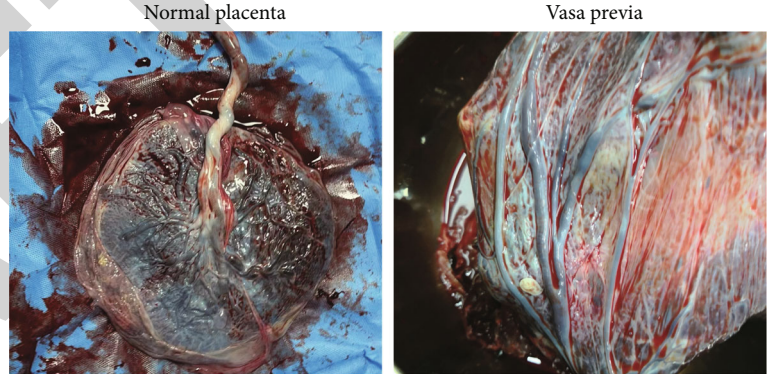


Figure 2: Gross placental specimen (normal placenta and vasa previa).

diagnostic accuracy of TA-CDUS and TV-CDUS in pregnant women with VP and VCI, we used delivery information as the gold standard. As demonstrated in Table 2 and Figure 3(a), the $LR^+$ is 492.29, and the $LR^-$ is 0.27 by TA-CDUS diagnosis, with an overall sensitivity of 72.97%, specificity of 99.85%, PPV of 77.14%, NPV of 99.81%, and accuracy value of 99.67%. Furthermore, TV-CDUS showed a total of 40 positive patients and 5,394 negative ones, which indicated a sensitivity, specificity, PPV, NPV, and accuracy of 89.19%, 99.87%, 82.50%, 99.93%, and 99.80% (Figure 3(b)), respectively, for categorization of a patient with VP and VCI, with the $LR^+$ of 687.65 and $LR^-$ of 0.11 (Table 3).

*3.3. Combining Diagnostic Value Using TA-CDUS and TV-CDUS.* Diagnosis can be established by combining several sonographic measurements [23], and several researchers recommend using TA-CDUS in combination with TA-CDUS

Table 1: The demographics findings in 51 cases who were diagnosed as VP with VCI using delivery information, TA-CDUS, or TV-CDUS.

| | Mean ± SD | Range |
|---|---|---|
| Age (years) | 28.65 ± 4.87 | 20~44 |
| Gravidity | 2.59 ± 1.08 | 1~5 |
| Parity | 0.65 ± 0.59 | 0~2 |
| Gestational age at delivery (weeks) | 35.43 ± 1.15 | 34~37 |
| Body mass index (BMI, kg/m$^{2)}$ | 23.84 ± 3.54 | 18.9~29.9 |
| Neonatal birth weight (g) | 2653.86 ± 233.71 | 2300~2999 |

[18, 24]. As shown in Figure 3(c) and Table 4, the combined use of TA-CDUS and TV-CDUS produces a high sensitivity of 97.30%, specificity of 99.98%, PPV of 97.30%, NPV of 99.97%, and accuracy of 99.96% as well as a positive and negative LR of 5,251.14 and 0.03, respectively.

*3.4. Comparison of Misdiagnosis and Missed Diagnosis Using TA-CDUS and TV-CDUS.* Ultrasound like any other radiological methods also has its limitations due to the misdiagnosis and missed diagnosis. According to the result of TA-CDUS, a total of 9 patients (0.17%) showed the missed diagnosis of VCI ($n = 8$) or VP ($n = 1$). Moreover, placenta previa with VP ($n = 7$) was the most common misdiagnosis, and the others causes for misdiagnosis were 1 patient with low-lying placenta + placental adhesions + lobulated placenta and 1 patient with low-lying placenta and VP. Additionally, 0.07% (4/5434) and 0.13% (7/5434) patients were missed and misdiagnosed based on the TV-CDUS. In detail, 3 cases and 1 case were missed diagnosed, who appeared to be only VCI or VP at delivery, respectively. Moreover, 7 patients were confirmed as placenta previa + VP ($n = 4$), VP + low-lying placenta + bilobed placenta ($n = 1$), VP + placental adhesions ($n = 1$), and VP + lobulated placenta ($n = 1$) based on the delivery information, who were all misdiagnosed as VP + VCI by TV-CDUS. No significant difference in the misdiagnosis ($P = 0.165$) and missed diagnosis ($P = 0.617$) was found between the examination by TA-CDUS and TV-CDUS.

## 4. Discussion

As the most useful modalities for imaging adult female genital organs, both TAS and TVS have been wildly used in antenatal ultrasound examination at home and abroad with superior spatial resolution, lack of ionizing radiation, and ability to assess blood flow [25–27]. Moreover, the improved sonographic assessment of the vascularity and blood flow within the uterus (both gravid and nongravid), fetus, and placenta using color Doppler has resulted in enhanced depiction of certain obstetric and gynecologic disorder [28].

Prenatal recognitions of VP and VCI provide elective delivery, thus avoiding potential fetal demise and neonatal morbidity [8, 29]. However, an increase in missed cases of VP is usually seen when the ultrasound examination does not involve color Doppler [1]. In our study, a total of 37 patients (0.68%) of 5434 pregnant mothers at delivery were clinically extraordinarily positive as VP prenatally with VCI, and the figure was similar with previous studies [30, 31]. The identification using TA-CDUS showed a total of 35 patients having VP with VCI, and taking the delivery information as "gold-standard," the overall sensitivity of TA-CDUS was 72.97%, specificity 99.85%, PPV 77.14%, NPV 99.81%, and accuracy 99.67% accompanying by a total of 9 patients with missed diagnosis of VCI ($n = 8$) or VP ($n = 1$). Moreover, placenta previa with VP ($n = 7$) was the most common misdiagnosis in our analysis, and the other causes for misdiagnosis were 1 patient with low-lying placenta + placental adhesions + lobulated placenta and 1 patient with low-lying placenta and VP.

In a study by S Baulies et al., which was performed on 9 patients to detect VP at 20~22 weeks, the findings of TV-CDUS were 100% of accuracy [32]. A retrospective study between 2006 and 2009 by Hasegawa J *et al.* showed that the diagnostic accuracy was 100% with TV-CDUS at second trimester [33]. The advantages of TVS over TAS have been well documented. For example, Mathis J *et al.* examined that the diagnostic performance of TVS was better than TAS for high-quality imaging of the uterus and the bilateral adnexa with a higher sensitivity and specificity [23]. Furthermore, TVS was considered superior in 63%, equal in 27%, and inferior in 10% of the cases as compared to TAS in the evaluation of pelvic pathology [34]. The results of this study showed that TV-CDUS had a sensitivity, specificity, PPV, NPV, and accuracy of 89.19%, 99.87%, 82.50%, 99.93%, and 99.80%, respectively, for categorization of a patient with VP and VCI. However, 3 cases and 1 case were missed diagnosed that appeared to be only VCI and VP at delivery, respectively. Moreover, 7 patients were confirmed as placenta previa + VP, VP + low-lying placenta + bilobed placenta, VP + placental adhesions, and VP + lobulated placenta based on the delivery information, who were all misdiagnosed as VP + VCI by TV-CDUS. All mentioned above indicated the higher diagnostic performance of TV-CDUS than TA-CDUS.

TVS as the procedure of choice in the evaluation of patients who have a suspected ectopic pregnancy is used as an adjunctive tool to complement TAS [35], and this combination is superior in imaging the placental type, location, insertion of the cord, and VP [36]. A prospective study by Nomiyama et al. focused on the detection of VCI and VP as primary objectives, and the result showed that the identification of a VCI site by ultrasound evaluation (TA-CDUS; TV-CDUS if cord insertion not seen in third trimester) had a sensitivity of 100%, a specificity of 99.8%, a PPV of 83%, and a NPV of 100% [15]. Furthermore, in a study by Catanzarite *et al.* which combined the TA-CDUS and TV-CDUS in the diagnosis of VP and VCI, reported 10 cases were confirmed at delivery, while the 11th case was a false-positive diagnosis that appeared to be a placenta previa with the specificity of 100% [37]. At present, the combined use of TA-CDUS and TV-CDUS produced a high sensitivity of 97.30%, specificity of 99.98%, PPV of 97.30%, NPV of 99.98%, and accuracy value of 99.96%, indicating the importance role of this combination in antenatal ultrasound

Table 2: Positive and negative likelihood ratios ($LR^+$ and $LR^-$) of TA-CDUS examination in determining VP combined with VCI taking gross examination as the gold standard.

| TA-CDUS | Gold standard | | | $LR^+$ | $LR^-$ |
|---|---|---|---|---|---|
| | Positive | Negative | Total | | |
| Positive | 27 (0.50%) | 8 (0.15%) | 35 (0.65%) | | |
| Negative | 10 (0.18%) | 5389 (99.17%) | 5399 (99.35%) | 492.29 | 0.27 |
| Total | 37 (0.68%) | 5397 (99.32%) | | | |

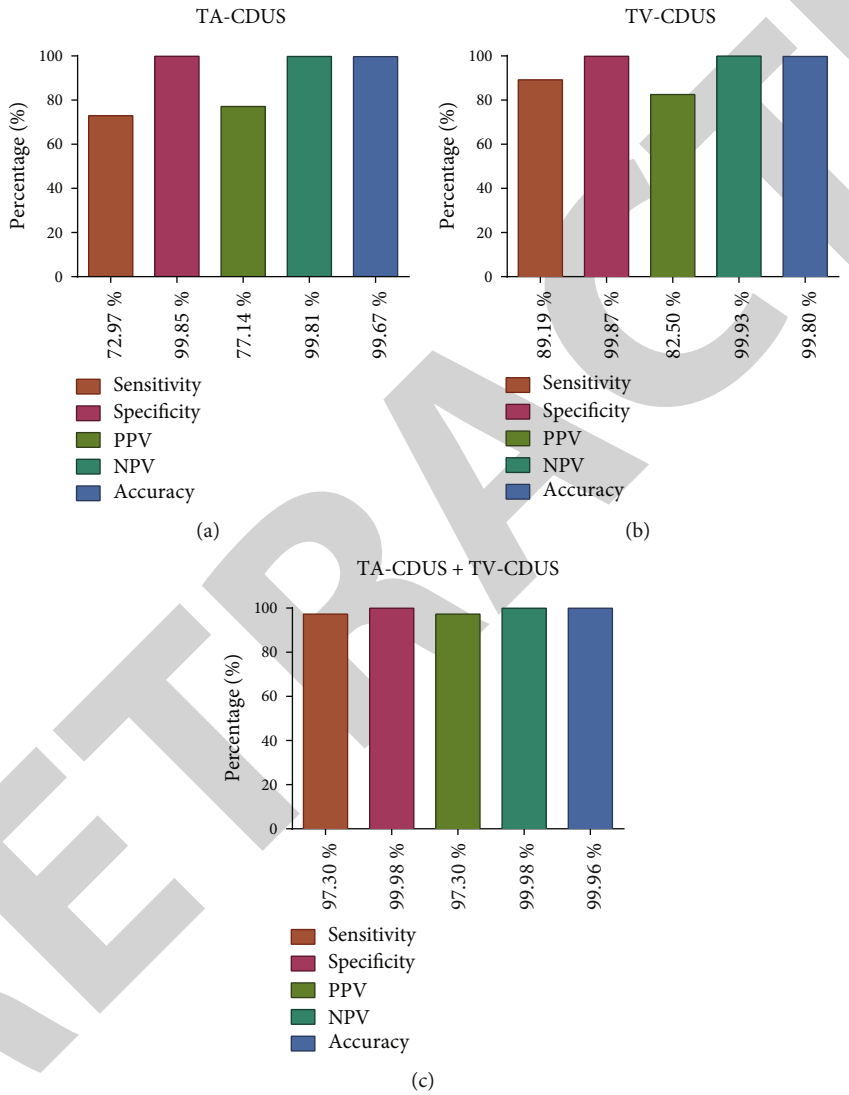


Figure 3: Sensitivity, specificity, PPV, NPV, and accuracy for the detection of patients with VP and VCI. Note: (a) TA-CDUS; (b) TV-CDUS; and (c) the combined use of TA-CDUS and TV-CDUS.

Table 3: Positive and negative likelihood ratios ($LR^+$ and $LR^-$) of TV-CDUS examination in determining VP combined with VCI taking gross examination as the gold standard.

| TV-CDUS | Gold standard | | | $LR^+$ | $LR^-$ |
|---|---|---|---|---|---|
| | Positive | Negative | Total | | |
| Positive | 33 (0.61%) | 7 (0.13%) | 40 (0.74%) | | |
| Negative | 4 (0.07%) | 5390 (99.19%) | 5394 (99.26%) | 687.65 | 0.11 |
| Total | 37 (0.68%) | 5397 (99.32%) | | | |

Table 4: Positive and negative likelihood ratios ($LR^+$ and $LR^-$) of combining diagnosis using TA-CDUS and TV-CDUS in determining VP plus VCI taking gross examination as the gold standard.

| TA-CDUS + TV-CDUS | Gold standard | | | $LR^+$ | $LR^-$ |
|---|---|---|---|---|---|
| | Positive | Negative | Total | | |
| Positive | 36 (0.66%) | 1 (0.02%) | 37 (0.68%) | | |
| Negative | 1 (0.02%) | 5396 (99.30%) | 5397 (99.32%) | 5251.14 | 0.03 |
| Total | 37 (0.68%) | 5397 (99.32%) | | | |

examination. The main limitation of the study was the retrospective nature of the study design. A prospective study using these two scans for pregnant women is the next step to be undertaken. Moreover, although highly visualization of VCI combined with VP using TA-CDUS/TV-CDUS imaging was found in this analysis, ultrasound like any other radiological methods also has its limitations due to the misdiagnosis and missed diagnosis.

## 5. Conclusion

TV-CDUS demonstrated higher diagnostic performance than TA-CDUS in pregnant women with VP and VCI, and these combinations are superior to TA-CDUS or TV-CDUS alone. The visualization of VCI combined with VP using TA-CDUS/TV-CDUS imaging is recommended as a routine part of obstetric sonography, since the identification of VCI, especially in the case of VP, could help to determine the mode and timing of delivery and improve fetal outcome.

## Data Availability

The data were presented in the study.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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*Retraction*

# Retracted: Emergency Medicine with Advanced Surgery Protocols: A Review

**Journal of Environmental and Public Health**

Received 1 August 2023; Accepted 1 August 2023; Published 2 August 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.

## References

[1] H. Mills, R. Acquah, N. Tang et al., "Emergency Medicine with Advanced Surgery Protocols: A Review," *Journal of Environmental and Public Health*, vol. 2022, Article ID 3513250, 6 pages, 2022.

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*Review Article*

# Emergency Medicine with Advanced Surgery Protocols: A Review

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Academic Editor: Weiguo Li



One of the most burning issues in health system is the concern of handling patients that requires emergency surgery. Emergency general surgery is done on both traumatic and nontraumatic acute disorders. Severe traumatic injury and bleeding is one of the causing agents for high mortality rate globally. Another group of patients that are in need of emergency surgery are those with heart failure, and in this particular paper, we analyzed emergency medicine with advanced surgery protocols focusing on gastric cancer, cardiac surgery, and bleeding as well as coagulopathy following traumatic injury.

## 1. Introduction

Emergency medicine is a field of practice that utilizes knowledge and skills required for the injury affecting patients. The set of skills involve prevention, diagnosis, and management of sensitive illness [1]. Emergency medicine deals with patients that are in a critical condition, which could either be seriously injured or seriously ill patients who need emergency attention [2]. Therefore, emergency medicine is mostly taken care of or given in hospitals and clinics where the vital care needed is readily available. David et al. made it clear that emergency medicine is practiced differently around the different parts of the world, since people define emergency medicine differently [2–4].

This difference that arises in the definition of emergency medicine arises because of the ailments that each nation has such that it would be of no use to apply the same understanding of emergency medicine. The population at large has also their duty to give full support to the advancement of emergency medical services and prehospital development, aid in disaster relief as well fight to prevent accidents, and recognize and advance academic emergency medicine. Once more, this has been amply noted in emergency medicine studies published in India, Japan, and some parts of Europe [4]. In this particular paper, we discussed the importance of emergency medicine focusing on the advanced surgery protocols in cardiac surgery, gastric cancer, and bleeding as well as coagulopathy following traumatic injury.

## 2. Major Bleeding and Coagulopathy

It takes one to have a very deep understanding of the biology behind the reaction to trauma as well to be able to manage trauma patients with severe injuries. This has led to modifications of known treatment of trauma combined with injuries such that there are recent advances in clinical and basic science research towards the treatment of patients with bleeding trauma [5]. In about 10 cases of bleeding trauma patients, 3 cases exhibit indications of coagulopathy and the situation where patients would bleed following emergency medicine operations. The bleeding is deemed to be one of the causes of avoidable death among injured patients

[6–9]. These patients with posttraumatic bleeding are said to be in a very critical condition as they can also die from multiple organ failure [10]. Thrombin-thrombomodulin complex generation mainly is a factor that has shown to cause early acute coagulopathy which is linked to traumatic injury [11]. Coagulation disease can be worsened by factors like therapeutic and environmental factors that cause acidaemia, hypothermia, dilution, hypoperfusion, and consumption of coagulation [12], and trauma causes brain injury as shown in Figure 1.

*2.1. Advanced Surgery for Bleeding.* In the situation that it occurs that a patient has been severely injured, and there is hemorrhagic shock, bleeding, and coagulopathy, it is advised that the patient undergoes damage-control surgery. For patients suffering from hypothermia, acidosis, and anatomical injuries that are inaccessible, simultaneous significant harm outside the abdomen may also go through a damage-control surgery [13]. It is believed that if a critically injured person does not receive bleeding management and appropriate resuscitation, blood transfusion has low chances of surviving.

This is more dangerous when the patient is suffering from a number of penetrating injuries and uncontrolled bleeding. The other group of patients at risk of losing their lives is those who have serious abdominal injuries and pelvic fractures that will be bleeding and retroperitoneal arteries. The methods of limiting hemorrhage, laparotomies, and delaying final surgical repair until coagulation has been established were all described by Morris et al. in 1983 [14]. The strategy is now known as damage control [15–17]. This method is now being employed on patients who have sustained a serious abdominal injury and to patients in need of adjunctive angioembolization. Patients suffering from traumatic amputation of a limb, severe stomach injuries, and injuries as soon as feasible can also be treated with damage control surgery. Improvements in the damage-control surgery include a temperature 34°C, pH 7.2 when carrying out the surgery [18, 19].

Additionally, an accelerated resuscitative laparotomy is performed as part of damage-control surgery for the abdomen in order to reduce bleeding, restore blood flow when necessary, and prevent contamination. This is now being done soon so as not to waste time on conventional organ repairs as these can be done at a later stage. The abdomen is packed; packing may allow to compress ruptures in the liver and to provide direct pressure to the sites where bleeding will be taking place. Rebleeding is avoided by removing the removal of packs for about 48 hours. In this part, the patient's temperature control is also very important. In the emergency operation, the patient's hypothermia reduces the productivity of the damaged body, and a large amount of heat energy dissipates during the operation. However, most surgeons tend to ignore the links of operating room warming, patient's body heat preservation, infusion fluid and irrigation fluid heating, and so on. Therefore, hypothermia generally exists in severely injured patients. In this case, the patient will suffer from systemic cell metabolism disorder, arrhythmia, reduction of cardiac output, prompting oxygen dissociation curve to move to the left and reducing the release of oxygen between tissues, etc., thus affecting the coagulation function, and the death rate of the patient will increase from 40% to 100%.

The next step of damage-control surgery would be intensive care, which is mainly about rewarming, coagulopathy correction, acid-base balance, and haemodynamic optimization. The final surgical repair, which is the third step, is normally carried out when the rewarming, coagulopathy correction, acid-base balance, and haemodynamic optimization have been reached [16, 17]. The surgical procedure's less harsh nature and brief duration are intended to lessen secondary procedure-related trauma.

*2.2. Reamed Nailing.* Long bone fractures are usually dealt with using reamed nailing technique. The method is known to be the standard method that can be safely used in treatment of long bone fractures. It has been a problem with reaming since it would lead to the undesired effects like heat generation, issues with reamer flutes, and fat embolization [18]; however, the technique has been improved such that to overcome fat intravasation caused by increased intramedullary pressure, and the reamed irrigator aspirator (RIA) device was developed. The device has shown to lessen the side effects of reaming as it minimizes remobilization [19, 20], and currently, this device is being used, especially in bone graft [21]. A device that cuts like RIA needs accurate cutting in the medullary canal compared to the usual reamers; therefore, another complex version of RIA device has been invented which overcomes the drawback of the cutting-head size of the firstly developed RIA device which is small and with issues also in connection between the drive shaft and the cutting head.

*2.3. Definitive Surgery.* Safe fracture fixation in badly injured people normally experience inflammatory changes especially in the neutrophil level [22]. There has been a technique that was developed which detects if the neutrophils are present in the body of a badly injured person [23]. This is of importance as it will contribute to make a decision that inflammatory and soft tissue injury-induced alterations can be returned back to normal by a surgery. Cardiac function was revealed to be more damaged when RIA 1 is used but showed to be successful when RIA 2 was used [24, 25]. This information is important as it ensures safe definitive surgery and also reinforces the importance of patient assessment to achieve the goal of safe definitive surgery [26]. Therefore, it is encouraged to use many factors together as they have shown to be helpful in surgery, and these advances for surgeries will be helpful in coming up with successful surgeries [27].

## 3. Gastric Cancer

Gastric cancer is considered to be in the top 3 of fatal cancers. Many death cases have been recorded to have been caused by gastric cancer [28]. The disease has been treated using the *H. pylori* treatment; however, the cases keep rising and the treatment has shown not be effective. The disease

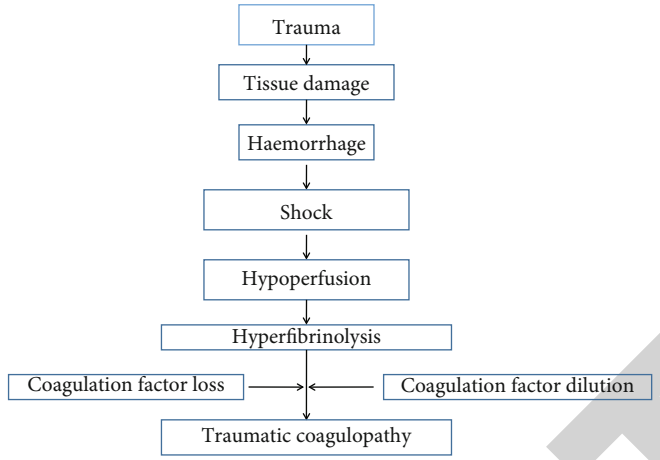


Figure 1: Conditions that are associated with trauma and traumatic coagulopathy shown in a series of steps.

Table 1: Invasive techniques in coronary artery bypass grafting.

| Technique | Description |
|---|---|
| Off-pump coronary artery bypass (OPCAB) | Any coronary artery bypass surgery carried out without cardiopulmonary bypass |
| Minimally invasive direct coronary artery bypass (MIDCAB) | Surgery performed off-pump through a small thoracotomy under direct vision |
| Endoscopically assisted atraumatic coronary artery bypass (Endo-ACAB) | Internal mammary artery harvested endoscopically, coronary anastomosis performed off-pump through a minithoracotomy under direct vision |
| Totally endoscopic coronary artery bypass (TECAB) | Surgery performed off-pump entirely endoscopically with robotic assistance |
| Hybrid | MIDCAB, Endo-ACAB, or TECAB with elective percutaneous coronary stenting of additional stenoses |

requires screening but the screening is very expensive; thus, many people only realize that they are suffering from gastric cancer when it becomes severe. Therefore, advanced treatment of gastric cancer has been invented which includes advanced minimally invasive surgical procedures. Thus, in recent years, the incidence and mortality of gastric cancer in many countries with high incidence of gastric cancer, including Japan, have shown a decreasing trend in different degrees. The reasons are mainly related to the decrease of Helicobacter pylori infection rate, the decrease of salt intake, the increase of fresh vegetable and fruit intake, and the radical endoscopic treatment after gastric cancer screening and early detection [29].

*3.1. Advances in Gastric Cancer Treatment.* Complete surgical resection has become the gastric cancer treatment such that total gastrectomy and subtotal gastrectomy are the popular methods that are now being used in treating gastric cancer. Gastrectomy procedure goes along in combination with lymphadenectomy to achieve oncologic resection and staging of gastric cancer and D3 (perigastric, eliac axis, and para-aortic lymph node stations) lymphadenectomies. Studies have revealed that patients have more survival rate when they are treated with this combination compared to when treated with lymphadenectomy alone [30].

Gastrectomy, in the treatment of stomach cancer, has become the choice of many as it comes along with many benefits such as reduced blood loss, lower morbidity, and a quicker recovery of bowel function compared to chemotherapy. The survival rates for chemotherapy and radiation have been shown to much lower compared to those for gastrectomy [31]. Cytoreductive surgery and heated intraperitoneal chemotherapy are also under investigation to treat peritoneal illness. Studies have revealed that patients with advanced gastric cancer who underwent heated intraperitoneal chemotherapy after cytoreductive surgery recovered [32].

## 4. Cardiac Surgery

Despite its high cost, cardiac surgery is the only accepted standard therapy for the treatment of heart disease on a global scale. Percutaneous and surgical treatments for coronary artery disease as well as surgical adjuvant such cardiac imaging and blood conservation have all benefited from advancements in cardiac surgery.

*4.1. Coronary Surgery vs. Percutaneous Coronary Intervention.* For single vessel disease, percutaneous coronary intervention was done; however, coronary stenting and surgical methods were not frequently employed. Coronary artery reperfusion therapy has significantly improved the clinical prognosis of patients with acute myocardial infarction (AMI). However, coronary angiography

confirmed that in some successful emergency percutaneous coronary intervention (PCI), the myocardial tissue on the verge of necrosis or severe ischemia did not fully and effectively restore blood perfusion, which was related to no-reflow phenomenon. The incidence of no-reflow after reperfusion in acute myocardial infarction is 10%~30%. No-reflow greatly reduces the clinical benefits of emergency PCI. Compared with patients with normal forward coronary blood flow, these patients often have cardiac insufficiency and angina pectoris after infarction. And bypass surgery is a far more intrusive alternative to coronary stenting for revascularization. Stents are employed because they have lower rates of restenosis than balloon angioplasty alone, and they also play a crucial role in the management of angioplasty-related problems [33].

*4.2. Pump Surgery.* During coronary artery bypass surgery, cardiopulmonary bypass can either be employed (known as "on-pump") or not used at all (known as "off-pump"). Up until recently, the majority of surgeons used on-pump procedures since it was thought that off-pump surgery reduced patients' risk of stroke. Off-pump surgery has been shown to perform better than on-pump surgery by reducing postoperative atrial fibrillation, the need for transfusions and inotropes, ventilation times, hospital stay length, and cost [34]. Numerous researches have also looked into the issue of patients receiving fewer grafts in off-pump groups [35]. Table 1 shows different ways of performing coronary surgery.

*4.3. Atrial Fibrillation Surgery.* With a high mortality rate and increased risk of stroke, postoperative atrial fibrillation affects roughly 38% of patients having mitral valve surgery. But for patients having mitral surgery, the Maze III procedure is the gold standard for treating atrial fibrillation currently: over 85% of patients who undergo the standard Maze surgery are cured of atrial fibrillation [36], but because to its complexity, the Maze III is only performed by a small number of surgeons. Though thoracoscopic and minimally invasive approaches have been made easier by new ablation technologies like radiofrequency, microwave, and cryotherapy, the indications for surgical treatment of atrial fibrillation will likely continue to be restricted to those with concurrent cardiac surgical pathology needing surgery.

*4.4. Preservation of Blood.* According to data from the National Blood Service, cardiac surgery uses a lot of blood. Therefore, blood conservation measures have been put in place. These tactics lead to postoperative bleeding and transfusions as well as a decreased supply of blood components. Both tranexamic acid and aprotinin are antifibrinolytics that, when used after heart surgery instead of a placebo, significantly reduce the need for blood transfusions and reoperations due to bleeding [37]. In this meta-analysis, neither medication was discovered to be linked to noticeably higher rates of adverse events. Blood is drawn from the surgical site or postoperative drains by cell salvage systems, which then heparinize, cleanse, and generate concentrated red blood cells that can be given back to the patient. According to calculations, the likelihood of needing a blood transfusion is nearly eliminated with washed cell salvage. Variations in transfusion thresholds were a substantial source of variability in the research included in both meta-analyses. There is no longer a need for placebo-controlled trials of either approach in cardiac surgery, according to both of these meta-analyses. Research that identify the risk-benefits of allogeneic blood transfusion in cardiac surgery as well as studies that determine the haematocrit that maximizes coronary anastomotic patency and myocardial oxygen delivery are presently required [38].

*4.5. Heart Failure Surgery.* In carefully choosing patients with ejection fractions under 20 percent, enough reserves of dormant myocardium, and acceptable coronary anatomy, it has been demonstrated that cardiac artery bypass grafting provides superior outcomes to cardiac transplantation. Relative contraindications to cardiac artery bypass grafting include right ventricular failure and increased pulmonary artery pressure. Operative mortality in this high-risk category has been decreased to 7% thanks to careful patient selection and temporary mechanical assistance, and the 5-year survival rate has reached approximately 80% [39]. In cardiac failure, mitral regurgitation frequently occurs. Due to the high rate of surgical mortality in the 1980s, it was thought that the elimination of the low resistance regurgitant channel would inevitably result in a postoperative decline in left ventricular function. Hospital mortality in one series was as low as 2% due to better understanding of the necessity to protect the subvalvular apparatus, correct and prevent annular dilatation, and enhance mitral valve repair procedures [39]. The Thoratec HeartMate left ventricular assist device was given approval by the US Food and Drug Administration in 2003 for long-term treatment of patients with end-stage heart failure. Data showing that the placement of a left ventricular assist device reduced 1-year mortality by a third relative to medical care were used to support approval [39]. In many patients, early bleeding and late infection continue to be issues.

## 5. Conclusion

At present, the professional differentiation of emergency department is getting finer and finer, and the theoretical knowledge and clinical skills of many specialists are becoming more and more specialized, which leads to the fact that although emergency department is a complete department, it has to shoulder more responsibilities, and many chronic diseases often exist at the same time in different regions and different ages. However, some chronic diseases are acute, or new acute diseases are acquired on the basis of many chronic diseases. At this time, the diseases of various systems cross each other and occur in one patient, which is by no means something that a single specialist can solve. Therefore, it is necessary for emergency doctors to comprehensively evaluate and analyze the pathophysiological state of patients, so as to give targeted treatment to patients, so that patients can get the most scientific treatment in the golden time. And there have been numerous advances in

surgical methods in cardiac surgery. Future research may concentrate on stem-cell-based therapy and biotechnology, particularly in relation to surgery for heart failure, while the proper management of trauma patients with massive bleeding and coagulopathy continues to be a major challenge in routine clinical practice, and the management of gastric cancer is a challenge requiring a multidisciplinary approach for optimal treatment, so future research on gastric cancer may concentrate on next-generation genomic analysis.

## Data Availability

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

## Conflicts of Interest

The authors declare no conflict of interest.

## Authors' Contributions

HM and RA contributed to conception and design of the study and wrote the first draft of the manuscript. NT, LC, SK, RG, MP, AA, DTH, and TNV contribute to the data collection and analysis. All authors approved the submitted version.

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*Retraction*

# Retracted: Impacts of Ultrasound-Guided Nerve Block Combined with General Anesthesia with Laryngeal Mask on the Patients with Lower Extremity Fractures

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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] X. Yang, L. Bao, X. Gong, and H. Zhong, "Impacts of Ultrasound-Guided Nerve Block Combined with General Anesthesia with Laryngeal Mask on the Patients with Lower Extremity Fractures," *Journal of Environmental and Public Health*, vol. 2022, Article ID 3603949, 8 pages, 2022.

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*Research Article*

# Impacts of Ultrasound-Guided Nerve Block Combined with General Anesthesia with Laryngeal Mask on the Patients with Lower Extremity Fractures

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*Objective*. Surgical reduction is the leading approach to patients with lower extremity fractures. The options of anesthetic drugs during surgery are of great significance to postoperative recovery of patients. There is no consensus on the optimum anesthesia method for patients undergoing lower extremity fracture surgery. Our study is aimed at investigating the impacts of nerve block combined with general anesthesia on perioperative outcomes of the patients. *Methods*. In this retrospective study, 48 patients experienced general anesthesia only, and 42 patients received never block combined with general anesthesia. The perioperative hemodynamics was recorded, including mean arterial pressure (MAP), oxygen saturation of blood (SpO2), and heart rate (HR). Visual analogue scale (VAS) and Montreal Cognitive Assessment (MoCA) were carried out to evaluate postoperative pain and cognitive status. Furthermore, adverse reactions and recovery condition were observed between the patients receiving different anesthesia methods. *Results*. At 15 minutes and 30 minutes after anesthesia, as well as 5 minutes after surgery, significant lower MAP was observed in the patients treated with general anesthesia ($83.04 \pm 8.661$, $79.17 \pm 9.427$, $86.58 \pm 8.913$) compared to those receiving never block combined with general anesthesia ($90.43 \pm 4.618$, $88.74 \pm 6.224$, $92.21 \pm 4.015$) ($P < 0.05$), and compared with general anesthesia group ($68.5 \pm 7.05$, $69.63 \pm 7.956$, $72.75 \pm 8.446$), the combined anesthesia group ($73.52 \pm 9.451$, $74.17 \pm 10.13$, $77.62 \pm 9.768$) showed obvious higher HR ($P < 0.05$). No significant difference in $SpO_2$ was found between the two groups at multiple time points ($P > 0.05$). As for the score of VAS and MoCA, remarkably lower VAS and higher MoCA at 6 h, 12 h and 24 h after surgery were presented in the combined anesthesia group compared to general anesthesia group ($P < 0.05$). At 24 h after surgery, the two groups showed normal cognitive function ($26.33 \pm 0.7244$ vs. $28.55 \pm 0.7392$). Incidence of nausea and vomiting in the combined anesthesia group was lower than that of the general anesthesia group ($P < 0.05$). The time to out-of-bed activity and hospital stay were shorter in the combined anesthesia group compared with general anesthesia ($P < 0.05$). *Conclusion*. The application of never block combined with general anesthesia contributed to the stability of hemodynamics, alleviation of postoperative pain and cognitive impairment, along with decrease in adverse reactions and hospital stay in the patients with lower extremity fractures.

## 1. Introduction

Age induced bone loss increases the risk of lower extremity fracture in the middle-aged and elderly populations [1, 2]. Approximately 33% of adult women and 50% of adult men suffered from extremity fracture before the age of 65 [3]. Lower extremity fracture has been reported to pose an escalating burden on public health care and result in long-term adverse effects on the quality of life of patients, such as impairments or loss of physical function [4]. Lower extremity fracture, as a prevalent type of fracture in clinic, is generally treated with surgical reduction, which is common in orthopedic surgery. The operation time of lower extremity fracture is relative long, which has a significant impact on the patient's respiratory and circulatory system [5]. In addition, the patients tend to experience acute pain during postoperative period as a result of large-scale traumatic injury, leading to an adverse impact on postoperative functional exercise [6]. Therefore, an appropriate anesthesia program is of great significance in reducing the occurrence of stress

reaction and complications, and accelerating the postoperative rehabilitation of patients.

General anesthesia is a common anesthesia method in lower extremity fracture surgery, but it's a challenging for the physiology and postoperative rehabilitation of elderly patients [7, 8]. Comparing with general anesthesia, ultrasound-guided nerve block has special advantages such as relatively high safety and physiological interference reduction. With the help of ultrasound guidance, nerve block can accurately locate the anesthesia site and clarify the paths of drug diffusion, which may end up with optimal anesthesia effect and decrease in unnecessary injury. In recent years, ultrasound-guided nerve block is increasingly used in fracture surgery, especially in elderly patients [9–11]. However, as described in previous studies, nerve block might lead to block failure or incomplete block. For instance, the failure rate of fascia iliaca compartment block used to block the lateral femoral cutaneous nerve is 10% - 37% [12]. 3 of 78 patients failed to receive lumbosacral nerve root block and 75 patients showed tapping sensation at L5 region without contraction of muscles [13]. Enhanced recovery after surgery (ERAS) is a combination of multimodal evidence-based strategies that has been proved to be an effective treatment for perioperative patient care in various diseases including fracture. It can reduce perioperative stress reaction of patients, shorten hospital stay, and decrease the incidence of postoperative complications and mortality, thus accelerating postoperative recovery of patients [14, 15]. On the basis of the concept of ERAS, combined anesthesia has been widely applied to a variety of surgeries, such as off-pump coronary artery bypass graft surgery [16] and hip replacement surgery [17]. It is well established that ultrasound-guided nerve block combined with additional intravenous anesthetic drugs contribute to improvement of the anesthetic effect in intertrochanteric fracture [18] and unilateral rib fracture [19].

In our study, we enrolled 90 patients undergoing lower extremity fracture surgery and divided them into two groups according to anesthesia scheme. Among them, 48 patients received general anesthesia alone, and the remaining patients underwent nerve block combined with general anesthesia. The purpose of this study was to explore the effects of nerve block combined with general anesthesia in patients with lower extremity fracture.

## 2. Materials and Methods

*2.1. Study Population.* A total of 90 patients undergoing lower extremity fracture surgery in our hospital from December 2019 to June 2021 were enrolled in this retrospective study. During the surgery, 48 patients experienced general anesthesia (general anesthesia group), consisting of 28 males and 20 females, who were 18-65 years of age ($49.67 \pm 3.21$ mean age). The remaining 42 patients aged 18 to 64 years ($50.32 \pm 2.98$ mean age), including 25 males and 17 females, received nerve block combined with general anesthesia (combined anesthesia group) based on the concept of ERAS. The body mass of general anesthesia group and combined anesthesia group was $58.5 \pm 2.3$ vs. $57.8 \pm 2.6$. In the general anesthesia group, there were 32 cases and 16 cases with class I and II of the American Association of Anesthesiologists (ASA), respectively. 28 and 14 of patients in the combined anesthesia group presented ASA class I and II, respectively. The operation time of general anesthesia group and combined anesthesia group was 65-85 min ($72.28 \pm 4.64$) and 63-84 min ($73.34 \pm 5.14$), respectively. Comparing the baseline data of the two groups, the difference was not statistically significant (Supplementary table 1, $P > 0.05$). All eligible patients were known to be diagnosed with American Society of Anesthesiologists (ASA) class I-II lower extremity fractures by imaging examinations such as CT and X-ray and presented complete clinical data. Those diagnosed patients with cognitive impairment, abnormal coagulation function, and contraindications of surgery and anesthesia, as well as dysfunction of multiple organs, were excluded in the study. The study was approved by the ethics committee of our hospital, and obtained signed written informed consent form from each included patient.

*2.2. Approaches of Anesthesia.* All patients received health education and psychological guidance after admission. 300 ml of 5% glucose was taken orally 2 hours before operation. Hemodynamic monitoring including mean arterial pressure (MAP), oxygen saturation of blood ($SpO_2$), and heart rate (HR) was performed before anesthesia. Furthermore, the peripheral venous access of the nonoperative upper limb was established and compound sodium chloride was infused (10 ml/kg/h). Dexmedetomidine (1.0 ug/kg) was injected intravenously 15 minutes before anesthesia to alleviate preoperative anxiety and pain caused by body position changing during anesthesia operation. The general anesthesia group was treated with intravenous injection of fentanyl citrate (drug approval number: H42022076) (5 $\mu$g/kg) and propofol (drug approval number: H20051842) (2 mg/kg), and cisatracurium besilate (drug approval number: H20090202) (0.2 mg/kg), successively. 3 minutes of mask controlled ventilation was conducted after the decrease of eyelash reflex, followed by oxygen inhalation through laryngeal mask, with ventilator parameter of tidal volume (TV) 8-10 ml/kg and respiratory rate (RR) 10-12 times/min. Inhalation of 2%~3% sevoflurane (drug approval number: H20070172) was used to maintain intraoperative anesthesia, and additional of fentanyl citrate and cisatracurium besilate was adopted as required. The parameter of end-tidal $CO_2$ pressure ($PETCO_2$) and bispectral index (BIS) was maintained 35-45 mmHg and 40-50, respectively.

The combined anesthesia group received nerve block combined with general anesthesia. Ultrasound-guided nerve block anesthesia of the affected limb was first applied to the patients with supine position. A portable ultrasonic instrument (frequency 6-13 Hz) was used to locate the femoral artery, femoral vein, and femoral nerve of the patient for performance of fascia iliaca compartment block. In brief, 25 ml of 0.5% ropivacaine mesylate (drug approval number: H20051865) as local anesthesia was implemented following punctured iliac fascia by the needle, and then the patients, who were kept in position of elevated hip and bended knee of the affected side, underwent sciatic nerve block under ultrasound. The needle was punctured into sciatic nerve after trochanter was located by ultrasound, followed by local anesthesia injection with 15 ml of 0.5% ropivacaine mesylate.

The blocking effect was detected by acupuncture, which followed the complete performance of sciatic nerve block. The sensory and motor block was measured every 5 minutes, and those patients should be excluded from the study if blocking failure happened to them within 30 minutes. Intravenous general anesthesia was carried out after confirmation of the block effect. The patients were given injection of fentanyl citrate (1 $\mu$g/kg) and propofol (2-2.5 mg/kg) and received 3 minutes of oxygen inhalation via mask after eyelash reflex was weakened. Inhalation of 2%~3% sevoflurane was performed after installation of laryngeal mask. During the operation, the patient was maintained spontaneous breathing. Fentanyl (0.05-0.1 mg) was added once if RR was more than 20 times/min, and manual or mechanical ventilation ($PETCO_2$: 35-55mmHg, $SpO_2 > 97\%$) was given in the case of insufficient respiratory ventilation. During surgery, if the decrease of MAP of patients was more than 20% of the basic value, ephedrine (3 mg/time) or phenylephedrine (0.01 mg/time) shall be given. Fentanyl (0.05-0.1 mg/time) was applied to the patients with MAP elevation more than 20% of the basic value and HR increase exceeding 10% of the basic value. The patients with HR < 50 beats/min should be treated with atropine (0.2 mg/time). The laryngeal mask was removed when the patient was fully awake after the operation.

*2.3. Postoperative Analgesia.* All patients were transferred to postanesthesia care unit (PACU) and received intravenous infusion of 8 mg of ondansetron (drug approval number: H10970065) after operation. Postoperative patient-controlled intravenous analgesia (PCIA) with 0.8 mg of fentanyl diluted to 100 ml by normal saline was used for postoperative pain alleviation within 48 hours. The loading dose of the first intravenous injection was 5 ml, and the predesigned infusion rate was 2 ml/h. Dose of PCIA was set to 2 ml/time, and 15 minutes were regarded as the lockout time.

*2.4. Outcome Evaluation.* Hemodynamics variables, including MAP, HR, and $SpO_2$, were monitored and recorded in the two groups before anesthesia, 15 minutes after anesthesia, 30 minutes after anesthesia, and 5 minutes after surgery.

Visual analogue scale (VAS) [20] was used to evaluate the pain intensity of patients at 6 h, 12 h, and 24 h after surgery. VAS score ranges from 0 to 10, and the scores are positively correlated with pain intensity. In general, no pain is described by 0 scores. 1-3 scores are regarded as mild pain, 4-6 scores indicates moderate pain, and 7-10 scores present severe pain. Postoperative cognitive status was assessed using Montreal Cognitive Assessment (MoCA) [21] . The scale includes 8 dimensions, including attention and concentration, orientation, executive function, abstract thinking, language, memory, visual structure skills, and calculation. There are 11 scoring items in total, with a total score of 30. The higher the score is, the higher the cognitive function. Generally, cognitive function is normal with a score greater than or equal to 26, the score of mild cognitive impairment and moderate cognitive impairment is between 18 and 26, and 10 and 17, respectively. The scores lower than 10 are regarded as severe cognitive impairment.

The adverse reactions of patients in the two groups receiving different anesthesia were observed after surgery, including dizziness and headache, nausea and vomiting, drowsiness, urinary retention, and respiratory depression.

*2.5. Statistical Analysis.* SPSS 22.0 software was adopted for data analysis. T test or F test was applied to analyze measurement data described as mean ± standard deviation. The counting data were expressed as percentage (%) and determined by Chi-square test. $P < 0.05$ indicated that the difference was statistically significant.

## 3. Results

*3.1. Hemodynamic Variables of the Two Groups at Multiple Time Points.* The patients in the two groups showed no significant difference in terms of MAP, HR, and $SpO_2$ before anesthesia ($P > 0.05$). At 15 minutes after anesthesia and 30 minutes after anesthesia, MAP was decreased in the two groups, and the patients treated with general anesthesia had lower MAP than the patients undergoing nerve block combined with general anesthesia ($P < 0.05$). MAP was increased at 5 minutes after surgery in both two groups, and higher MAP was showed in the combined anesthesia group compared to general anesthesia group ($P < 0.05$). As for changes of HR, the two groups exhibited declined HR at 15 minutes after anesthesia, and the downward trend was more obvious in general anesthesia group ($P < 0.05$). At 30 minutes after anesthesia and 5 minutes after surgery, more elevated HR was observed in the patients receiving nerve block combined with general anesthesia compared to those who were given general anesthesia ($P < 0.05$). However, there was no significant different in $SpO_2$ between the two groups at multiple time points ($P > 0.05$, Table 1).

*3.2. Alleviation of Postoperative Pain by General Anesthesia Combined with Nerve Block.* VAS was performed to assess the postoperative pain in both groups. As listed in Table 2, combined anesthesia group and general anesthesia group exhibited the strongest pain intensity at 6 h after surgery ($3.548 \pm 0.5038$ vs. $4.667 \pm 0.5955$, $P < 0.05$), and the VAS score in the two groups at 12 and 24 h after surgery was lower than that at 6 hours after surgery ($P < 0.05$). Furthermore, VAS score of combined anesthesia group at 12 h and 24 h after surgery was $2.571 \pm 1.129$ and $1.952 \pm 1.229$, respectively, which was significant lower than that of general anesthesia group ($3.708 \pm 1.051$, $3.063 \pm 1.21$) ($P < 0.05$).

*3.3. Reduced Cognitive Impairment by General Anesthesia Combined with Nerve Block.* MoCA was applied to evaluate cognitive status of all patients during perioperative period. The MoCA score before surgery was not significant different between combined anesthesia group and general anesthesia group ($P > 0.05$), with normal cognitive function ($28.43 \pm 0.8007$ vs. $28.35 \pm 0.5645$). The MoCA score of general anesthesia group and combined anesthesia group was $23.4 \pm 0.7646$ and $26.69 \pm 0.4679$ at 6 h after surgery, which was obviously lower than that before surgery ($P < 0.05$). In addition, at 12 h and 24 h after surgery, the two groups both showed elevated MoCA score, and the

Table 1: Hemodynamics variables of the two groups at multiple time points.

| Group | $N$ | MAP(mmHg) | | | | HR (beats/minute) | | | | SPO2 (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Before anesthesia | 15 minutes after anesthesia | 30 minutes after anesthesia | 5 minutes after surgery | Before anesthesia | 15 minutes after anesthesia | 30 minutes after anesthesia | 5 minutes after surgery | Before anesthesia | 15 minutes after anesthesia | 30 minutes after anesthesia | 5 minutes after surgery |
| General anesthesia | 48 | 94.56 ± 4.136 | 83.04 ± 8.661 | 79.17 ± 9.427 | 86.58 ± 8.913 | 77 ± 8.495 | 68.5 ± 7.05 | 69.63 ± 7.956 | 72.75 ± 8.446 | 97.35 ± 1.329 | 97.23 ± 1.491 | 96.88 ± 1.817 | 96.98 ± 1.591 |
| Combined anesthesia | 42 | 95.33 ± 3.545 | 90.43 ± 4.618 | 88.74 ± 6.224 | 92.21 ± 4.015 | 76.48 ± 9.195 | 73.52 ± 9.451 | 74.17 ± 10.13 | 77.62 ± 9.768 | 97.14 ± 1.69 | 97.31 ± 1.76 | 97 ± 1.9 | 97.29 ± 1.715 |
| $t$ | | 0.9423 | 4.944 | 5.597 | 3.771 | 0.2808 | 2.88 | 2.379 | 2.536 | 0.6632 | 0.2345 | 0.3187 | 0.8794 |
| $P$ | | 0.3486 | < 0.0001 | < 0.0001 | 0.0003 | 0.7795 | 0.005 | 0.0195 | 0.013 | 0.5089 | 0.8151 | 0.7507 | 0.3816 |

Table 2: VAS score for evaluation of postoperative pain.

| Group | $N$ | 6 h after surgery | 12 h after surgery | 24 h after surgery | $F$ | $P$ |
|---|---|---|---|---|---|---|
| General anesthesia | 48 | 4.667 ± 0.5955 | 3.708 ± 1.051 | 3.063 ± 1.21 | 32.09 | < 0.0001 |
| Combined anesthesia | 42 | 3.548 ± 0.5038 | 2.571 ± 1.129 | 1.952 ± 1.229 | 26.82 | < 0.0001 |
| $t$ | | 9.549 | 4.945 | 4.311 | | |
| $P$ | | < 0.0001 | < 0.0001 | < 0.001 | | |

patients undergoing nerve block combined with general anesthesia presented much higher score than those receiving general anesthesia ($P < 0.05$, Table 3).

*3.4. The Postoperative Adverse Reactions and Recovery Condition of the Two Groups.* Adverse reactions were observed and compared between the two groups, including dizziness and headache, nausea and vomiting, drowsiness, urinary retention, and respiratory depression. As shown in Table 4, we found that the incidence of nausea and vomiting was 25% and 7.14% in general anesthesia group and combined anesthesia group ($P < 0.05$). Although lower incidence of dizziness and headache, drowsiness, and urinary retention was found in combined anesthesia group compared to general anesthesia group, the difference was not significant ($P > 0.05$). No patients suffered from respiratory depression in both groups, and the patients in general anesthesia group showed higher total incidence of adverse reactions than those in combined anesthesia group ($P < 0.05$). Furthermore, we observed that the time to out-of-bed activity and hospital stay of the patients receiving combined anesthesia were significantly shorter than that of patients only undergoing general anesthesia ($P < 0.05$).

## 4. Discussion

Surgical reduction is the main treatment for lower extremity fracture. Various factors during the perioperative period, including trauma, blood loss, pain, changes in total circulation, and emotional tension, result in strong stress response in the patients. In addition, postoperative swelling of affected limbs, incision pain, and strong stimulation of nerves at the fracture site exacerbated the acute pain after surgery. Approximately 25%-35% of the patients suffered from postoperative pain, which affected physical function of the affected limb and negatively affected the postoperative rehabilitation [22]. Therefore, attention should be paid to the design of anesthesia scheme in the operation of lower extremity fracture.

In the past, epidural block anesthesia was widely used in patients undergoing lower extremity surgery due to its advantages of good anesthetic effect. However, it is not applicable to those patients with spinal ligament calcification or intervertebral space stenosis [23]. Furthermore, the respiratory and circulatory systems of some patients will also be affected [24]. In contrast, general anesthesia is more convenient for anesthesia management of patients, but it will affect the stability of hemodynamics of patients. Therefore, it is often combined with nerve block in clinic to improve postoperative outcomes in fracture surgery [19, 25, 26]. In our retrospective study, we analyzed the impacts of general anesthesia and nerve block combined with general anesthesia in patients undergoing lower extremity fracture. We monitored the hemodynamic changes between the two groups at multiple time points and found that MAP at 15 minutes and 30 minutes after anesthesia, as well as 5 minutes after surgery in the two groups was lower than that of before anesthesia, respectively. Comparing to the general anesthesia group, the combined anesthesia group presented obvious higher MAP at multiple time points except for before anesthesia ($P < 0.05$). Furthermore, more stable MAP was revealed in the combined anesthesia group compared with the general anesthesia group (95.33 ± 3.545, 90.43 ± 4.618, 88.74 ± 6.224, 92.21 ± 4.015) vs. (94.56 ± 4.136, 83.04 ± 8.661, 79.17 ± 9.427, 86.58 ± 8.913). No significant difference in HR before anesthesia was found between the general anesthesia group (77 ± 8.495) and combined anesthesia group (76.48 ± 9.195). However, at 15 minutes and 30 minutes after anesthesia, along with 5 minutes after surgery, the combined anesthesia group had higher HR when it was compared with general anesthesia group ($P < 0.05$). As for $SpO_2$ variables, there was no significant different between the two groups at multiple time points ($P > 0.05$). As reported in previous studies [18], Liu et al. indicated that compared with the combined spinal-epidural anesthesia, the general anesthesia with laryngeal mask airway and nerve block contributed to slight intraoperative hemodynamic variations of the elderly patients with intertrochanteric fracture surgery. In the hip surgery, significant reductions in MAP at induction was observed in the patients treated with general anesthesia compared to those undergoing general anesthesia combined with nerve block. Besides that, block group presented no significant changes in cardiac output, cardiac index, stroke volume, and stroke volume index [27]. Peripheral nerve block damages the conduction of noxious stimulation and significantly reduces stress response. A large number of studies have confirmed that nerve block effectively optimizes perioperative analgesia and reduces the use of intraoperative and postoperative analgesics [28–30]. However, the locations where nerve block can be performed are relatively limited. A certain dose of additional intravenous sedatives or general anesthesia is required to obtain the best anesthetic effect, resulting in guarantee of adequate oxygen supply during surgery. A study of total knee arthroplasty demonstrated that femoral nerve block combined with general anesthesia alleviated postoperative pain and exhibited declined 6 h and 24 h VAS scores in resting state after surgery [31]. In the present study, comparing to general

Table 3: MoCA score for assessment of perioperative cognitive function.

| Group | *N* | Before surgery | 6 h after surgery | 12 h after surgery | 24 h after surgery | *F* | *P* |
|---|---|---|---|---|---|---|---|
| General anesthesia | 48 | 28.35 ± 0.5645 | 23.4 ± 0.7646 | 24.54 ± 0.5035 | 26.33 ± 0.7244 | 536.2 | < 0.0001 |
| Combined anesthesia | 42 | 28.43 ± 0.8007 | 26.69 ± 0.4679 | 27.93 ± 1.113 | 28.55 ± 0.7392 | 45.78 | < 0.0001 |
| *t* | | 0.5143 | 24.23 | 18.99 | 14.33 | | |
| *P* | | 0.6084 | < 0.0001 | < 0.0001 | < 0.0001 | | |

Table 4: Incidence of postoperative adverse reactions (*n*, %) and recovery condition in the two groups.

| Group | Nausea and vomiting | Dizziness and headache | Drowsiness | Urinary retention | Respiratory depression | Total adverse reactions | Time to out-of-bed activity (h) | Hospital stay (d) |
|---|---|---|---|---|---|---|---|---|
| General anesthesia | 12 (25) | 2 (4.17) | 5 (10.42) | 3 (6.25) | 0 (0) | 22 (45.83) | 42.18 ± 4.4323 | 11.9 ± 0.9579 |
| Combined anesthesia | 3 (7.14) | 0 (0) | 1 (2.38) | 2 (4.76) | 0 (0) | 6 (14.29) | 30.09 ± 4.3782 | 7.79 ± 0.9762 |
| *Chi-square* | 5.143 | 1.79 | 2.325 | 0.09454 | / | 10.4 | | |
| *t* | / | / | / | / | / | / | 12.98 | 20.13 |
| *P* | 0.0233 | 0.181 | 0.1273 | 0.7585 | / | 0.0013 | < 0.0001 | < 0.0001 |

anesthesia group, the combined anesthesia group had much lower VAS score at 6 h, 12 h, and 24 h after surgery. We also found that the patients receiving nerve block combined with general anesthesia showed higher MoCA score at postoperative multiple time points Ultrasound-guided nerve block is associated with improvement in the controllability of anesthetic dispersion and reduction in the damage to peripheral nerves and blood vessels. It leads to little effect on patients' cognitive function. As reported by total knee arthroplasty study, the rate of postoperative cognitive dysfunction at 4 d and VAS scores at 4-48 h after surgery was lower in the group receiving ultrasound-guided femoral nerve block in contrast to the group undergoing intravenous infusions of fentanyl [32]. Our study compared the postoperative adverse reactions between the two groups. The incidence of nausea and vomiting was 25% and 7.14% in general anesthesia group and combined anesthesia group, respectively. No remarkable difference was observed in terms of incidence of dizziness and headache, drowsiness, and urinary retention between the two groups. The increase in the incidence of nausea and vomiting might be related to the excessive use of general anesthesia drugs. Opioids cause gastrointestinal peristalsis to slow down by activating U-type opioid receptors distributed in the presynaptic nerve endings of the intestinal muscle plexus. At the same time, opioid receptor causes central reaction, leading to nausea and vomiting [33]. Furthermore, nerve block combined with general anesthesia is conductive to early recovery, which was presented by short time to out-of-bed activity and hospital stay.

In conclusion, ultrasound-guided nerve block combined with general anesthesia contributed to maintaining the stability of hemodynamics and alleviating cognitive impairment. Furthermore, it is conducive to relief of postoperative pain, resulting in early recovery of lower extremity function. However, some limitations existed in this study, including lack of follow-up data and analysis of pain related inflammatory response. Besides, in the future, larger clinical samples of lower extremity fractures are needed to verify and refine our results.

## Data Availability

The data used to support the findings are in the article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Supplementary Materials

Baseline data of the two groups. *(Supplementary Materials)*

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*Retraction*

# Retracted: Chemical Structures and Pharmacological Properties of Typical Bioflavonoids in *Polygonati Rhizoma* (PGR)

**Journal of Environmental and Public Health**

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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] M. Luo, Z. Hu, Z. Zhong, L. Liu, C. Lin, and Q. He, "Chemical Structures and Pharmacological Properties of Typical Bioflavonoids in *Polygonati Rhizoma* (PGR)," *Journal of Environmental and Public Health*, vol. 2022, Article ID 4649614, 7 pages, 2022.

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*Review Article*

# Chemical Structures and Pharmacological Properties of Typical Bioflavonoids in *Polygonati Rhizoma* (PGR)

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Most medicines are coming with toxic and detrimental side effects. In addition, microbials are resisting the medicine. Therefore, alternative drugs with low toxic and side effects and low microbial resistance are needed. Plants offer good potential candidates due to a broad range of chemicals they contain. These chemicals have been studied, and research is still going on to probe chemical properties of plant chemicals. In China, traditional Chinese medicine is practised, whereby plant extracts are obtained, and then sold in packages for reasons like memory enhancement, cancer treatment, boosting immune system, and so on. Among the herbs cultivated in China is *Polygonati rhizoma* (PGR). This plant contains various bioflavonoids such as diosgenin, kaempferol, catechin, daidzein, and 3′-methoxydaidzein. In this review, we discussed the pharmacological effects of these chemicals, including luteolin antimicrobial activity in a manner that it circumvents antibiotic resistance; rutin antivenom property; kaempferol as an agent that mitigates neuropathic pain; genistein anticancer property; isorhamnetin's ability to alleviate chronic obstructive pulmonary diseases (COPD); proanthocyanidins' ability to deal with diabetic neuropathy and analgesic property of catechin.

## 1. Introduction

Plant secondary metabolites serve as a defence system that protects plants from physical, chemical, and biological attacks. More often, such chemical components are referred to as natural products. It is known that these chemical components do have a broad spectrum of therapeutic effects. Research on natural products has therefore been one of the major scientific endeavours [1].

Pei et al. [2] points out that traditional Chinese medicine is over 3000 years old, and it focuses on aspects like multiple pathways, multiple targets, and multiple components. *Polygonati Rhizoma* (PGR) is one of the Chinese traditional herbs and is known for having antihypertensive, anti-inflammation, anticancer, cardioprotective, and neuroprotective effects. It is also reported that the herb treats Alzheimer's disease (AZ). Research has found that the herb improves memory and learning abilities of AZ mice [3]. This paper serves to discuss on a few bioflavonoids in *Polygonati rhizoma* and their medicinal properties. The chemical substances discussed in this review were luteolin, rutin, rutin succinate, kaempferol, genistein, catechin, proanthocyanidin, and isorhamnetin.

## 2. Flavonoids in PGR

Wang et al. [4] named three of the flavonoids found in PGR which are rutin, syringetin-3-O-glycoside, and isorhamnetin (Figure 1). Scientists extracted 10 chemical components from 10 sections of PGR. The list is endless. Some records indicate that 7-hydroxy-2-(4-hydroxyphenyl)-chroman-4-one (DFV), diosgenin, sitosterol, $\beta$-sitosterol, baicalein, methylprotodioscin, 3′-methoxydaidzein, (2R)-7-hydroxy-2-(4-hydroxyphenyl) chroman-4-one, and (+)-Syringaresinol-O-beta-D-glucoside are other flavonoids contained in the PGR [5]. The purpose of this review article is to summarize and discuss several main bioflavonoids contained in PGR and their pharmacological effects.

*2.1. Luteolin.* Guo et al. [6] observed that luteolin 'chelates' streptolysin O toxin inhibits its cytotoxicity and haemolytic effects. Group A *Streptococcus* (GPAS) bacteria produce the aforementioned toxin and cause a wide range of diseases. Multidrug resistance (MDR) is persisting. As a result, herbal medicine is chipping in as one of the ways to circumvent the MDR [7]. Luteolin (Figure 2) has an antibacterial activity [8]. According to Zhang et al. [9], luteolin circumvents antibiotic resistance in *Trueperella pyogenes*. Scientists aim at the virulent part of pathogenic bacteria. In most cases, this virulence moiety is a toxin, which is a hemolysin-like protein. This approach is also another attempt to "bypass" antibiotic resistance [10].

*2.1.1. Luteolin and Streptolysin O (SPO) Toxin.* According to Guo et al. [6], luteolin inhibits SPO haemolytic effect. The team adopted the erythrocyte homolytic assay reported by Dong et al. [11] and Dong et al. [12]. Previous research had reported that luteolin achieved anti-group A *Streptococcus* activity with the (minimal inhibit concentration) MIC of 128 $\mu$g/mL. Guo et al. reported a lower MIC. The research team went on to analyze interaction between luteolin and SPO. The methodologies used were molecular docking and molecular dynamics (MD) simulations. Howbeit, Morra et al. [13] said that MD simulations are better than molecular docking. It was observed that luteolin binds SPO domains 1 and 3. The domains were characterised by $\beta$ pleats hedged both sides by helices. The binding site is deemed to be a semiopen hydrophilic binding site. A magnitude of −7.2 kcal/mol binding energy was computed following luteolin-SPO interaction. Hydrogen bonds, van der Waals' forces, and hydrophobic interactions were the main forces involved during luteolin-SPO interaction. Tyrosine residues, glycine, aspartate, and isoleucine were the amino acids involved in luteolin-SPO interaction. Tyrosine residues were dominating the rest.

Guo et al. went further to make use of the MD simulations to comprehend the mechanism of the luteolin-SPO interaction. Conformational changes in SPO were found to be fluctuating. However, fluctuations were minimum when luteolin was bound to the SPO as compared to SPO alone. Therefore, the inference was that, luteolin stabilises the SPO conformation. No side-chain conformation was observed before or after luteolin-SPO interaction, which might help maintain the conformational stability of SPO and thus inhibit toxin assembly [6].

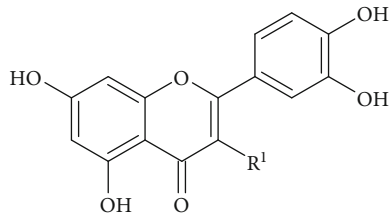
*2.2. Rutin and Rutin Succinate.* Rutin and its derivatives are part and parcel of the polyphenols called flavonoids. Rutin has the characteristics of bioavailability and solubility, which has not been studied in depth, which is a great challenge. Notwithstanding, rutin analogues were used instead to try and overcome bioavailability and solubility issues. Either natural or artificial rutin analogues can be used to understand pharmacological effects of rutin. Analogues like troxerutin and isoquercetin are useful. Artificially, rutin can be modified by adding succinate moieties on glycoside hydroxyl groups of rutin (Figure 1). Alternatively, metal ions can be conjugated to rutin [14].

*2.2.1. Rutin, Rutin Succinate, and Snake Venom.* Snakebites are complex to treat. It has been a custom to treat snakebites by antivenoms from animals. As an illustration, *Bothrops* antivenom is used to treat individuals bitten by *Bothrops* snakes. Nonetheless, the incapacity to block local-induced snakebite effects and after-bite complications like oxidative stress is reported. Polyphenols, therefore, are a rightful candidate for snake venom treatment since they exhibit antioxidant properties. Research was done by Sachetto et al. where rutin succinate was tested for antivenom properties [14].

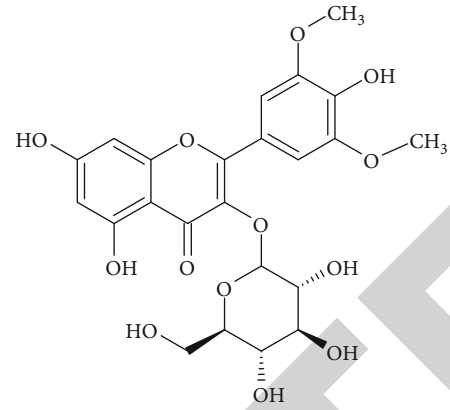
Sachetto et al. observed that rutin succinate has the ability to inhibit *Bothrops jararaca* (viper) venom *in vitro*. Rutin succinate inhibits of *Bothrops jararaca*'s hyaluronidase enzyme activity. The inhibitory effect varies with the inhibitor concentration. Other proteins of the viper venom (VV) were studied. These include venom metalloproteinases (VVMPs) and venom serine proteinases (VVSPs). Based on the findings of the research team, the inhibition rate of VVSPs inhibitors (which the research team called AEBSF) was 99.4%. VV activation of coagulation factors is one of the challenges to be addressed after snake bites. In vitro studies have shown that VV causes coagulation. Sachetto et al. analyzed the effect of VV on prothrombin activation. The team preincubated VV with rutin succinate and found that prothrombin activation was reduced by 98%, which greatly reduced the probability and degree of coagulation and also had a large positive effect on the treatment of snake venom [14]. Rutin succinate is expected to be a natural drug replacing specific inhibitors.

*2.2.2. Rutin and Rutin Succinate Silence VV Toxic Effects and Lethality.* Sachetto et al. probed survival analysis of mice following administering the VV via intraperitoneal route. Two different doses were prepared. The first dose was twice lethal dose 50 ($2LD_{50}$) and the second dose was thrice lethal dose 50 ($3LD_{50}$). In their study, the first dose was used to induce envenomation. They then determined homeostatic parameters using the first dose. Severity of the venom was studied using the second dose. Incubation of rutin and rutin succinate was done with VV doses to observe the antivenom properties of the bioflavonoids, rutin, and rutin succinate.

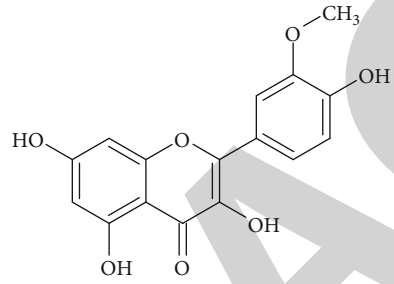
In a space of 48 h, the first dose did not potentiate death in mice. According to their haematologic observations,




Rutin, $R^1$ group is rutinoside




Syringetin-3-O-glycoside




Isorhamnetin

Figure 1: Some flavonoids contained in PGR.

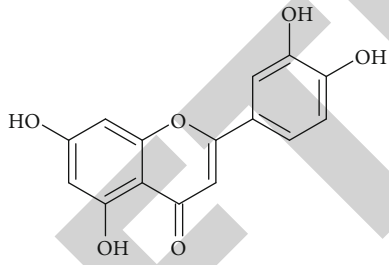



Figure 2: Chemical structure of luteolin.

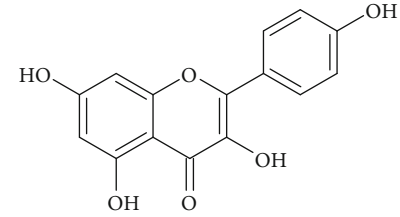



Figure 3: The chemical structure of kaempferol.

incubating VV with rutin succinate mitigated leukocyte circulation in comparison with the VV alone mice group. The statistical $p$ value for this result was less than 0.05. In the VV alone group, erythrocyte parameters were decreased by a range of 44-58%. This was not the case with VV + rutin succinate group. The inference is that rutin succinate prohibited a fall in erythrocyte parameters. The VV perturbed homeostatic balance causing hypofibrigenemia and thrombocytopenia. The experimental mice groups had lower platelets than normal following VV administration. It was found out that platelets dropped down to 53-86% below the expected platelet count.

The severe VV dose killed 50% of the mice in a space of 4 h. Other mice groups survived. After 48 h, the survival rate of $3LD_{50}$ alone group was 33.3%. It then follows that rutin succinate prohibits lethality of mice following VV administration [14].

*2.3. Kaempferol.* Kaempferol (Figure 3) was discovered in 1930. A Hungarian scientist by the name Albert Szent Györgyti managed to isolate a new chemical from oranges and it was believed to be one of the vitamins. Albert was a professor at the University of Szeged. It was then discovered that kaempferol is a flavonoid found in a broad spectrum of plants including Chinese plants like *Polygonati rhizoma* [2, 15].

*2.3.1. Kaempferol and Its Central Nervous System (CNS) Therapeutic Effects.* In recent studies, kaempferol and its derivatives have pharmacological effects on a number of degenerative diseases like glioblastoma, Alzheimer, epilepsy, Parkinson, neuropathic pain, ischemic stroke, major depressive disorder, and anxiety disorders. These ailments are known for interfering with the nervous system [15].

*2.3.2. Neuropathic Pain and Kaempferol.* The International Association for the Study of Pain defines neuropathic pain

(neuralgia) as the nervous system pain generated when dysfunction and or abrasion of the nervous system occurs. A plethora of factors destroy nerves and thus resulting in neuropathic pain. Ailments like strokes, multiple sclerosis, cancer, herpes zoster, and diabetic neuropathy can cause neuropathic pain. This disease is generally divided into two categories, mononeuropathy and polyneuropathy. Mononeuropathy is the damage of the single nervous pathway; whereas polyneuropathy is characterised by damage of numerous nerves and the pain is generalised and well located [16].

According to [15] best knowledge, there is not an article of late that reported isolation of kaempferol to carry out experiments and see if it treats neuropathic pain. Nonetheless, some studies assessed total kaempferol extracts that contained kaempferol [17]. In one of those studies, kaempferol exerted hypoglycaemic effect in diabetes mellitus animal models. It then implies that antioxidant activity of kaempferol prevented oxidative damage, thus, avoiding neuropathic pain [17].

*2.3.3. Kaempferol and Major Depressive Disorder.* The World Health Organisation (WHO) defines major depressive disorder (MDD) as a mental health disorder that is characterised by loss of interest in pleasurable activities, incapacity to carry out daily routine activities for at least a fortnight, and tenacious sadness. The common symptoms accompanied by the ailment are suicidal thoughts, loss of determination, and thoughts to harm self. Tetracyclic antidepressants treat MDD. The drugs work by blocking receptors of neurotransmitters like dopamine, serotonin, and norepinephrine. The monoamine oxidase inhibitor depressants (MAOIs) interfere with the activity of monoamine oxidase enzyme hence escalating the CNS dopaminergic, serotonergic, and noradrenergic neurotransmitters. Stroke, hypertension, and heart attack are reported fatal results if the MAOIs are taken with food which is rich in tyramine. The food includes cheese and fermented food products [18].

To rectify the challenges, scientists had to look for alternatives. Such alternatives must deal with any of the transduction or endocrinological pathways that lead to MMD. Reports say that neuroinflammation and oxidative stress trigger MDD pathophysiology. Gao et al. [19] reported that kaempferol exhibits antidepressant effect due to its antioxidant capacity. Also, kaempferol exerted anti-inflammatory properties which were achieved via escalating prefrontal cortex AKT (serine/threonine kinase)/$\beta$-catenin cascade. The team assessed the antidepressant effects of narirutin flavonoids and kaempferol-3-O-glycoside (K3G) using female wild Wistar rats. The team designed their experiment in a manner that five groups of Wistar were given different obesogenic diets. There was a group which got 30 mg/kg body weight and K3G three weeks prior to mating. The rest of the groups were regimented to their respective diets till they reproduce and begin to lactate. According to the results of Gao et al., too much caloric diets during perinatal periods have the potential to escalate behavioural changes in animal models and humans. The group supplemented with K3G and narirutin did not suffer from depression.

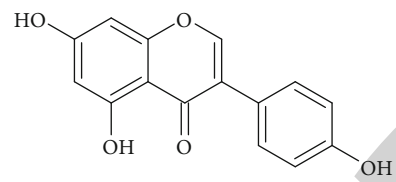



Figure 4: Genistein structure.

*2.4. Genistein.* Genistein (Figure 4) is an isoflavonoid found in plants as well. The chemical is known for having anticancer properties particularly cancer that results following radiation exposure. It is reported that genistein protects the DNA from radiation damage by hunting for radicals generated. A number of experiments revealed that mice which were exposed to radiation did not develop cancer following genistein administration [20].

Zhang et al. [20] designed an experiment to investigate the anticancer potency of genistein on irradiated IEC-6 cells. The team discovered that cell apoptosis induced by radiation was mitigated by genistein. Also, gastrointestinal injury by ionizing radiation was found to be improved.

*2.5. Proanthocyanidins.* Proanthocyanidins (PACs) are oligomers of flavonoids. These chemicals can be described as condensed tannins which are gallic acid and catechin derivatives. It is known that PACs are made up of prodelphinidins, procyanidins, and propelargonidins. The PACs recently drew a lot of scientists' attention due to their antihyperglycaemic, antioxidant, anti-inflammatory, and anticell death properties [21]. Gong et al. [22] conducted an experiment to probe PACs' ability to treat diabetic neuropathy induced by cadmium.

*2.5.1. PACs and Glucolipid Metabolism.* Gao et al. investigated the effects of PACs in diabetic neuropathy mice, induced by cadmium exposure. The fasting blood glucose (FBG) was determined during the entire course of their study. The FBG levels in different groups were higher than the normal accepted range. The group treated with PACs had shown a decrease in FBG levels thus indicating the potency of PACs in lowering FBG levels. Further biochemical parameters like plasma triglycerides (TG) content, total cholesterol (TC), low-density lipoprotein-C (LDL-C), and high-density lipoprotein-C (HDL-C) among others. It was then found that in diabetic neuropathy (DP) mice, TD, TC, and LDL-C levels decreased in comparison with the control groups.

*2.5.2. Effects of PACs on Transduction Pathway.* Gao et al. further probed the effects of PACs on Keap1/Nrf2 and p38 MAPK pathways in relation to oxidative stress. Western blotting technology was employed to carry out this investigation. Expression of proteins involved in p38 MAPK and Keap1/Nrf2 pathways was done. It was then found that MAPK and p38 were expressed significantly in diabetes neuropathy mice. Nonetheless, upon PACs administration, the protein expression dropped.

Nrf2 expression decreased markedly whereas Keap1 levels escalated in diabetes neuropathy mice group. Upon treating the mice with PACs, Nrf2, and Keap1 expression levels reversed. Therefore, the inference is that PACs protect the diabetic neuropathy mice from harm by a mechanism that involves p38 MAPK and Keap1/Nrf2 transduction pathways [19].

*2.6. Catechin and Neuropathic Pain.* According to Foudah et al. [23], chronic constriction injury causes neuropathic pain development in Sprague-Dawley rats. The team used a neutral plate to evaluate spontaneous pain in rats. Catechin lessened the pain. A parameter known as motor nerve conduction velocity was determined to see if catechin had an effect. The research team observed catechin improved motor nerve conduction velocity in mice. Chronic constriction injury had resulted in loss of motor nerve conduction.

*2.6.1. Catechin and Nuclear Factor-Kappa Beta (NF-κ β).* Chronic constriction rats had an elevated level of DNA binding activity of NF-$\kappa$ $\beta$ in sciatic nerve cells. The DNA-NF-$\kappa$ $\beta$ binding activity decreased following catechin administration. Nociceptive response is related to the NF-$\kappa$ $\beta$ activation. Escalation of NF-$\kappa$ $\beta$ activation is linked with an improvement in nociceptive response. Increased inflammatory response results in pain. Inflammatory cytokine production increases during inflammation and pain. A reduction in pain that depended on catechin concentration was reported [23].

*2.7. Isorhamnetin and Chronic Obstructive Pulmonary Disease (COPD).* Brandsma et al. [24] said that COPD is a severe disease that causes inflammation of the lungs resulting in narrow airways. The disease can lead to emphysema. The disease is treated with bronchodilators and corticosteroids. The COPD patients are insensitive to corticosteroids according to some research. Therefore, alternative anti-inflammatory therapy is needed. Plant-derived chemical are suitable for treating COPD due to the anti-inflammatory properties [25]. A recent study shows that isorhamnetin (Figure 5) relieves inflammation of the respiratory system [26].

*2.7.1. Isorhamnetin Pharmacological Effect in COPD Animal Models.* In mice, isorhamnetin (IHN) improves cigarette smoke-induced COPD. Xu et al. [26] administered lipopolysaccharides in mice via intratracheal inhalation route two times. Mice were also exposed to cigarette smoke. These treatments led to the manifestations of typical COPD clinical symptoms. Erythrocytes increased in cigarette smoke-induced COPD. A decrease in the number of red blood cells was observed following administration of isorhamnetin.

It is known that COPD inflammation results in deposition of collagen fibres surrounding the airway. Consequently, lung tissue elasticity is mitigated, and COPD is worsened [27]. Cigarette smoke-induced fibrosis was probed by staining lung tissues sections with Masson trichrome. The control tissue had a very thin layer of collagen deposit. The cigarette smoke group resulted in thick layer of collagen around bronchioles and vessels. The layer diminished in the isorhamnetin + cigarette smoke group [26].

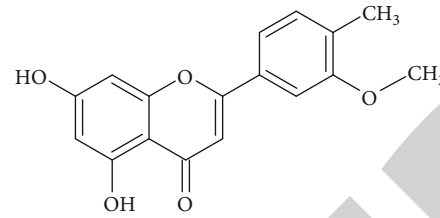



Figure 5: Chemical structure of isorhamnetin.

*2.7.2. Isorhamnetin Mode of Action in Treating COPD.* The major pathway underlying inflammation is Nrf 2/Keap 1 [28]. Xu et al. [26] determined superoxide dismutase enzymes (SOD)1 and 2; Nrf 2 and heme oxygenase 1. Isorhamnetin enhances the expression of the above-mentioned proteins. This expression depended on the dosage of isorhamnetin. At low concentration (30 mg/kg), isorhamnetin did not enhance the expression of heme oxygenase 1. The research team observed that after isorhamnetin treatment, Keap 1 was down regulated, Keap 1 as the feedback regulator of Nrf 2. In addition, a protein known as p 62 controls the Nrf 2/Keap 1 pathway. The protein interacts with the Keap 1 directly leading to the disintegration of the Keap1 via ubiquitination [29]. Isorhamnetin promoted p62 accumulation thus Keap 1 disintegration [26].

## 3. Conclusion

Synthetic drugs have many side effects, and scientists are gradually turning their research back to natural products. Flavonoids are one of the natural products of interest. *Polygonati rhizoma* contains many flavonoids and has been used in many parts of the world. In this paper, some typical chemical substances contained in seminal vesicles were reviewed, including luteolin, rutin, kaempferol, genistein, proanthocyanidins, and isorhamnetin, and their typical pharmacological activities were also described, showing antimicrobial, anticancer, antioxidant, anti-inflammatory, and anti-snake venom properties. These active natural chemicals contained in the yellow spirit are expected to replace synthetic drugs as new research targets for disease treatment.

## Data Availability

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

## Conflicts of Interest

The authors declare no conflicts of interest.

## Authors' Contributions

ML contributed to conception and design of the study, and wrote the first draft of the manuscript. ZH, ZZ, LL, and CL

contributed to the data collection and analysis. QH contributed to manuscript revision, read, and project management. All authors approved the submitted version.

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