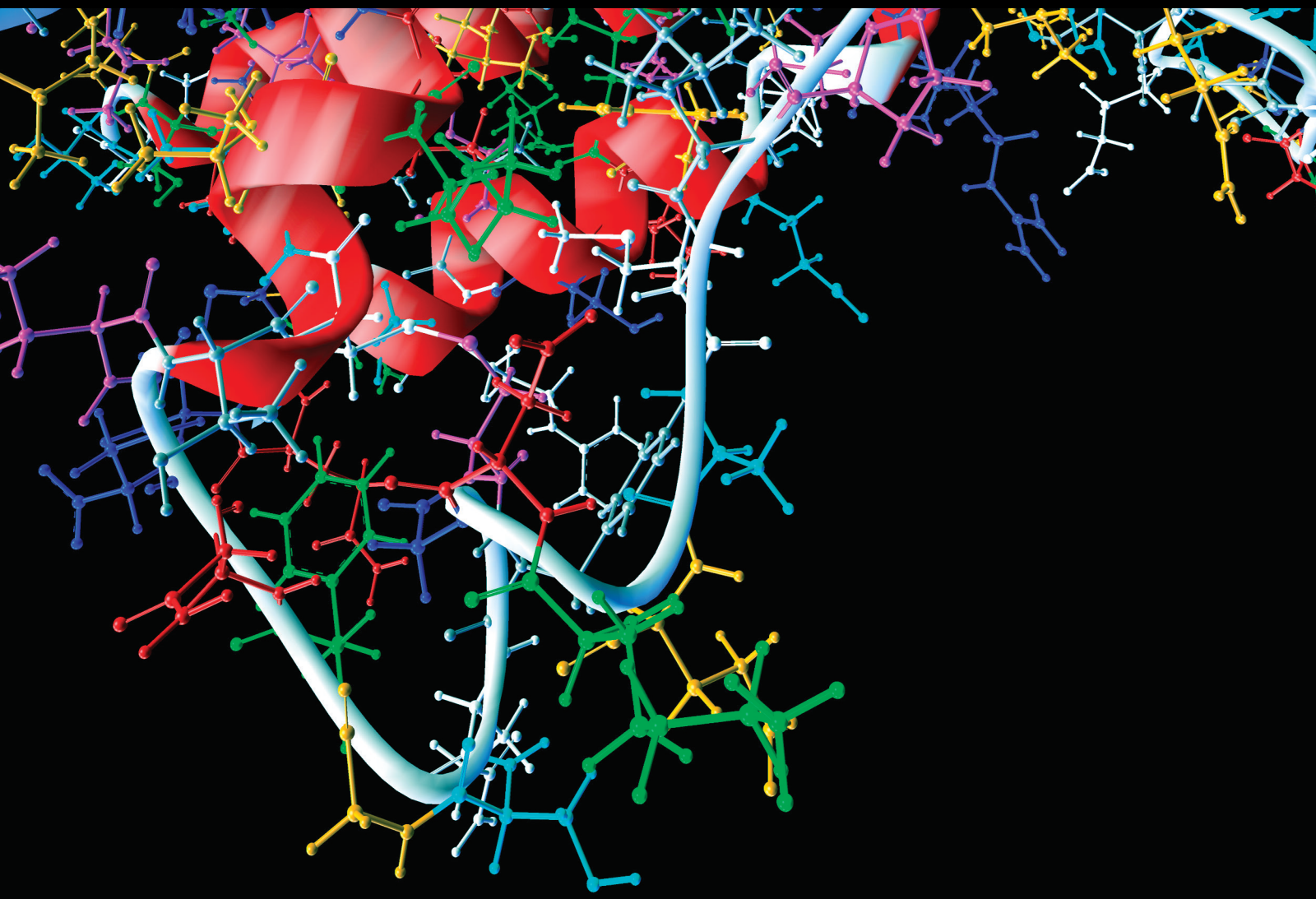
Computational and Mathematical Methods in Medicine

Database-Based Deep Learning and Optimization Algorithms for Age-Related Diseases and Conditions

Lead Guest Editor: Xi Lou
Guest Editors: Yawen Tang and Fangyuan Qin



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Contents

Contents

Hindawi
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Volume 2022, Article ID 3972958, 7 pages
https://doi.org/10.1155/2022/3972958

Research Article

Effect of Functional Electrical Stimulation on Gait Parameters in Children with Cerebral Palsy: A Meta-Analysis

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Received 12 August 2022; Accepted 1 September 2022; Published 22 September 2022

Academic Editor: Xi Lou

Objective. At present, there are controversies on the effectiveness of functional electrical stimulation devices in gait improvement in the clinic, and the results reported in limited literature are contradictory. This paper summarizes and analyzes the relationship between functional electrical stimulation treatment and gait parameter changes in children with cerebral palsy, thus exploring the above controversies' results. *Methods*. Two researchers conducted a detailed search of the literature from the establishment of the database to June 2022. Literature retrieved from databases, including PubMed, Embase, Ovid, Cochrane Library, and Web of Science and the search process followed the principles of Cochrane. The search keywords were "cerebral palsy", "functional electrical stimulation", "gait", or "walk". Gait and balance parameters were extracted from the literature. Gait parameters, such as walking speed and step length, were included in the meta-analysis. The study used standard mean difference (STD) and 95% confidence interval (CI) to calculate the mean difference between the two groups. The statistic I^2 was used to evaluate the heterogeneity between the evaluation studies. Begg's test detected publication bias and the funnel chart was used for visual analysis. Furthermore, Review Manager software was used to make a risk bias map for literature publication bias analysis. *Results*. 9 literatures were included in the analysis, with a total of 282 children with cerebral palsy, including 142 patients in the functional electrical stimulation treatment group and 140 patients in the comfort treatment, general nursing, or other physical therapy. The randomization scheme and result report used in most studies were low risk, which was important for the credibility of this study. Most studies have limitations in the blinding method of participants and subjects, and most of them were single-blind studies, which might have a high risk. The results showed that functional electrical stimulation could increase the walking speed of children with cerebral palsy (SMD = 0.82, $P < 0.0001$) and increase the walking step length of children with cerebral palsy (SMD = 1.34, 95%CI = 1.07, 1.60, $Z = 9.91$, $P < 0.0001$). Funnel plot analysis showed that the literature distribution was uniform and symmetrical, and Begg's test showed no publication bias in included literature. *Conclusion*. This study compared the effects of the functional nerve stimulation treatment group and control group on improving gait parameters of children with cerebral palsy. The results indicated that functional nerve stimulation treatment could increase the gait speed and step length of children with cerebral palsy, which could improve the walking of children with cerebral palsy. Furthermore, this study needs more research data to support our findings. The results of this study might better guide the clinical practice and better use of health as well as financial resources.

1. Introduction

Cerebral palsy (CP) is a common neurological disease caused by nonprogressive disorders in the development of the central nervous system. The clinical symptoms include a series of motor and posture disorders [1]. Children with cerebral palsy usually show obstacles in neuromotor, musculoskeletal, and sensory systems, resulting in muscle strength loss and dysfunction. Furthermore, cerebral palsy can impair motor control and hinder various motor skills required by children's daily activities, such as walking [2, 3].

As patients grow up, the gradual increase in weight, muscle strength, and involuntary muscle contraction cause abnormal biomechanics, thus leading to abnormal walking

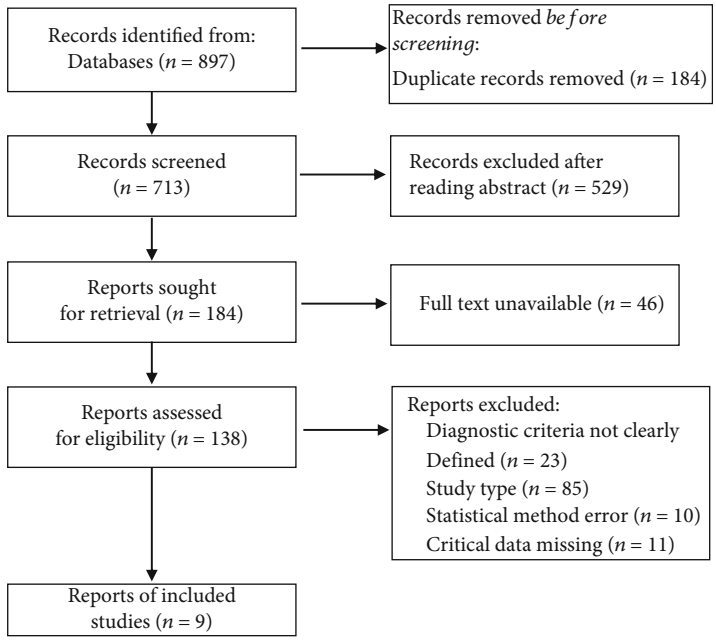

Figure 1: Document screening and exclusion process.

and gait patterns in children [4]. However, walking and gait are the abilities necessary for moving and exploring the environment. These problems bring the most severe functional impairment and the highest frequency of abnormalities in children with cerebral palsy, which greatly challenges clinical rehabilitation and intervention [5, 6]. Therefore, defining gait parameters is particularly important because they reflect the changes in the physical structure and function of children with cerebral palsy [7]. The improvement of gait parameters enhances motor function, allowing children with cerebral palsy to explore different ground environments and improve social interaction and participation, which has a positive impact on clinical rehabilitation and intervention [8].

Functional electrical stimulation (FES) is a kind of neural stimulation device which has been widely used in clinical rehabilitation and intervention. Currently, it is mainly used to stimulate muscles or nerves with impaired motor control ability to enhance the control and execution of functional actions [9]. FES is applied in the gait cycle mainly by stimulating appropriate muscle groups, such as the common peroneal nerve, to facilitate the ankle joint dorsiflexion and prevent the foot from falling. Therefore, FES can correct the gait swing state deviation and improve the walking ability [10]. In clinical rehabilitation, FES is mainly used to increase muscle strength, reduce muscle spasms, and improve exercise mode. Moreover, the FES device is small in size and easy to use, thus it is widely used in the clinic [10].

Currently, limited data support the role of FES in supporting walking by improving muscle strength and reducing muscle spasms [11]. Meanwhile, current literature data are based on clinical experiences or case reports, which lack evidence-based data on the walking gait improvement of FES. At the same time, there are controversies on the effectiveness of functional electrical stimulation devices in gait improvement in the clinic, and the results of limited literature reports are contradictory. For example, Armstrong et al. reported in a randomized controlled trial of 21 participants that the gross motor function measurement (GMFM) of the intervention group undergoing FES cycle training was superior to that of the routine nursing control group [12]. In contrast, Ozen et al. conducted a randomized controlled trial of 25 participants. They observed significant improvements in the evaluation of exercise ability in the FES cycle training group and the sham stimulation group, including GMFM measurement. However, the two groups had no statistical differences [13]. Due to the contradiction and inconsistency of clinical evidence, a high-quality systematic review and meta-analysis are required.

In this study, we summarized and analyzed the relationship between functional electrical stimulation and gait parameter changes in children with cerebral palsy to explore the controversial results. More updated clinical experimental studies were included in our research to ensure that the analysis results had all current experimental evidence, thus obtaining more accurate results and avoiding bias.

2. Materials and Methods

2.1. Literature Search Strategy and Inclusion and Exclusion Criteria. The two researchers conducted a detailed search of the literature from the beginning of the database to June 2022. The search process followed the principles of Cochrane, and the following databases were searched: PubMed, Embase, Ovid, Cochrane Library, and Web of Science. The search keywords were “cerebral palsy”, “functional electrical stimulation”, “gait”, or “walk”. The other 2 researchers collected literature that met the criteria after reading the titles and abstracts. Disparities arising from literature retrieval were resolved through negotiation and discussion.

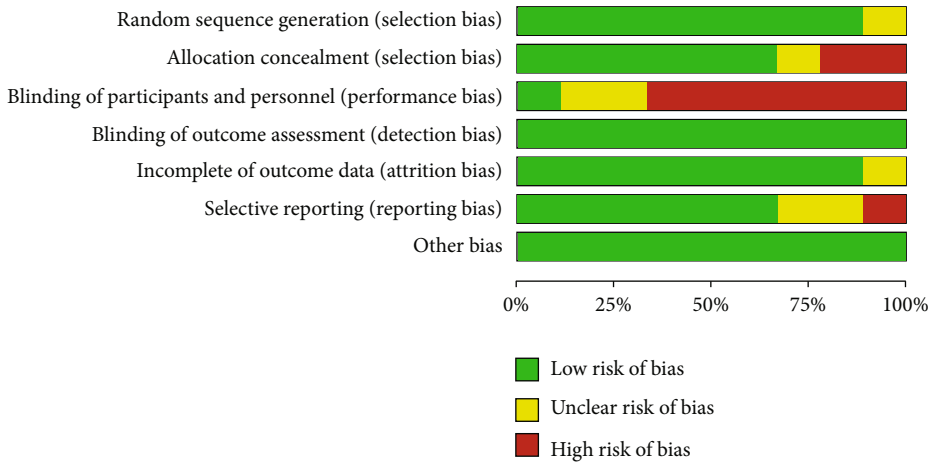

Figure 2: Summary of study bias risk.

The inclusion criteria were as follows: (1). The randomized controlled trial included the FES application test group and corresponding control group, and the control group could not be another electrical stimulation group; (2): The subjects were children with cerebral palsy under 18 years old; (3): During walking, the muscles were treated with functional electrical stimulation; (4): Detailed quantitative gait analysis data were provided; (5): Only English articles were analyzed.

Exclusion criteria were as follows: (1): Nonrandomized controlled trials, including prospective trials or retrospective studies, or it was impossible to determine whether the literature was a randomized controlled trial; (2): Other percutaneous electrical stimulation studies; (3): Gait disorder caused by other neurological diseases; (4): Adult patients.

2.2. Document Data Extraction and Analysis. Gait and balance parameters were extracted from the included literature. Gait parameters, such as walking speed and step length, were included in the meta-analysis. Other parameters were not included in the meta-analysis as the data identified in the literature.

Meta-analysis was performed using Review Manager software (version 5.4 of the Nordic Cochrane Centre, Copenhagen, Denmark). Forest maps were established to assess the data differences between the FES test group and the control group. The study used stand error of mean (STD) and 95% confidence interval (CI) to calculate the mean difference between the two groups. The statistic I^2 was used to assess the heterogeneity between the evaluation studies. The random effect model was used when I^2 was greater than 50% and the heterogeneity was significant. Otherwise, the fixed effect model was used. Publication bias was detected by Begg's test and the funnel chart was conducted for visual analysis.

2.3. Document Quality Evaluation. By following the analysis guidelines provided by the Cochrane Library, the bias risk analysis tool of Review Manager software was used to prepare the risk bias map. The bias risk analysis included the generation of random sequence, the concealment of the allocation scheme, the blinding of participants and subjects, the blinding of results evaluation, the integrity of results, the bias of results report, and other biases. The bias risk included three levels, namely, low, high, and unclear. The results were marked with red, green, and yellow color blocks.

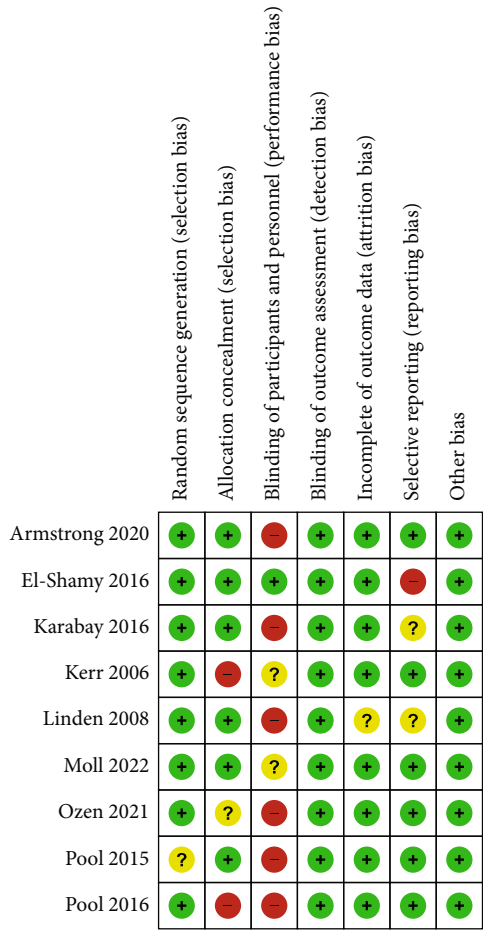

Figure 3: Details of bias risk of each study.

3. Results

3.1. Retrieval Results and Literature Quality Evaluation. The document search and screening process is shown in Figure 1.

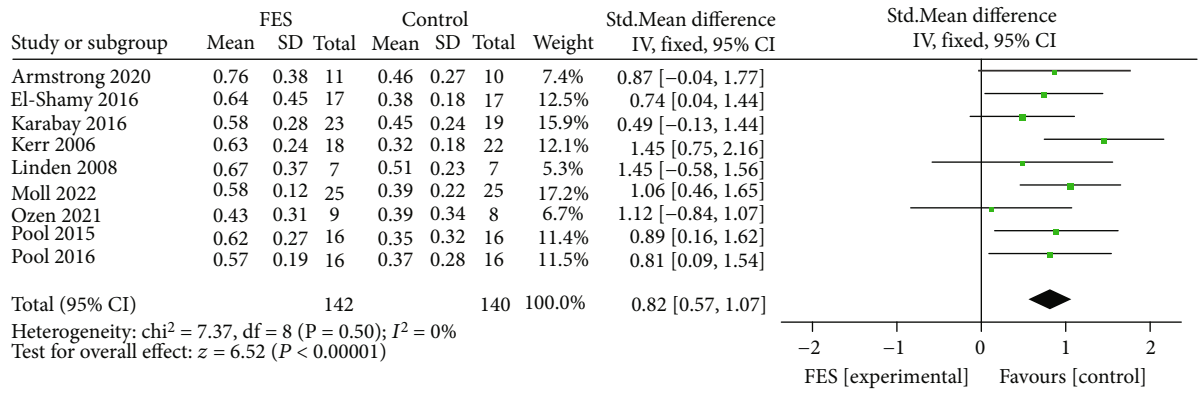

Figure 4: Forest diagram of walking speed meta-analysis in FES group and control group.

In this study, a total of 897 articles about the effect of functional electrical stimulation on gait parameters of children with cerebral palsy were retrieved from the database. After screening according to the above literature inclusion and exclusion criteria, 9 literatures [12–20] were finally included in the analysis, with a total of 282 children with cerebral palsy. Among them, 142 patients were divided into the functional electrical stimulation treatment test group, and 140 patients were included in the control group, treating with comfort treatment, general nursing, or other physical therapy. To reduce the heterogeneity of the study, FES combined with other treatments such as botulinum toxin treatment was excluded. In this paper, the functional electrical stimulation treatment group was taken as the experimental group, and the comfort treatment, general nursing, or other physical therapy groups were taken as the control group. The 9 included studies were all subject to literature quality assessment. Figures 2 and 3 are the summaries of bias risk and the detailed analysis bar chart of bias risk of each included document. Each study had its own high risk and indeterminate situation. In general, the randomization scheme and results report used in most studies are low-risk, which was critical to this study's credibility. Most studies have limitations in the blinding method of participants and subjects, and most of them were single-blind studies, which might have a high risk.

3.2. Effect of Functional Electrical Stimulation on Walking Speed of Children with Cerebral Palsy. A total of 282 children in 9 studies were included to analyze the impact of functional electrical stimulation on the walking speed of children with cerebral palsy. See Figure 4 for details. The data showed that the walking speed was increased after functional electrical stimulation compared with the control group (SMD = 0.82, 95%CI = 0.57, 1.07, $Z = 6.52$, $P < 0.0001$). While $I^2 = 0\%$, $P = 0.5$ indicated that there was no significant heterogeneity among the studies. The funnel chart in Figure 5 showed that the literature distribution was uniform and symmetrical, and Begg's test illustrated no publication bias among studies.

3.3. Effect of Functional Electrical Stimulation on Walking Steps of Children with Cerebral Palsy. A total of 282 children in 9 studies were included to analyze the impact of functional electrical stimulation on the walking steps of children with cerebral palsy. See Figure 6 for details. The data showed that compared with the control group, the walking step length was increased after functional electrical stimulation treatment (SMD = 1.34, 95%CI = 1.07, 1.60, $Z = 9.91$, $P < 0.0001$). And $I^2 = 31\%$, $P = 0.17$, indicating no significant heterogeneity among the studies. The funnel chart showed that the literature distribution was uniform and symmetrical (Figure 7), and Begg's test indicates no publication bias among studies.

4. Discussion

The current research results preliminarily support the use of functional electrical stimulation in treating children with cerebral palsy with walking disorders and activity restriction. The meta-analysis of gait parameters indicated that walking ability was improved after treatment. Our results are consistent with previous studies on functional electrical stimulation to improve gait speed [21]. Therefore, functional electrical stimulation is a feasible treatment for children with cerebral palsy who have difficulty in walking.

The Meta-analysis results showed that the gait speed of children with cerebral palsy has improved after functional electrical stimulation treatment. However, a higher gait speed has dual characteristics. On the one hand, higher gait speed is related to lower gait stability, poor muscle fine control, and joint stiffness. Therefore, children with cerebral palsy may generally adopt compensation strategies to increase gait stability by reducing gait speed and decreasing the risk of falls [22]. Due to the lower instability of walking than the perception threshold of children, children may gradually increase their gait speed when they try to control their gait autonomously, which is also a manifestation of their self-control ability [23]. Here, the gait speed shows a dual explanation. Therefore, it is biased and insufficient to simply explain whether each treatment method effectively improves the gait of children with cerebral palsy from the perspective of gait speed. At this time, it is necessary to refer to the spatial-temporal parameters of gait, including step size analysis, to judge the impact on gait comprehensively. Since walking is a dynamic task, the impairment of motor

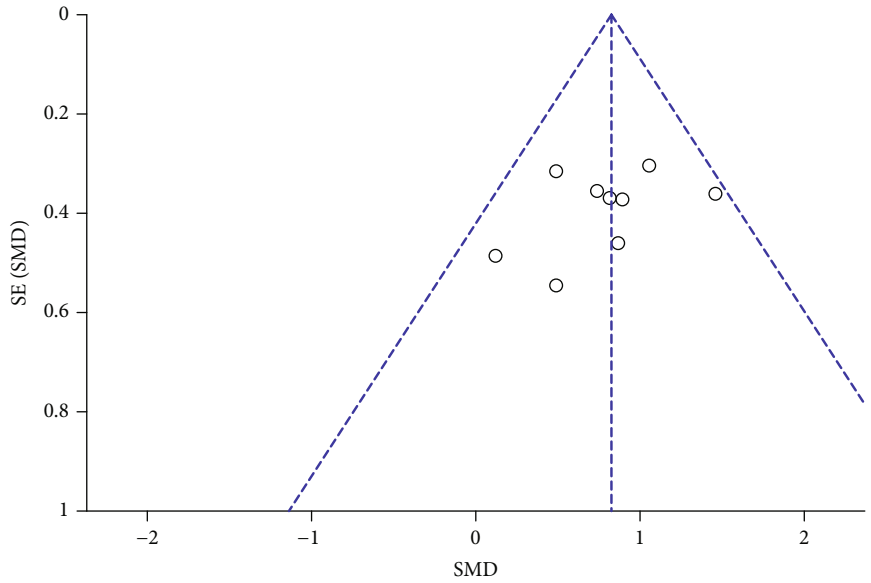

Figure 5: Funnel chart of walking speed meta-analysis in FES group and control group.

Study or subgroup	FES Mean	FES SD	FES Total	Control Mean	Control SD	Control Total	Weight	Std. Mean difference IV, fixed, 95% CI
Armstrong 2020	0.12	0.08	11	0.04	0.02	10	7.6%	1.29 [0.33, 2.25]
El-Shamy 2016	0.09	0.04	17	0.06	0.01	17	13.6%	1.00 [0.29, 1.72]
Karabay 2016	0.08	0.02	23	0.05	0.02	19	14.6%	1.47 [0.78, 2.16]
Kerr 2006	0.08	0.04	18	0.03	0.01	22	12.6%	1.76 [1.02, 2.51]
Linden 2008	0.09	0.07	7	0.04	0.03	7	5.6%	0.87 [−0.25, 1.98]
Moll 2022	0.11	0.04	25	0.06	0.02	25	17.1%	1.56 [0.92, 2.20]
Ozen 2021	0.07	0.03	9	0.06	0.03	8	7.6%	0.32 [−0.64, 1.28]
Pool 2015	0.11	0.07	16	0.05	0.03	16	12.5%	1.09 [0.34, 1.84]
Pool 2016	0.12	0.06	16	0.02	0.02	16	8.7%	2.18 [1.28, 3.08]
Total (95% CI)			142			140	100.0%	1.34 [1.07, 1.60]

Heterogeneity: chi² = 11.54, df = 8 ($P = 0.17$); $I^2 = 31\%$
Test for overall effect: $z = 9.91$ ($P < 0.00001$)

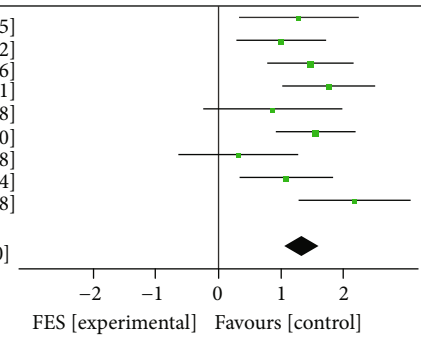

Figure 6: Forest diagram of step size meta-analysis in FES group and control group.

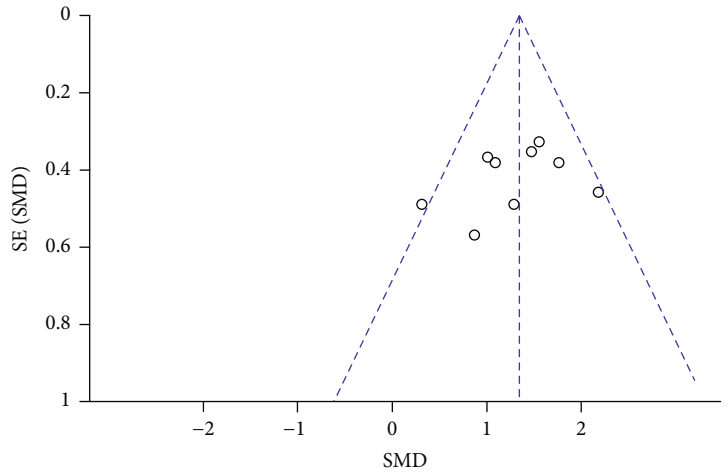

Figure 7: Funnel chart of step size meta-analysis in FES group and control group.

ability of children with cerebral palsy makes it difficult to maintain balance during dynamic walking. Children need to shorten their steps and reduce the swing of their bodies to sustain gait stability and maintain the center of gravity [24]. When the children's walking ability improves, their ability to maintain the center of gravity is better, and their

ability to resist the body swing is stronger. At this time, the children's walking strategy may correspondingly increase the step size and the walking speed. Functional electrical stimulation device application can support muscles or nerves with impaired motor control ability to enhance control and execution during walking [9]. FES is applied in the gait cycle mainly by stimulating the common peroneal nerve and the corresponding calf muscles to correct the gait swing state deviation and improve the walking ability [10]. The meta-analysis results of this study showed that functional electrical stimulation treatment could increase the walking speed of children with cerebral palsy (SMD = 0.82, $P < 0.0001$) and increase the walking step length of children with cerebral palsy (SMD = 1.34, 95%CI = 1.07, 1.60, $Z = 9.91$, $P < 0.0001$). The results indicated that increased walking pace and step lengths could improve the walking ability in children with cerebral palsy.

However, we realize that it is necessary to strengthen the understanding of the etiology and symptoms of cerebral palsy. After all, there are still contradictions among current literature, which requires a sounder basic theory to provide a more convincing explanation for the clinic. Ideally, theoretically unquestionable research can provide the best clinical intervention. This study included the most complete updated evidence-based medical evidence, which might promote the selection of gait treatment measures. After all, functional electrical stimulation devices are small in size and easy to use compared with other devices. Their role in improving gait is also supported by current evidence-based medical evidence. However, the number of high-quality randomized controlled trials of functional electrical stimulation therapy and the number of patients participating in the trials are insufficient. The limited number of literature is also the inadequacy of this paper. Therefore, improving the gait parameters of patients with functional nerve stimulation therapy requires a larger number of patient samples and more in-depth research.

In conclusion, this study compared the effects of the functional nerve stimulation treatment group and control group on improving gait parameters of children with cerebral palsy. The results illustrated an increase in gait speed and step length of children with cerebral palsy after treating with functional nerve stimulation. Therefore, functional nerve stimulation can improve the walking of children with cerebral palsy. Meanwhile, this study needs more research data to determine the benefits. The results of this study may better guide the clinical practice and better use of health and financial resources.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

The two authors Qiantao Zhu and Guanchen Gao contributed equally to this work.

Acknowledgments

The project was supported by Hainan Province Clinical Medical Center.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 9287737, 9 pages
https://doi.org/10.1155/2022/9287737

Research Article

Exercise Intervention Improves Blood Glucose Levels and Adverse Pregnancy Outcomes in GDM Patients: A Meta-Analysis

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Received 6 August 2022; Revised 7 September 2022; Accepted 8 September 2022; Published 22 September 2022

Academic Editor: Xi Lou

Objective. The objective of this study is to systematically evaluate the effect of exercise on gestational diabetes (GDM). *Methods*. The databases of PubMed, Cochrane Library, Web of Science, Embase, CNKI, VIP, and Wanfang were searched to collect publications regarding physical exercises and GDM. The two researchers screened the literature, extracted the data, and analyzed the risk of bias of the included data using RevMan 5.3 software. The primary outcomes analyzed included the fasting blood glucose, 2-h postprandial blood glucose, glycosylated hemoglobin, premature delivery, cesarean section, neonatal macrosomia, premature rupture of membranes, and neonatal hypoglycemia. *Results*. A total of 9 studies with 1289 GDM patients were included. Compared with the control group, exercise could significantly reduce the 2-h postprandial blood glucose (MD = −0.62, *95% CI* (-0.91 to -0.34), $Z = 4.29$, $P < 0.0001$), improve HbA1c(RR = −0.47, *95% CI* (-0.81 to -0.13), $Z = 2.69$, $P = 0.007$), reduce the cesarean section rate (RR = 0.83, *95% CI* (0.71-0.98), $Z = 2.25$, $P = 0.02$), and decrease the incidence of neonatal macrosomia in GDM patients (RR = 0.57, *95% CI* (0.34-0.95), $Z = 2.17$, $P = 0.03$). *Conclusion*. Exercise intervention can improve the blood glucose level of GDM patients, such as 2-h postprandial blood glucose and HbA1c. Meanwhile, exercise can also reduce adverse pregnancy outcomes, such as premature birth and macrosomia. Therefore, prescribing exercise to GDM patients can effectively manage GDM and improve adverse pregnancy outcomes.

1. Introduction

Gestational diabetes (GDM), defined as any degree of glucose tolerance, is one of the most common conditions during pregnancy [1, 2] that increase the risk of adverse perinatal outcomes for both the mothers and infants, such as premature birth, macrosomia, and premature rupture of membranes. [3, 4]. The global prevalence of GDM is 2-32%, and about 18.4 million live births are affected by GDM in China [5]. Recently, the incidence of GDM in China has also been gradually increasing [3, 6]. Not only patients with GDM have an increased probability of developing type 2 diabetes in the future, their children are also more prone to develop metabolic diseases such as diabetes, obesity, and hypertension [7]. Therefore, blood glucose control for pregnant women is essential to protect the health and safety of mothers and fetuses. When pregnant women were diagnosed with GDM, they are frequently recommended to do more exercise and eat regularly [8]. Drug intervention may only be considered when the target blood glucose level can still not be reached after exercise intervention. Nonetheless, the use of medications is curtailed by concerns of adverse effects on the mother and fetus [9]. Therefore, effective interventions and safe guidance to control blood glucose level of pregnant women are desirable.

Physical exercise is considered to be an important part of GDM lifestyle intervention. Previous studies have shown that physical activities before or during pregnancy can reduce the risk of GDM [10]. Furthermore, a regular exercise during pregnancy can also reduce the blood glucose level of pregnant women [11]. A previous study reported that healthy pregnant women should perform a moderate-intensity exercise at least 4 times a week, at least 30 minutes each time [7]. Regrettably, only a limited proportion of

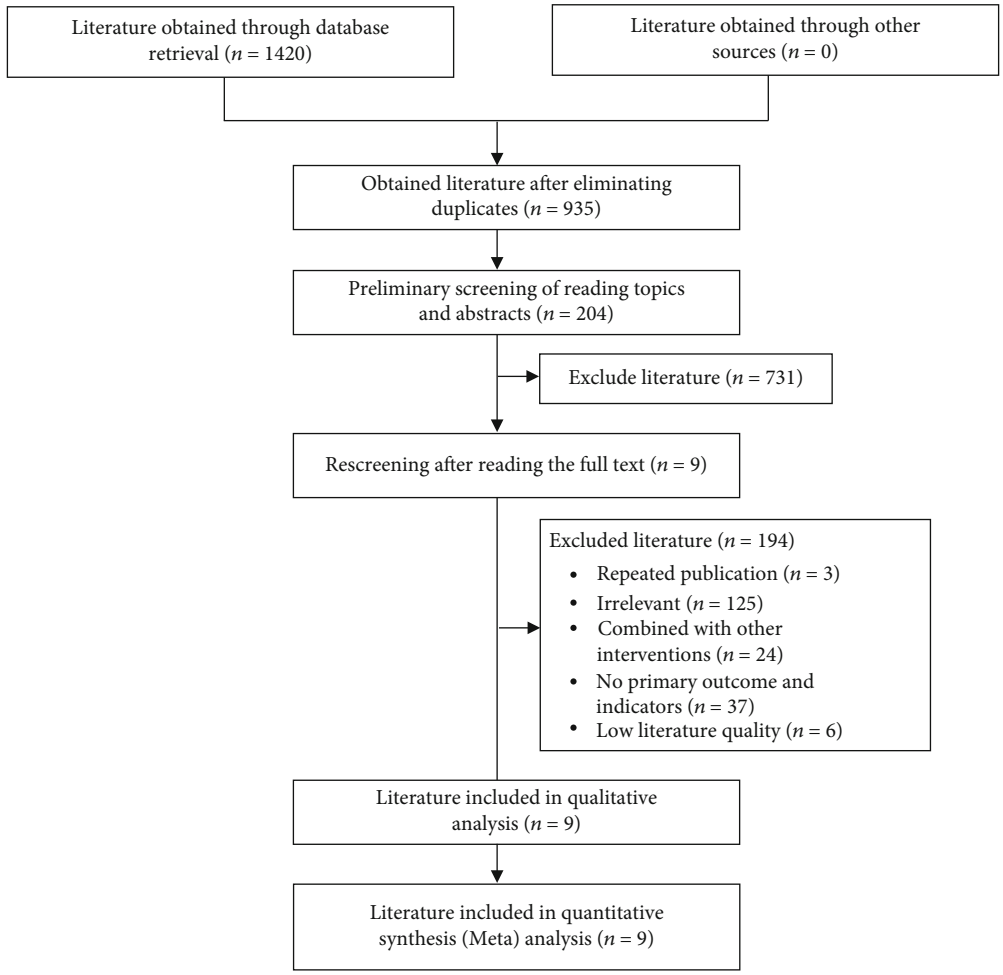

Figure 1: Flow chart of included literature screening.

pregnant women can achieve this exercise frequency or intensity. Thus, in this study, we systematically analyzed the effect of physical exercise on the blood glucose level of GDM patients and adverse pregnancy outcomes, thus providing reference for guiding the prescription of physical exercise for GDM patients.

2. Research Objects and Research Methods

2.1. Literature Search. We searched the Chinese and English electronic databases CNKI, VIP, Wanfang, PubMed, Cochrane Library, Web of Science, and EMBASE databases from inception to July 5, 2022, using a combination of search words that included (sports OR exercise OR activity OR training OR physical) AND (gestational diabetes mellitus OR GDM).

2.2. Inclusion and Exclusion Criteria. Inclusion criteria are as follows: (1) The research object was diagnosed with GDM; (2) a complete exercise intervention program that included exercise time, frequency, and intensity was performed; (3) outcome index ≥3; and (4) the type of study was randomized controlled trial (RCT). Exclusion criteria are as follows: (1) patients with conditions other than GDM; (2) incomplete outcome indicators or data that were unable to extract; (3) medications were added to the intervention, in addition to physical exercise; and (4) the full text of the literature cannot be obtained.

2.3. Quality Evaluation and Risk of Bias Assessment. A total of 9 RCT literature were included in this study, of which four had only one missing or unclear outcome index [3, 11–13], and five had two missing or unclear outcome indexes [2, 4, 8, 14, 15]. The risk-of-bias tool recommended by the Cochrane Handbook [16, 17] was used for evaluating of risk of bias in each included study. The components for risk of bias evaluation included (1) selection bias; (2) group hidden; (3) blinding method of both doctors and patients; (4) result evaluation blind method; (5) completeness of the report results; (6) reporting bias; and (7) other biases. In this paper, if the score meets the index, it is the low risk. But, if it does not, it is the high risk. And if the score is unclear, it is the unclear risk.

2.4. Statistical Analysis. The Review Manager (RevMan) 5.3 software was used for statistical analysis. For continuous variables, fasting blood glucose, 2-h postprandial blood glucose and glycosylated hemoglobin (HbA1C), and mean difference (MD) with 95% CI were pooled. For dichotomous variables

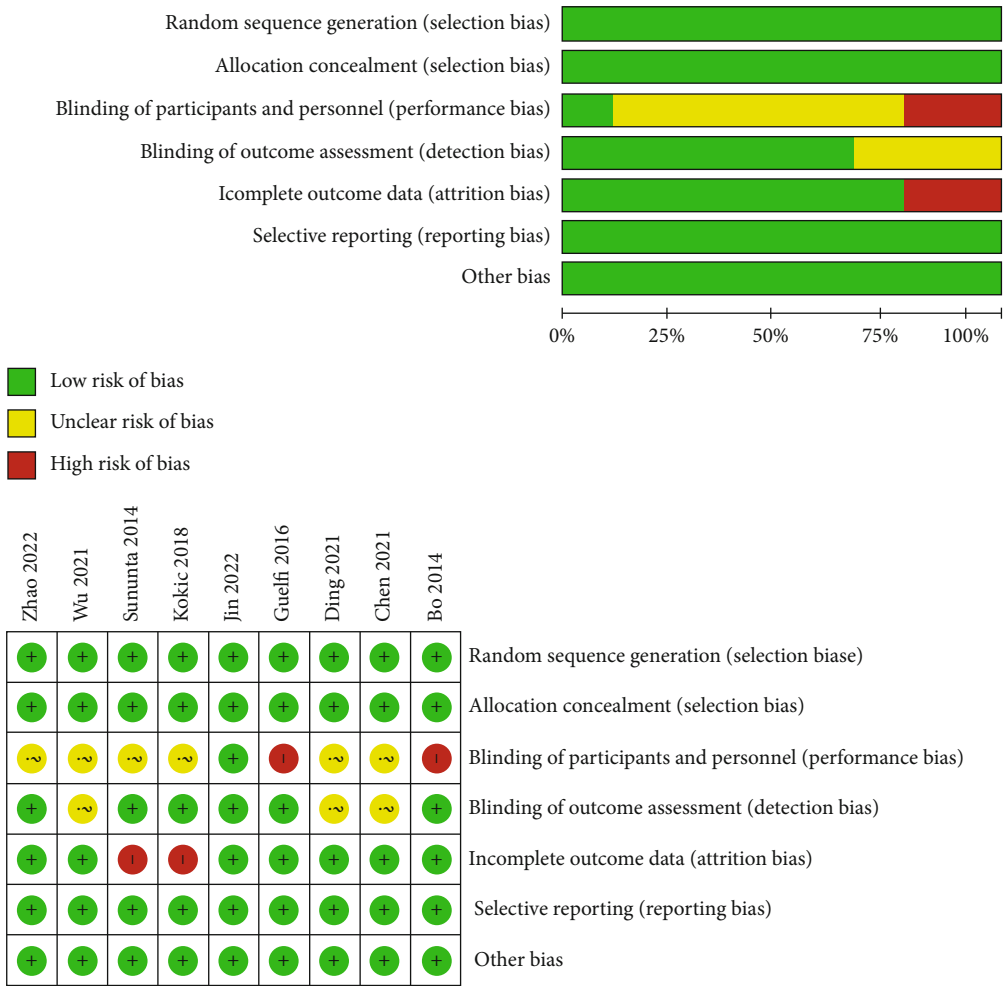

Figure 2: Risk-of-bias assessment of each included literature.

such as preterm birth rate, cesarean section rate, neonatal macromorbidity rate, premature rupture of membranes rate, and neonatal hypoglycemia rate, relative risk (RR) and 95% CI were used as effect indicators. The I^2 and P tests were carried out for assessing interstudy heterogeneity. In the presence of $P < 0.10$ and $I^2 \leq 50\%$, the fixed-effect model was used. Otherwise, the random-effect model was used. A two-sided $P < 0.05$ was regarded to denote statistical significance.

3. Results

3.1. Literature Screening Results. A total of 1420 studies were retrieved from the database, including 1168 English publications and 252 Chinese publications. After removing duplicate publications, 935 literature remained. By browsing the title and abstract of the literature, 925 studies were excluded. Finally, 9 English literature were included in this study for analysis (Figure 1), including 4 high-quality literature and 5 medium-quality literature. The risk-of-bias assessment of each included publication is shown in Figure 2.

3.2. Overall Characteristics of Included Literature. Data from a total of 1289 GDM patients from 9 studies were meta-analyzed. Four papers used mild-intensity exercises such as strolling, brisk walking, cycling, and stretching, and 5 papers used moderate-intensity exercises such as resistance, aerobic, gymnastics, and yoga. The exercise time ranged from 30 to 60 minutes. The main outcome indicators were fasting blood glucose, 2-h postprandial blood glucose, premature birth, cesarean section, and neonatal macrosomia. The secondary outcome indicators were HbA1c, premature rupture of membranes, and neonatal hypoglycemia. Detailed information for the 9 included studies are listed in Table 1.

3.3. Meta-Analysis Results

3.3.1. Effect of Exercise on Fasting Blood Glucose in Patients with GDM. A total of 9 studies [2, 3, 9–14] with 1289 subjects, including 647 in the interventional group and 642 in the control group, reported the effect of exercise on fasting blood glucose in GDM patients. The heterogeneity test was performed on the included subjects ($I^2 = 96\%$, $P < 0.00001$), and the random effect model analysis was used, MD = −0.22, *95% CI* (-0.47, 0.03). Brisk walking, walking, and stretching/cycling were divided into mild exercise groups [$MD = -0.35$, 95% CI (-0.96, 0.26), $Z = 1.13$, $P = 0.26$], and the rest were moderate exercise groups [$MD = -0.11$, 95% CI is (-0.23, 0.01), $Z = 1.75$, $P = 0.08$] according to the type of exercise.

Table 1: General information of the literature included in this study.

Included literature	Country	Study type	Sample size		Exercise interventions			Exercise time (min)	Outcome indicators
			Experimental group	Control group	Movement mode	Frequency	Intensity		
Bo [13]	Italy	RCT	101	99	Brisk walking	Daily	Mild	20	①②④⑤⑥⑦
Chen [8]	China	RCT	79	60	Strolling	Daily	Mild	30	①②③④⑤
Ding [14]	China	RCT	210	218	Strolling	Daily	Mild	60	①②④⑤⑥⑧
Guelfi [11]	Australia	RCT	85	84	Stretch/ride	2-3 times a week	Mild	60	①②③④⑤
Jin [12]	China	RCT	65	66	Gymnastics	3 times a week	Moderate	50	①②④⑤⑥⑦⑧
Kokic [4]	Australia	RCT	18	20	Aerobic/resistance exercise	3 times a week	Moderate	50-55	①②⑤⑥
Sununta [15]	Thailand	RCT	85	85	Yoga	3 times a week	Moderate	45	①②③
Wu [2]	China	RCT	75	75	Aerobic/resistance exercise	5 times a week	Moderate	30	①②④⑤⑥
Zhao [3]	China	RCT	43	46	Resistance exercise	3 times a week	Moderate	50-60	①②④⑤⑥⑦⑧

Note: ① Fasting blood glucose; ② blood glucose 2 hours after a meal; ③ glycosylated hemoglobin (HbA1c); ④ premature birth; ⑤ cesarean section; ⑥ neonatal macrosomia; ⑦ premature rupture of membranes; ⑧ neonatal hypoglycemia.

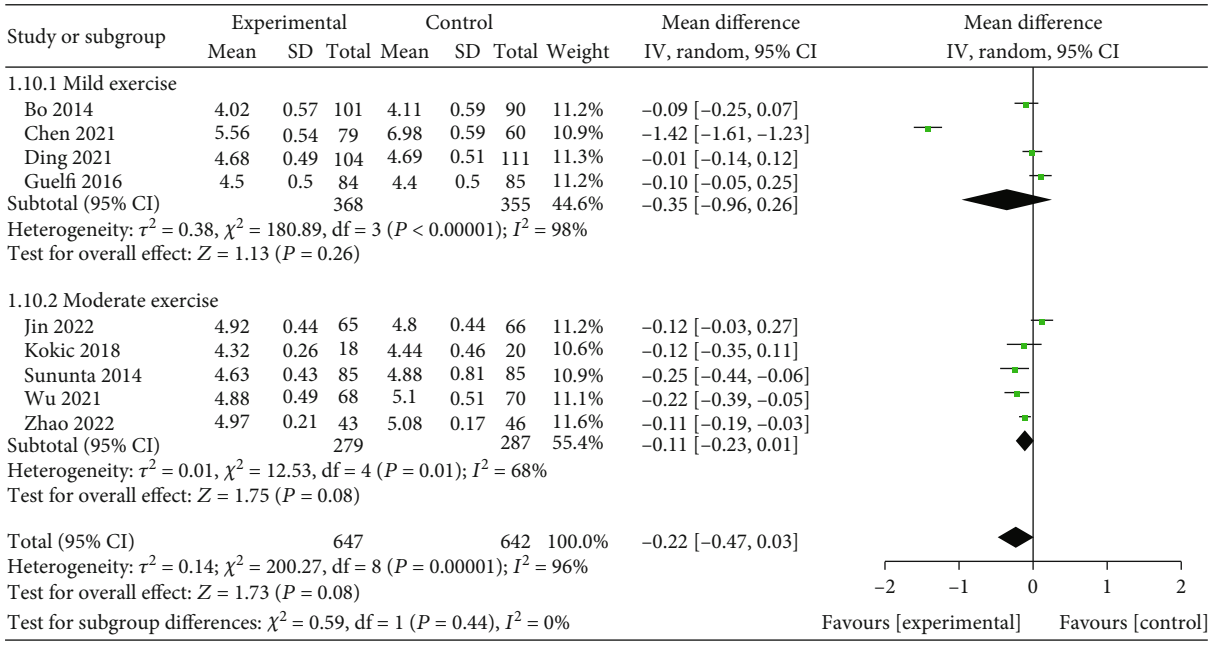

Figure 3: Forest diagram of the effect of exercise on fasting blood glucose in patients with GDM.

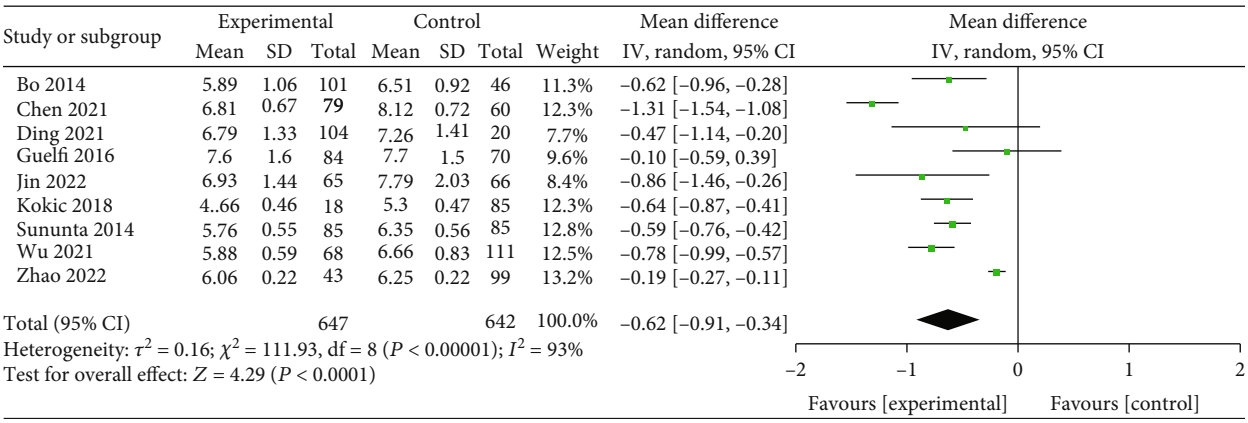

Figure 4: Forest diagram of the effect of exercise on 2-h postprandial blood glucose in patients with GDM.

Combined analysis of the two groups, MD was -0.22, 95% CI was (-0.47, 0.03), combined effect size test $Z = 1.73$, $P = 0.08$, indicating that different exercises in the two groups had no effect on fasting blood glucose in patients with GDM (Figure 3). Analysis between the two groups showed no significant difference ($P = 0.44$).

3.3.2. Effect of Exercise on 2-h Postprandial Blood Glucose in Patients with GDM. Significant heterogeneity between studies was observed ($I^2 = 93\%$, $P < 0.001$). Random-effect model showed that exercise could significantly reduce 2-h postprandial blood glucose in GDM patients (MD = −0.62, *95% CI* (-0.91 to -0.34), $Z = 4.29$, $P < 0.001$, Figure 4).

3.3.3. Effect of Exercise on HbA1c. In total, 4 studies [3, 9, 11, 14] that included 330 controls and 350 from the interventional group assessed the effect of exercise on HbA1c in patients with GDM. As shown in Figure 5, the meta-analysis performed with the random-effect model ($I^2 = 97\%$, $P < 0.001$) found that exercise could significantly reduce HbA1c in GDM patients (MD = −0.47, *95% CI* (-0.81 to -0.13), $Z = 2.69$, $P = 0.007$).

3.3.4. Effect of Exercise on the Premature Birth Rate. There was no heterogeneity, for which the fixed-effect model analysis was used. Meta-analysis using data pooled from 7 studies [2, 3, 9–13] that included 1081 patients indicated that exercise did not affect preterm birth rate in GDM patients [pooled effect size $RR = 0.78$, 95% CI (0.46, 1.32), $Z = 0.93$, and $P = 0.35$, Figure 6].

3.3.5. Effect of Exercise on Cesarean Section Rate. The effect of exercise on the cesarean section rate was reported in 8 studies [2, 3, 9–13] that included 562 cases in the interventional group and 557 in the control group. The cesarean section rates were 29.71% in the interventional group and 36.98% in the control group. The pooled analysis (Figure 7) using the fixed-effect model ($I^2 = 0\%$, $P = 0.55$) suggested that

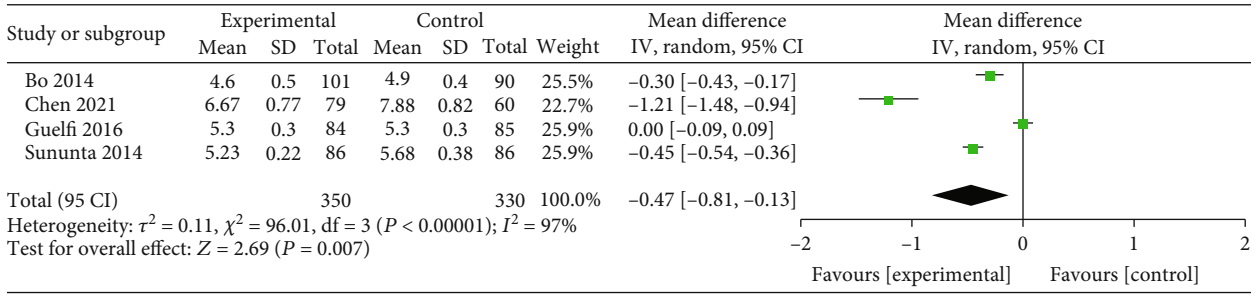

Figure 5: Forest diagram of the effect of exercise on glycosylated hemoglobin (HbA1c) in patients with GDM.

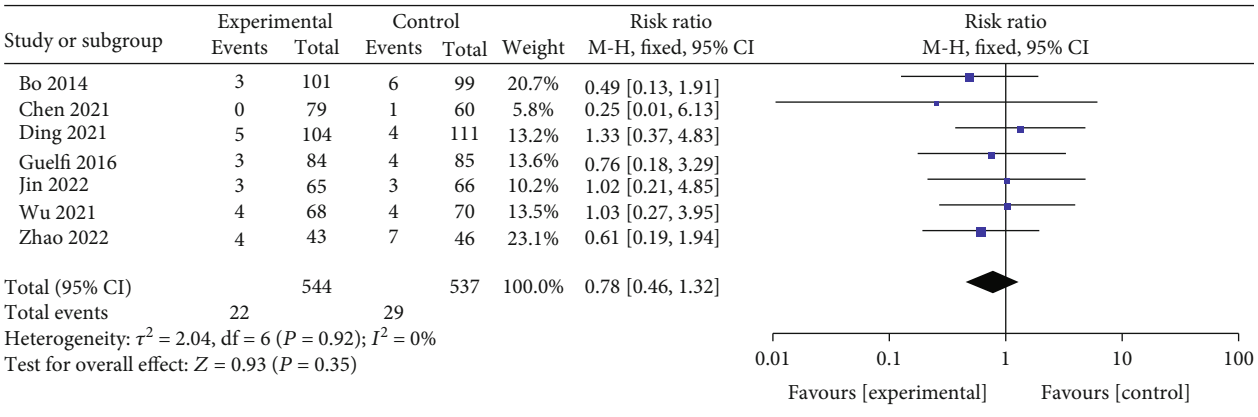

Figure 6: Forest diagram of the effect of exercise on the premature birth rate of GDM patients.

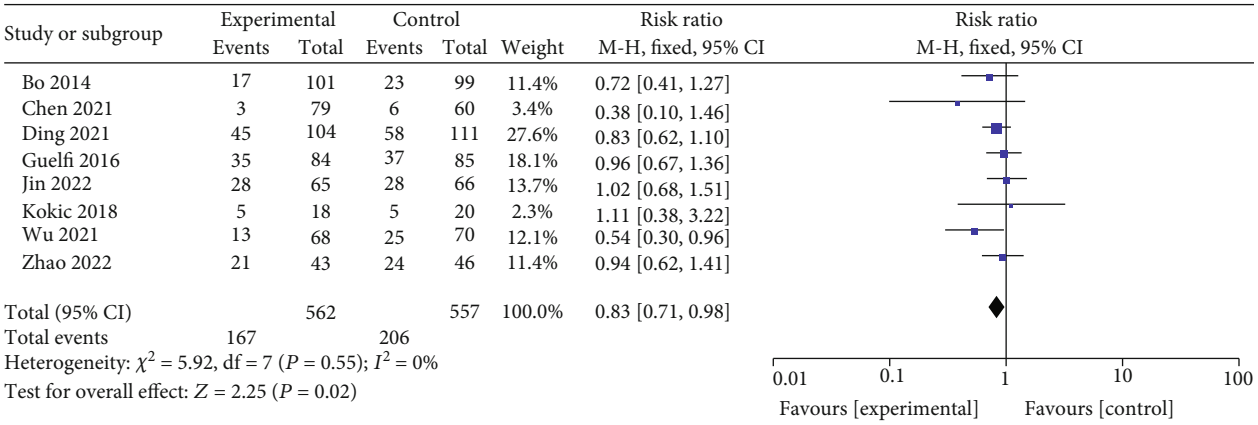

Figure 7: Effect of exercise on cesarean section rate of GDM patients.

exercise could significantly reduce the rate of cesarean section rate (RR = 0.83, 95% CI 0.71-0.98, $Z = 2.25$, $P = 0.02$).

3.3.6. Effect of Exercise on the Incidence of Neonatal Macrosomia. Neonatal macrosomia born to GDM patients were assessed in 5 studies [2, 10–13] that included 381 patients in the interventional group and 392 in the control group. Macrosomia was noted in 21 cases (5.51%) in the interventional group and 38 in the control group (9.69%). As outlined in Figure 8, the combined effect calculated using the fixed-effect model ($I^2 = 0\%$, $P = 0.48$) shows an RR of 0.57 (*95% CI* 0.34-0.95, $Z = 2.17$, $P = 0.03$), indicating that exercise could significantly reduce the risk of giving birth to newborns with macrosomia in GDM patients.

3.3.7. Effect of Exercise on the Incidence of Premature Rupture of Membranes. The RR pooled from 4 publications that included 227 patients in the interventional group and 281 patients in the control group was 0.84 (*95% CI* 0.53-1.34, $Z = 0.72$, $P = 0.47$) from the fixed-effect model ($I^2 = 0\%$,

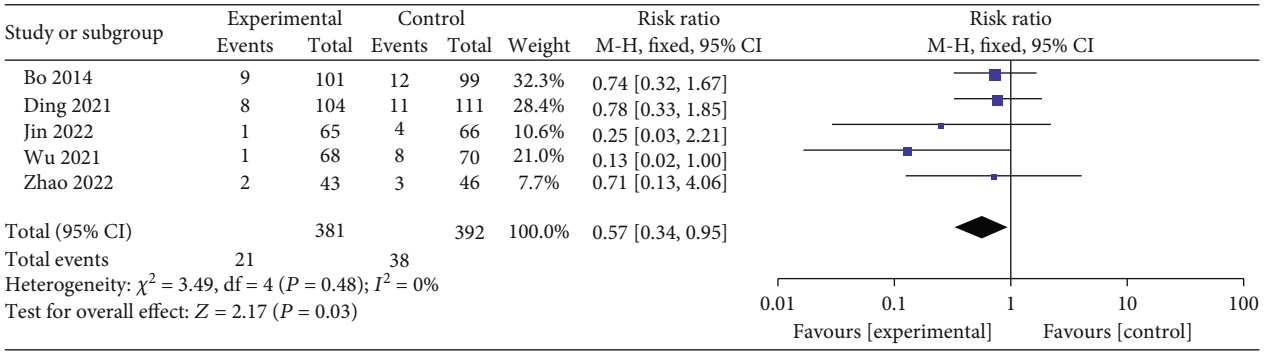

Figure 8: Effect of exercise on the incidence of neonatal macrosomia in patients with GDM.

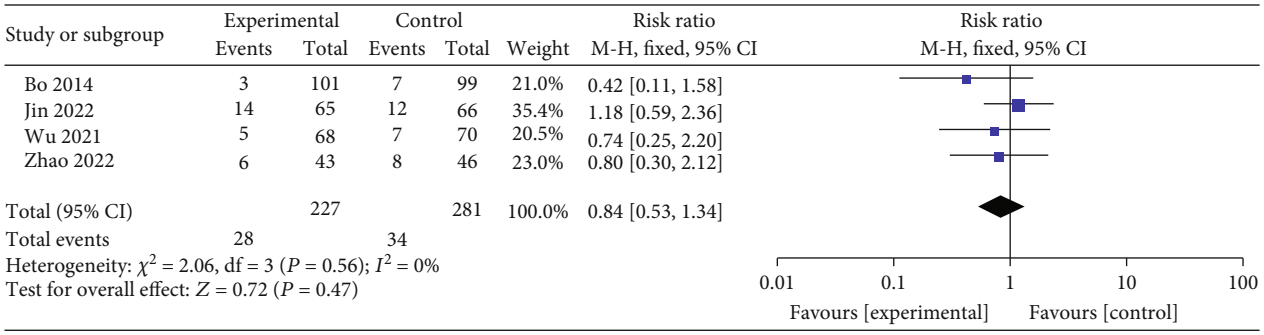

Figure 9: Forest diagram of the effect of exercise on the incidence of premature rupture of membranes in GDM patients.

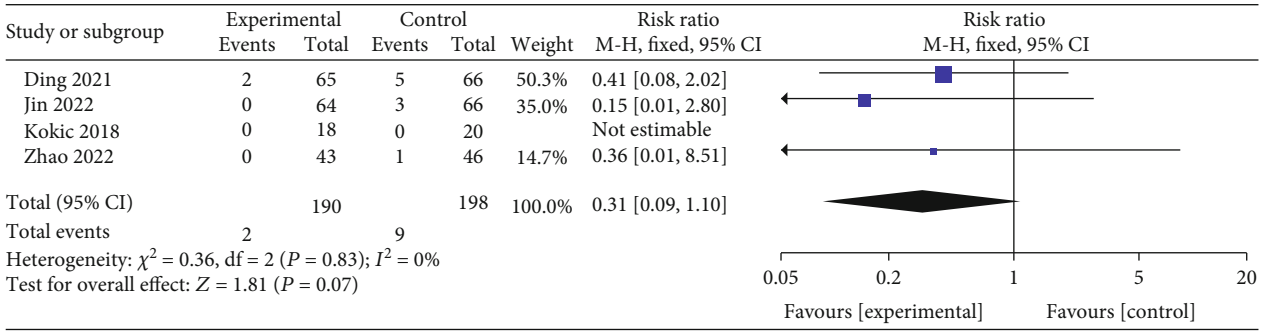

Figure 10: Forest diagram of the effect of exercise on the incidence of neonatal hypoglycemia in GDM patients.

$P = 0.56$) and suggested that exercise did not significantly reduce the incidence of premature rupture of membranes (Figure 9).

3.3.8. Effect of Exercise on the Incidence of Neonatal Hypoglycemia. Data combined from a total of 388patients, including 190 in the interventional group and 198 in the control group with the fixed-effect model ($I^2 = 0\%$, $P = 0.83$), showed that exercise did not significantly reduce the risk of neonatal hypoglycemia (RR = 0.31, *95% CI* 0.09, 1.10, $Z = 1.81$, $P = 0.07$, Figure 10).

4. Discussion

In this study, we pooled data from 9 RCTs, including 4 high-quality and 5 medium-quality studies. The risk-of-bias assessment indicated that 4 publications were of low risk, and the other 5 were at medium risk for bias. A total of 1289 pregnant women diagnosed with GDM were included. The results showed that exercise during pregnancy had a positive effect GDM by significantly improving blood glucose control, such as fasting blood glucose, 2-h postprandial blood glucose, and HbA1c. This finding was consistent with the results of other studies [7, 18, 19]. In this meta-analysis, the forest maps showed that the pooled MD for fasting blood glucose, 2-h postprandial blood glucose, and HbA1c were -0.22, -0.62, and -0.47, respectively, indicating that mild to moderate physical exercise could effectively manage blood glucose level in GDM. This result was consistent with the recommendations of some guidelines [7, 20], and exercise could improve blood glucose control in the state of insulin resistance [21]. Therefore, exercise for about 150 minutes a week could reduce the blood glucose level of people with impaired glucose tolerance. Some previous studies have

shown that this exercise can also reduce the risk of future type 2 diabetes mellitus in GDM patients [13], among which resistance exercise was better, and aerobic exercise had the best effect [22, 23].

Premature birth and macrosomia neonatorum are common adverse pregnancy outcomes [3, 10, 24]. Previous studies reported that these adverse outcomes were closely related to overweight and GDM [12, 22, 25]. Hence, it is particularly important to take certain interventions during pregnancy to prevent the incidence of premature and macrosomia [26, 27]. The meta-analysis results in this study showed that exercise intervention could reduce the incidence of premature infants and macrosomia. The cesarean section rate in the exercise intervention group was 29.71%, which was significantly lower than that in the control group. The incidence of macrosomia in the exercise intervention group was 5.51%, which was also lower than that in the control group. However, the incidence of other adverse outcome indicators, such as premature delivery, premature rupture of membranes, and neonatal hypoglycemia, did not differ significantly between the exercise group and control group.

This study showed that exercise intervention could improve the blood glucose level of GDM patients (fasting blood glucose, 2-h postprandial blood glucose, and HbA1c) and reduce adverse pregnancy outcomes (premature birth and macrosomia), which was consistent with some research results. Therefore, exercise has an excellent therapeutic effect on the treatment of GDM and could reduce the incidence of adverse pregnancy outcome for GDM patients. However, this study also had some shortcomings. For example, we only searched the commonly used databases, which might have omitted other potential publications. In addition, only 9 literature that met the inclusion/exclusion criteria were included. Some indicators of these articles were not clearly defined. And these literature come from different countries and regions, and the original exercise habits may be different. At last, not all exercise methods with the same intensity and frequency were used in exercise activities, which might introduce potential sources for inter-study heterogeneity. The differences in the age of the patients enrolled in this paper and the differences in exercise activities that do not all use the same way, intensity, and frequency of exercise methods will lead to certain limitations in this paper.

5. Conclusion

(1) Exercise intervention improves the blood glucose level of GDM patients, such as 2-h postprandial blood glucose and HbA1c

(2) Exercise intervention reduces adverse pregnancy outcomes, such as premature birth and macrosomia

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Xiaoyan Li and Rong Luo contributed equally to this work.

Acknowledgments

The study was supported by the First Affiliated Hospital of Hainan Medical University.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 1122994, 8 pages
https://doi.org/10.1155/2022/1122994

Research Article

Meta-Analysis of Dyslipidemia and Blood Lipid Parameters on the Risk of Primary Open-Angle Glaucoma

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Received 20 June 2022; Revised 7 September 2022; Accepted 9 September 2022; Published 21 September 2022

Academic Editor: Xi Lou

Objective. We aimed to explore the effect of blood lipid parameters on the risk of primary open-angle glaucoma (POAG) by meta-analysis. *Methods.* The databases of PubMed, Scopus, CNKI, and Wanfang were systematically searched from inception to April 2022, and the relevant research literature was obtained, screened, and analyzed. *Results*. A total of 15 studies were included in this meta-analysis, including 11 reporting dyslipidemia and risk of POAG and 5 reporting specific lipid level and risk of POAG. Dyslipidemia increased the risk of POAG with an odd ratio (OR) of 1.25 (95% CI: 1.23, 1.26). Total triglyceride and total cholesterol were not related to the prevalence of POAG, but high-density lipoprotein cholesterol was significantly negatively correlated with the risk of POAG with an OR of 0.96 (95% CI: 0.94, 0.99). *Conclusion.* Dyslipidemia is a risk factor for POAG. Given the small sample size and significant interstudy heterogeneity, additional studies are needed to establish this conclusion.

1. Introduction

Glaucoma is a group of ocular conditions characterized by progressive optic nerve damage with corresponding visual field defect. Pathologically, glaucoma is characterized by the loss of retinal ganglion cells, the thinning of the retinal nerve fiber layer and the morphological change of the optic disc. Primary open-angle glaucoma (POAG) is a type of glaucoma with an open, normal-appearing anterior chamber angle and raised intraocular pressure, in the absence of other underlying diseases [1]. According to prior reports, the number of patients with glaucoma worldwide is 76 million with an incidence of 3.54% in people aged 40-80, which is expected to be increased to 112 million by 2040. The exact pathogenesis of POAG remains unclear. The risk factors identified include elevated intraocular pressure [2], advanced age [3], race [4], and a family history of glaucoma [5]. The study by Jonas et al. that first evaluated the relationship between blood lipid levels and POAG found no significant correlations [6]. A recent metastudy showed that the total triglyceride level in POAG was significantly higher than that of the control group [7]. This finding is echoed by a recent meta-analysis [8]. Nonetheless, the associations between specific blood lipid parameters and the risk of POAG remain scarcely investigated. The purpose of this study is to explore the relationship between dyslipidemia, specific blood lipid parameters, and the prevalence or risk of POAG through a meta-analysis.

2. Materials and Methods

2.1. Literature Search. The databases PubMed, Scopus, CNKI, and Wanfang were searched from inception to May 6, 2022. The search language was limited to Chinese and English. The search terms were as follows: "glaucoma, open angle" or "open angle glaucomas" and "cholesterol," "glyceride," "high-density cholesterol lipoprotein," "low-density cholesterol lipoprotein," and "blood lipid," "lipid metabolism," or "hypercholesterolemia, dyslipidemia," and "odds ratio".

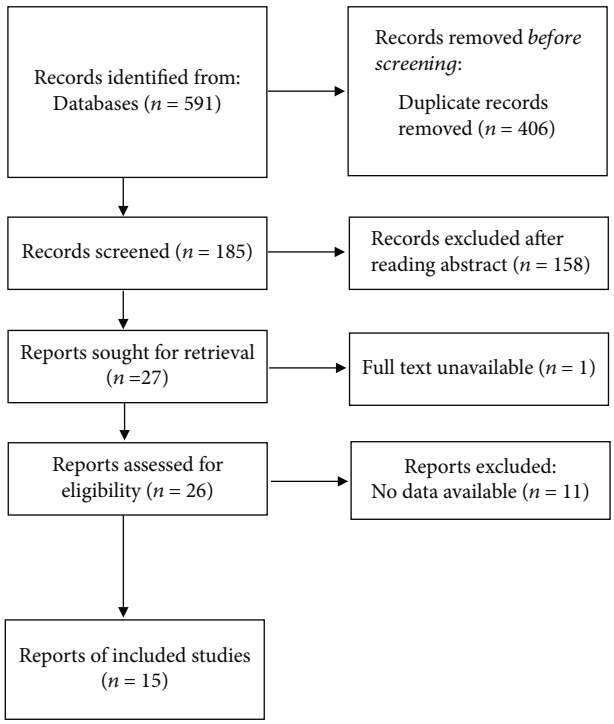


Figure 1: Literature screening flowchart.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria: (i) The study purpose was to explore the effect of blood lipid level (or abnormal lipid metabolism) on the risk of POAG; (ii) Study design was cross-sectional, case-control, or cohort study; (iii) Publication language limited to Chinese or English; (iv) Study population is not limited by age, race, and gender.

Literature exclusion criteria: (i) The literature content is inconsistent or weakly relevant; (ii) Animal experiments, in vitro tests, letters, reviews, case reports, abstracts, or incomplete reports; (iii) No data available in terms of study exposure (no blood lipid level) or relevant outcomes; (iv) No original text.

2.3. Data Sorting. Yan completed the content extraction from eligible publications, while Huang and Wang checked independently. The contents extracted included study author name, year of publication, study type, inclusion criteria of patients, number of patients, main observation indicators, and other information.

2.4. Literature Quality Evaluation. The quality of the included publications was evaluated by the scale reported by Viswanathan et al. [9, 10]. The quality assessment method included 15 items involving the design, criteria for observational studies, and data analysis evaluation. It evaluated the methods of research objects selection, results and exposure measurement, and the methods of controlling confounders, potential conflicts of interest and the risk of deviation related to different designs. A score of 0 or 1 would be assigned to each item assessed, and the total score would be 15 points.

2.5. Statistical Analysis. All data in this study were analyzed by Stata v16.0 software. Two-sided $P < 0.05$ denoted statistically significance. The binary enumeration data was expressed as odds ratio (OR) with 95% confidence interval (95% CI). If the OR was not provided, it was calculated according to the number of events in the diseased and non-diseased population. The specific calculation equation is OR = (number of exposed persons in the diseased group/number of nonexposed persons in the diseased group)/(number of exposed persons in the nondiseased group/number of nonexposed persons in the nondiseased group). The heterogeneity test between different studies was described by the I^2 statistic with the following equation $I^2 = (Q - df)/Q$, in which Q represents the $\chi 2$ statistic and df denotes its degrees of freedom). I^2 corrected by degrees of freedom ≥50% or <50% was deemed to indicate high or low inter-study heterogeneity, respectively. All studies were pooled using the fixed-effect models. The association between hyperlipidemia and glaucoma was evaluated according to the study design, and subgroup analysis was performed. Publication bias was assessed using Begg's funnel plot, along with Begg's test. The Begg's test is a rank correlation funnel plot asymmetry test method, and when $P > 0.05$, it can be considered that the funnel plot has no obvious asymmetry. When the data is less than 10 points, the funnel plot and asymmetric test methods cannot judge whether there is publication bias due to the low-test power. In this study, we do not report funnel plots with fewer than 10 points, but still report the results of Begg's test.

3. Results

3.1. Literature Search. The screening process of this study is shown in Figure 1. A total of 591 articles were retrieved, including 585 relevant Chinese and English documents and 6 ambiguous documents. After removing 406 duplicate documents, 158 documents were screened and excluded by reading the title and abstract. The full-texts of the remaining 27 documents were read, and 11 publications were excluded for absence of original text ($n = 1$) and data unavailability ($n = 10$). Of the 15 included literature, 11 reported abnormal lipid metabolism and risk of POAG, and 5 reported the relationship between blood lipid level and POAG.

3.2. Basic Information Included in the Study. The 11 literature that reported the prevalence or risk of dyslipidemia in POAG are shown in Table 1. A total of 2879714 patients, including 155928 POAG, were involved in 4 cross-sectional studies, 4 case-control studies, and 3 cohort studies. Eight studies were conducted in Asian populations (3 in Taiwan and 5 in South Korea), and 3 in European and American populations (all conducted in the United States). The five literature that reported the risk of blood lipid level are shown in Table 2. A total of 23296 patients, including 1315 POAG, were studied in 2 cross-sectional studies and 3 case-control studies in Asian populations (3 in China and 2 in South Korea). The quality of the literature was evaluated, and the results are shown in Table 3.

Table 1: The basic information of reported studies on the risk of dyslipidemia.

Author	Year	Research type	Data sources	OAG diagnostic criteria	Diagnostic criteria of dyslipidemia	Inclusion period	Age
Jung et al. [11]	2020	Cohort	KNHIS-NSC 2002-2013	Complied with ICD-10 H40.1 and received the prescription of anti-glaucoma drugs during the study period	Hypercholesterolemia: Conformed to ICD-10 E78; received cholesterol drug prescription or TC ≥ 240 mg/dL	2002-2008	≥65 years old, accounting for 16.2%
Rim et al. [12]	2018	Case-control	KNHIS-NSC 2002-2013	Complied with KCD H401 and received the prescription of antiglaucoma drugs during the study period	Hyperlipidemia: accorded to KCD classification	2004-2007	Middle aged and elderly people
Lee et al. [13]	2017	Cross-sectional	KNHANES 2008-2012	Complied with MISGEO-K	Hyperlipidemia: received cholesterol drug prescription or TC ≥ 240 mg/dL	2008-2012	>40 years old
Chen et al. [14]	2016	Case-control	NHI	Complied with ICD-9-CM 365.11	Hyperlipidemia: ICD-9-CM 272	2001-2011	>40 years old, with an average of 57 years old
Kim et al. [15]	2016	Cross-sectional	KNHANES 2010-2012	Complied with ISGEO	Hyperlipidemia: TG ≥ 150 mg/dL or cholesterol drug treatment	2008-2012	>40 years old, with an average of 56 years old
Chung et al. [16]	2014	Cross-sectional	the Longitudinal Health Insurance Database 2000 (LHID2000) of NHI	Complied with ICD-9-CM 365.1 or 365.11	Not mentioned	2002 -2012	≥18 years old
Newman-Casey et al. [17]	2011	Cohort	US i3 InVision data Mart database	ICD-9-CM 365.1, 365.10, 365.11, 365.12 and 365.15	Hyperlipidemia: ICD-9-CM	2001-2007	>40 years old
Lin et al. [18]	2010	Case-control	NHI	ICD-9-CM 365.1-365.11	Elixhauser comorbidity index [19]	2005	>40 years old
Motsko and Jones [20]	2008	Case-control	US Ingenix LabRx database	ICD-9-CM 365.1	Lipid metabolism disorder: ICD-9-CM 272	2001-2004	With an average of 73.6 years old
Girkin et al. [21]	2004	Cohort	The Birmingham (Alabama) Department of Veterans Affairs Medical Center (BVAMC)	ICD-9-CM 365.1	Lipid metabolism disorder: ICD-9-CM 272	1997-2002	>50 years old
Kim et al. [5]	2016	Cross-sectional	KNHANES 2008-2011	MISGEOCK I or II standard	Disorder of lipid metabolism: TC > 200 mg/dL or LDLC > 130 mg/dL or HDLC < 60 mg/dL or TG > 150 mg/dL	2008-2011	>40 years old, with an average age of 59.7 years old

Note: The Korean National Health Insurance System-National Sample Cohort (KNHIS-NSC), Korean National Health and Nutrition Examination Survey (KNHANES)⊠ the International Classification of Diseases, 10th Revision (ICD-10), Korean Classification of Diseases (KCD), the Modified International Society of Geographical and Epidemiological Ophthalmology Criteria for the Korean Population (MISGEO-K), the Modified International Society of Geographical and Epidemiological Ophthalmology Criteria (MISGEO), the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), Taiwan National Health Insurance plan (NHI), and the International Society of Geographical and Epidemiological Ophthalmology Criteria (ISGEOC).

3.3. Abnormal Lipid Metabolism and Risk of POAG. Meta-analysis of 11 literature indicated that the OR for POAG with abnormal lipid metabolism was 1.25 (95% CI: 1.23, 1.26). Significant interstudy heterogeneity ($I^2 = 99.8\%$, $P < 0.001$) was noted and presented in Figure 2. Subgroup analysis found that both cross-sectional and case-control studies

Table 2: The basic situation of reported studies on blood lipid level and disease risk.

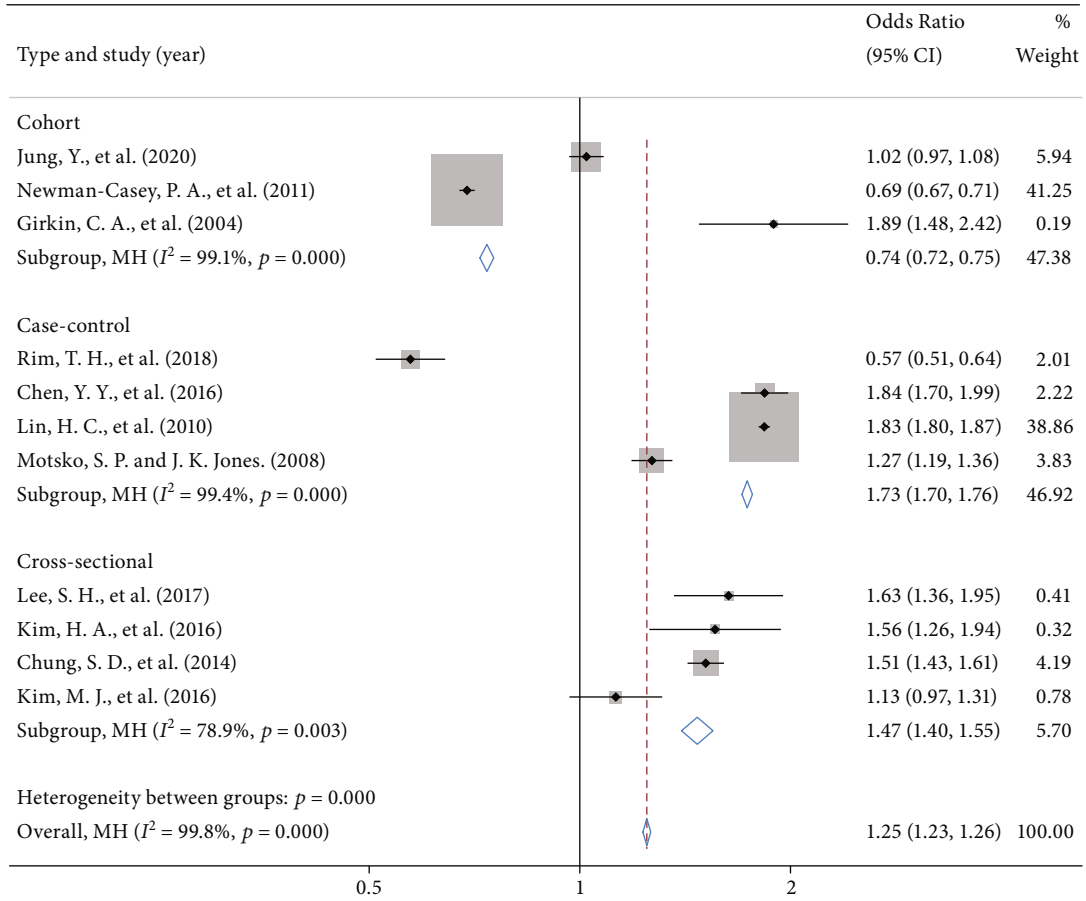
Authors	Year	Research type	Data sources	OAG diagnostic criteria	Report blood lipid parameters	Blood lipid unit	Inclusion period	Age
Lei et al.[22]	2020	Case-control	Collected by Department of Ophthalmology and Visual Sciences; eye, ear, nose, and throat, Hospital of Fudan University	Complied with ISGEOC standards	TG, TC	Per mmol/L	2017	Average age of 60 years old
Shon and Sung [23]	2019	Cross-sectional	KNHANES 2018-2020	Complied with ISGEOC standards	TG, TC, HDLC	Per SD	2008-2012	Average age of 63 years old
Wu [24]	2019	Case-control	Shantou University -Chinese University of Hong Kong joint Shantou international eye center	POAG includes HTG and NTG, which need to meet the inclusion criteria, respectively	TG, TC, HDLC, LDLC	Per mmol/L	——	>40 years old
Tang et al.[25]	2017	Case-control	Eye, ear, nose, and throat, Hospital of Fudan University	Not mentioned	TC, HDLC	Per mmol/L	2015-2016	Average age of 40 years old
Kim, et al.[26]	2014	Cross-sectional	KNHANES 2009–2010	Complied with ISGEOC standards	TG, TC, HDLC, LDLC	Per mg/dL	2009–2010	19-39 years old

Note: Korean National Health and Nutrition Examination Survey (KNHANES), the Modified International Society of Geographical and Epidemiological Ophthalmology Criteria (ISGEO), the Modified International Society of Geographical and Epidemiological Ophthalmology Criteria for the Korean Population (MISGEO-K), total cholesterol (TC), total triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C).

Table 3: Evaluation scores of included studies using the Viswanathan M design scale.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	总分
Jung et al. [11]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Rim et al. [12]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Lee et al. [13]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Chen et al. [14]	1	1	1	1	1	1	0	0	1	0	1	0	1	1	1	11
Kim et al. [15]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Chung et al. [16]	1	1	0	0	0	1	0	0	0	0	1	0	1	0	1	6
Newman-Casey et al. [17]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Lin et al. [18]	1	1	0	0	0	1	0	0	0	0	1	0	1	0	1	6
Motsko and Jones. [20]	1	1	0	0	0	1	0	0	1	0	1	0	1	0	1	7
Girkin et al. [21]	1	1	1	0	1	1	0	0	1	0	1	0	1	0	1	9
Kim et al. [5]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Lei et al. [22]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Shon and Sung [23]	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	10
Wu et al. [24]	1	1	0	1	1	1	0	0	1	0	1	0	1	0	1	9
Tang et al. [25]	1	1	0	1	1	1	0	0	1	0	1	0	1	0	1	9

Note: Quality criteria and evaluation of design and data analysis for observational studies criteria (1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Was the study population representative of the general population? (4) Was the participation rate of eligible persons at least 50%? (5) Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (6) Were sample size justification, power description, or variance and effect estimates provided? (7) For the analyses in this paper, were the exposures of interest measured prior to the outcomes being measured? (8) Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (9) Were the exposure measures (independent variables) clearly defined, objective, valid, reliable, and implemented consistently across all study participants? (10) Were the exposures assessed more than once over time? (11) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (12) Were the outcome assessors blinded to the exposure status of participants? (13) Was the statistical analysis appropriate? (14) Was loss to follow-up after baseline 20% or less? (15) Were the key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposures and outcomes? (1: yes; 0: no or not applicable).



NOTE: Weights and between-subgroup heterogeneity test are from Mantel-Haenszel model

Figure 2: Forest chart reporting the study on the relationship between dyslipidemia and the risk of POAG.

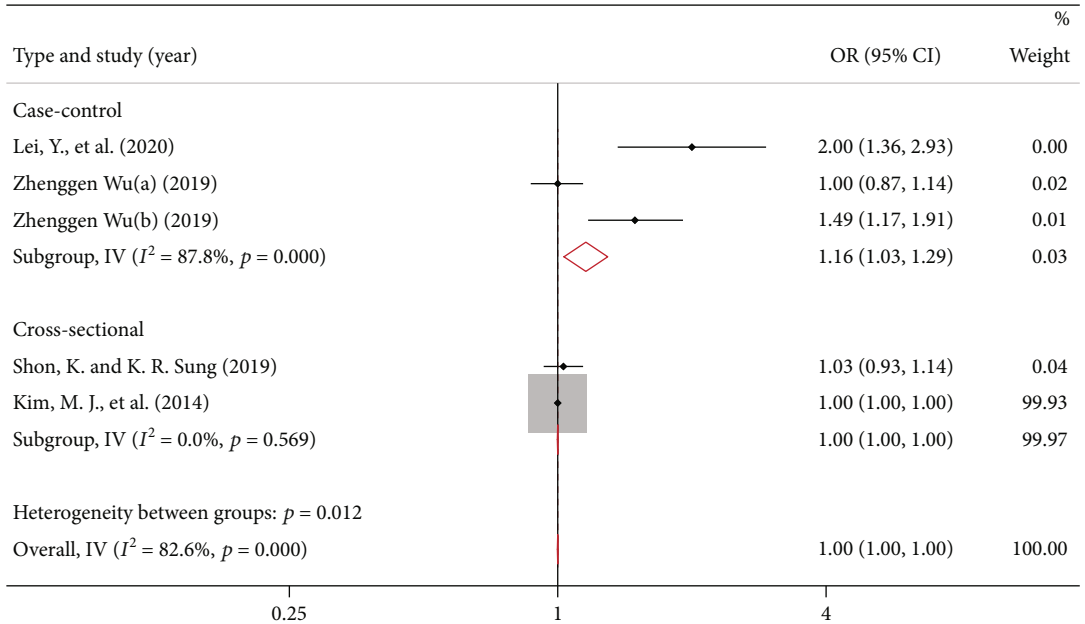


Figure 3: Forest map reporting the odds ratio for POAG risk by TG level.

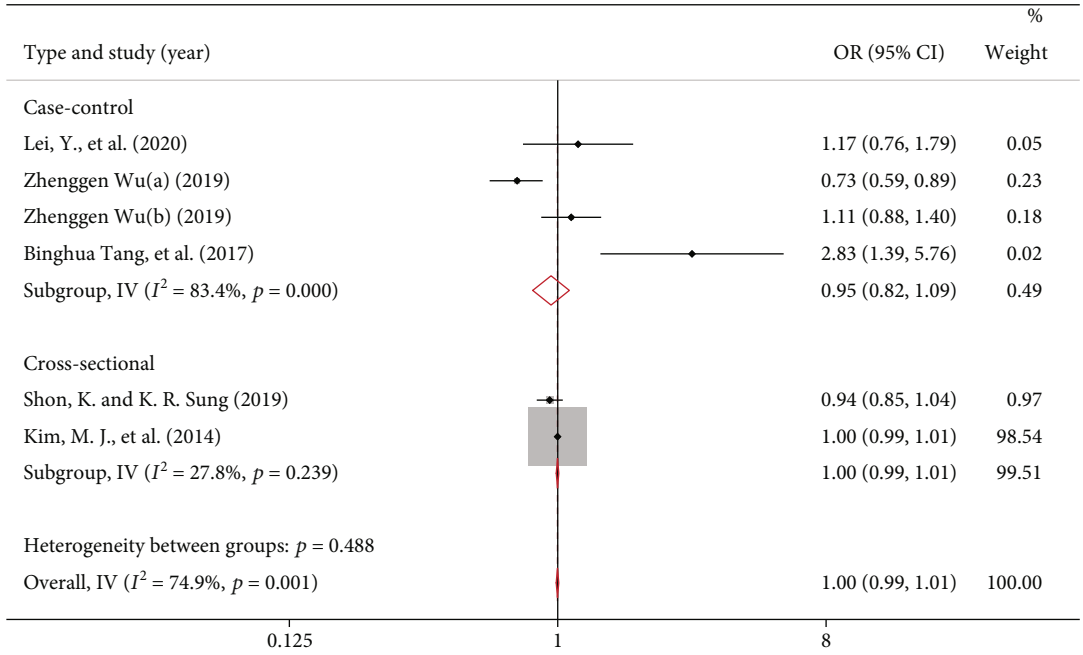


Figure 4: Forest map reporting the study on the association between total cholesterol and POAG risk.

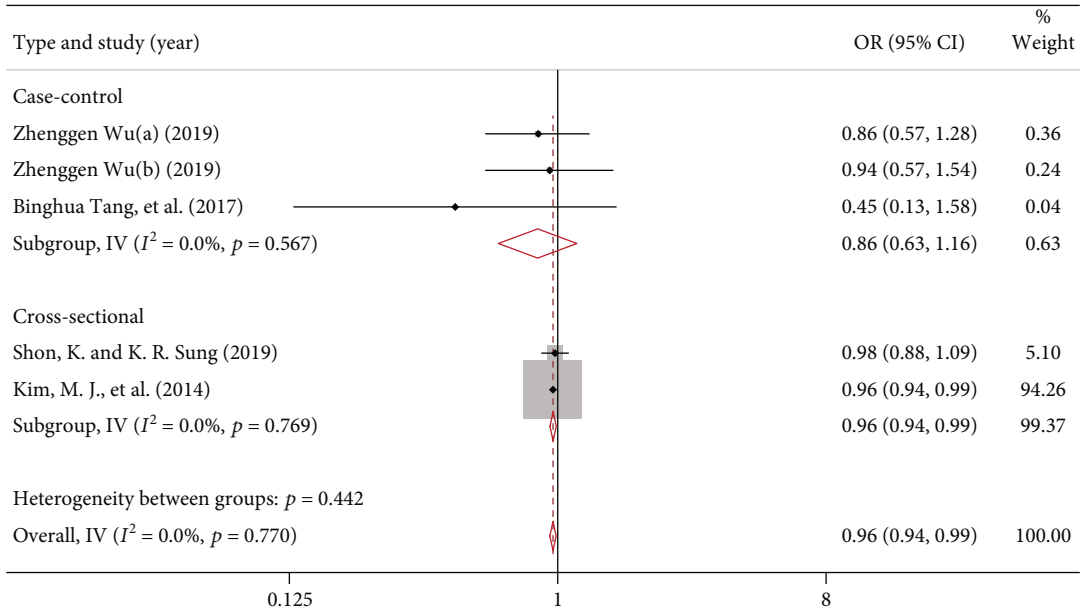


Figure 5: Forest map reporting the study on the association between HDLC and POAG risk.

showed a positive correlation between dyslipidemia and risk of POAG with an OR of 1.47 (95% CI: 1.40, 1.55) for cross-sectional studies and 1.73 (95% CI: 1.70, 1.76) for case-control studies. Nonetheless, cohort studies showed a negative correlation between dyslipidemia and the risk of POAG with an OR of 0.74 (95% CI: 0.72, 0.75). The funnel plot (Figure S1, supplementary data) showed that the points were distributed on both sides, showing an inverted funnel shape, and $P = 0.755$ by Begg's test. Still, some studies were not within the confidence interval due to significant heterogeneity.

3.4. Blood Lipid Level and Risk of POAG. Meta-analysis conducted on the 5 literature reporting associations between blood lipid levels and risk of POAG showed the OR for POAG by triglyceride (TG) was 1.00 (95% CI: 1.00, 1.00). There was great heterogeneity among the studies ($I^2 = 82.6\%$, $P < 0.001$), as shown in Figure 3. Subgroup analysis showed significant positive correlation between TG and risk of POAG (OR = 1.73, 95% CI: 1.70, 1.76) in case-control studies but not in cross-sectional studies. No publication bias was found by Begg's test ($P = 0.086$).

For specific lipid levels, the meta-analysis showed that the OR for POAG risk by total cholesterol (TC) or high-density lipoprotein cholesterol (HDLC) were 1.00 (95% CI: 0.99, 1.01) and 0.96 (95% CI: 0.94, 0.99), respectively. Figure 4 ($I^2 = 74.9\%$, $P = 0.001$) and Figure 5 ($I^2 = 0\%$, $P = 0.770$) demonstrated significant interstudy heterogeneity for both analyses. Subgroup analysis showed that TC was not associated with POAG risk in case-control studies and cross-sectional studies. In addition, HDLC was negatively correlated with the risk of POAG with an OR of 0.96 (95% CI: 0.94, 0.99), but not in the cross-sectional study (OR = 0.86, 95% CI: 0.63, 1.16). No publication bias was found, $P = 0.707$ and $P = 0.221$ by Begg's test, respectively.

4. Discussion

Abundant prior studies have reported the relationship between abnormal lipid level and risk of POAG with no consistent conclusions. Abnormal lipid metabolism usually refers to the increase of TC or TG, which may be accompanied by the decrease of HDLC [27]. Lipid metabolism is an important risk factor for cardiovascular disease [270]. Previous studies have suggested that abnormal lipid metabolism may increase POAG risk by reducing blood flow velocity and changing lipid components in the aqueous humour [24, 25]. Apolipoprotein B and apolipoprotein E in the aqueous humour of POAG patients were significantly increased, which may then change cholesterol transport. On the other hand, genetic factors may also modulate the the association between lipid metabolism and risk of POAG. It has been shown that several genes involved in lipid metabolism were significantly related to POAG risk, such as ATP binding cassette subfamily A member 1gene and caveolin 1 gene [28, 29].

The aim of this study is to assess the correlation between lipid abnormalities or specific blood lipid levels and the risk of POAG. The results showed that dyslipidemia increased the risk of POAG in cross-sectional and case-control studies, but not in cohort studies. This disparity might be related to the effect of confounding factors. For instance, patients with diagnosed hyperlipidemia were more likely to receive treatment. In a large cohort study by Newman-Casey et al., significant negative correlation between hyperlipidemia and POAG (hazard ratio 0.95, 95% CI 0.91, 0.98) was noted even after correcting for a series of covariates. In previous studies, statins have been shown to reduce the adverse effect of hyperlipidemia on POAG by decreasing intraocular pressure while reducing cholesterol [30]. It is currently unclear whether hyperlipidemia and the use of lipid-lowering medications are independent risk factors for POAG, which should be further clarified in future studies.

For a specific blood lipid parameter, this study did not find that TC and TG were related to an increased risk of POAG. A recent cross-sectional study in Singapore found that high levels of HDL-3 cholesterol were associated with a reduced risk of POAG (OR, 0.91; 95% CI, 0.84-0.99, $P = 0.021$), but no association was found between conventional lipids (e.g., TC, HDLC, and low-density lipoprotein cholesterol) and POAG [31]. Although we noted a negative correlation between HDLC and POAG, it is limited by small sample size and needs further confirmation.

This study suffers from several limitations. First, significant interstudy heterogeneity was noted, which might be related to the diversity of study designs and subject population. However, further subgroup analysis or meta-regression to clarify the source of heterogeneity was difficult due to quantitative limitations. Second, part of the results of this study included less than 10 studies. The funnel plot and asymmetry test methods cannot judge whether the funnel is symmetrical or not due to the low-test performance. More original research is needed in the future to clarify our preliminary conclusions. Third, most of the studies included were cross-sectional or case-control in design, and the number of cohort studies was small, so the causal relationship between dyslipidemia and POAG risk could not be inferred. Fourth, this study failed to clarify the impact of other identified risk factors for POAG. In addition, the OR values reported in some studies were not corrected by covariates, especially intraocular pressure. Finally, this study analyzed the correlations between specific lipid and risk of POAG, providing evidence to clarify the impact of individual lipid on the risk of POAG. However, given the small number of studies included, additional studies are needed in the future to firmly establish this conclusion.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Guimei Huang and Jiayi Wang contributed equally to this work.

Acknowledgments

The study was supported by Qionghai People's Hospital.

Supplementary Materials

This section provides additional information about the funnel chart for reporting the relationship between dyslipidemia and the risk of POAG (Supplementary Figure S1). *(Supplementary Materials)*

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 5728967, 7 pages
https://doi.org/10.1155/2022/5728967

Research Article

Effect of Hypertonic Saline Solution Combined with Furosemide on Acute Heart Failure: A Meta-Analysis

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Received 10 August 2022; Revised 1 September 2022; Accepted 7 September 2022; Published 21 September 2022

Academic Editor: Xi Lou

Background. The efficacy of hypertonic saline solution (HSS) combined with furosemide in treating acute heart failure is controversial. This meta-analysis explores the efficacy of HSS combined with furosemide for the treatment of acute heart failure. *Methods*. Literature were searched from databases, including PubMed, Web of Knowledge, Embase, Central, CMKI, Wanfang, and VIP. The inclusion criteria were as follows: (1) subjects: patients with acute heart failure; (2) the experimental group and the control group were properly set up; (3) intervention measures: patients in the experimental group were treated with HSS + furosemide, and patients in the control group were treated with furosemide; (4) the outcomes included at least one of the following indicators: readmission rate, mortality, 24 h urine volume, weight loss, and serum creatinine; and (5) randomized controlled trial (RCT). The method recommended by Cochrane Collaboration Network was used to evaluate the risk bias. The heterogeneity among the studies was evaluated through the chi-square test, and the publication bias was assessed by the Egger test. The results were described using risk ratio (RR), mean difference (MD), and 95% confidence interval (CI). *Results*. The readmission rate in the HSS + furosemide group was lower than that in the furosemide group (RR = 0.53, 95% CI [0.46, 0.60], $P < 0.00001$), with no heterogeneity among the literature ($P = 0.21$, $I^2 = 29\%$). Patients in the HSS + furosemide group had a lower mortality rate than that in the furosemide group (RR = 0.55, 95% CI [0.46, 0.65], $P < 0.00001$). The chi-square test result indicated no heterogeneity among the literature ($P = 0.25$, $I^2 = 23\%$). Furthermore, the 24 h urine volume of patients in the HSS + furosemide group was higher than that in the furosemide group (MD = 497.29, 95% CI [457.61, 536.96], $P < 0.00001$). There was no heterogeneity among the literature ($P = 0.58$, $I^2 = 0\%$). In contrast, patients in the HSS + furosemide group demonstrated a lower serum creatinine level than those in the furosemide group (MD = −0.45, 95% CI [-0.51, -0.39], $P < 0.00001$). However, heterogeneity was observed among the literature ($P < 0.00001$, $I^2 = 81\%$). The weight loss in the HSS + furosemide group was higher than that in the furosemide group (MD = 1.83, 95% CI [1.51, 2.15], $P < 0.00001$). There was no heterogeneity among the literature ($P = 0.42$, $I^2 = 2\%$). Egger test showed no publication bias among the literature ($P > 0.05$). *Conclusion*. Despite the heterogeneity and bias in our study, the combination of HSS with furosemide is promising in patients with acute heart failure. However, further research is still needed to confirm.

1. Introduction

The incidence rate and mortality of acute heart failure have steadily increased due to aging populations [1, 2]. The general purpose of treatment is to improve the symptoms of acute heart failure, stabilize hemodynamics, maintain important organ functions, avoid the recurrence of acute heart failure, and improve the long-term prognosis [3–5]. Therefore, a customized individual treatment plan should be formulated according to the inducement, severity, and classification of basic cardiovascular disease and acute heart failure [6–8].

The main measures for treating acute heart failure include cardiotonic, diuretic, and vasodilation [9, 10]. The use of diuretics can reduce edema symptoms and preload. However, about 1/3 of patients may have diuretic resistance

during treatment [9, 10]. Hence, the diuretic effect of diuretics is weakened or disappeared before reaching the treatment goal of reducing edema [11–14]. Diuretic resistance is independently associated with total mortality, sudden death, and death from pump failure [15, 16]. It is necessary to increase diuretics or use multiple diuretics in combination to cope with diuretic resistance. Excessive use of diuretics may accelerate the deterioration of renal function [15–18].

Some studies [15, 18, 19] have demonstrated that furosemide combined with hypertonic saline solution (HSS) could protect patients' renal function, thus increasing diuretic effect and benefiting patients. However, the efficacy of HSS combined with furosemide in treating acute heart failure is controversial. Some studies [20] pointed out that the curative effects of combined use of HSS and simple use of furosemide on patients were similar since researchers observed no significant difference in serum creatinine level, body weight, and urine output between the two treatment regimens. Therefore, this study aims to conduct a meta-analysis to explore the efficacy of HSS combined with furosemide in treating acute heart failure.

2. Methods

2.1. Literature Search. The literature search was conducted in the following databases, including PubMed, Web of Knowledge, Embase, Central, CMKI, Wanfang, and VIP. The starting and ending time of the literature search was from the establishment of the database to June 16, 2022. There was no restriction on the language of documents.

2.2. Literature Screening. The inclusion criteria were as follows: (1) subjects: patients with acute heart failure; (2) the experimental group and the control group were set up; (3) intervention measures: patients in the experimental group were treated with HSS + furosemide, and patients in the control group were treated with furosemide; and (4) the outcomes included at least one of the following indicators: readmission rate, mortality, 24 h urine volume, weight loss, and serum creatinine, the readmission rate was the primary endpoint, and the remaining indicators were secondary endpoints; and (5) randomized controlled trial (RCT).

The exclusion criteria were as follows: (1) animal experiment, (2) repeated publications, (3) case reports or expert comments, (4) unable to get a full text, and (5) key data are missing and could not be supplemented by the contact author.

2.3. Literature Evaluation and Data Extraction. Two researchers independently reviewed and evaluated the title. They abstracted each RCT according to the identified retrieval strategy to select the literature that met the inclusion criteria. The bias risk assessment of the selected RCTs adopted the method recommended by the Cochrane Collaborative Network, namely, ① whether the random allocation method was appropriate, ② whether the blind method was adopted, ③ whether the allocation was concealled, ④ whether the baseline was comparable, and ⑤ whether to describe withdrawal and loss of follow-up. Based on the above criteria, the included studies were divided into three levels: ① low bias: all quality evaluation criteria were fully met, ② unclear: any one or more quality evaluation criteria were only partially satisfied, and ③ high bias: any one or more of the quality evaluations were completely unsatisfactory. The extracted data mainly included the first author, year of publication, number of cases, country, intervention measures, baseline characteristics, and outcome indicators. After completing the above work, two researchers cross-checked and resolved their differences through discussion.

2.4. Statistical Analysis. RevMan5.2 software was used to consolidate and analyze the data. The chi-square test was used to determine whether there was heterogeneity among the studies. The judgment criteria were as follows: if $P \geq 0.1$ and $I^2 \leq 50\%$, it was considered that there was no heterogeneity between the literature, and the fixed effect model was used for analysis. The larger the sample size, the larger the variance of the effect size, and the larger the corresponding weight distribution. If $P < 0.1$ and $I^2 > 50\%$, it was considered that there was heterogeneity between literature, and the random effect model was selected. Subgroup analysis was used to analyze the sources of heterogeneity. The publication bias was evaluated by the Egger test. Count data and measurement data were expressed in risk ratio (RR) and mean difference (MD), respectively. There is a 95% confidence interval (CI) of the calculated results. Two-way $P < 0.05$ indicates statistically significant.

3. Results

A total of 834 literature were obtained through database retrieval, 824 literature were excluded, and 10 studies were finally included. The flow chart of literature screening is shown in Figure 1. 10 articles included 2781 patients with acute heart failure. Among them, 1388 patients were in the HSS + furosemide group, and 1393 patients were in the furosemide group. The basic characteristics of the literature and the bias risk assessment are shown in Table 1.

3.1. Impact of HSS on Readmission Rate. 7 articles compared the readmission rates of patients in the HSS + furosemide group and the furosemide group. The heterogeneity test results ($P = 0.21$, $I^2 = 29\%$) indicated no heterogeneity among the literature, and the fixed effect model was used. The readmission rate in the HSS + furosemide group was lower than that in the furosemide group (RR = 0.53, 95% CI [0.46, 0.60], $P < 0.00001$), as shown in Figure 2.

3.2. Impact of HSS on Mortality. 7 articles compared the mortality of patients in the HSS + furosemide group and the furosemide group. The heterogeneity test results ($P = 0.25$, $I^2 = 23\%$) indicated no heterogeneity among the literature, and the fixed effect model was used. The mortality of the HSS + furosemide group was lower than that of the furosemide group (RR = 0.55, 95% CI [0.46, 0.65], $P < 0.00001$), as shown in Figure 3.

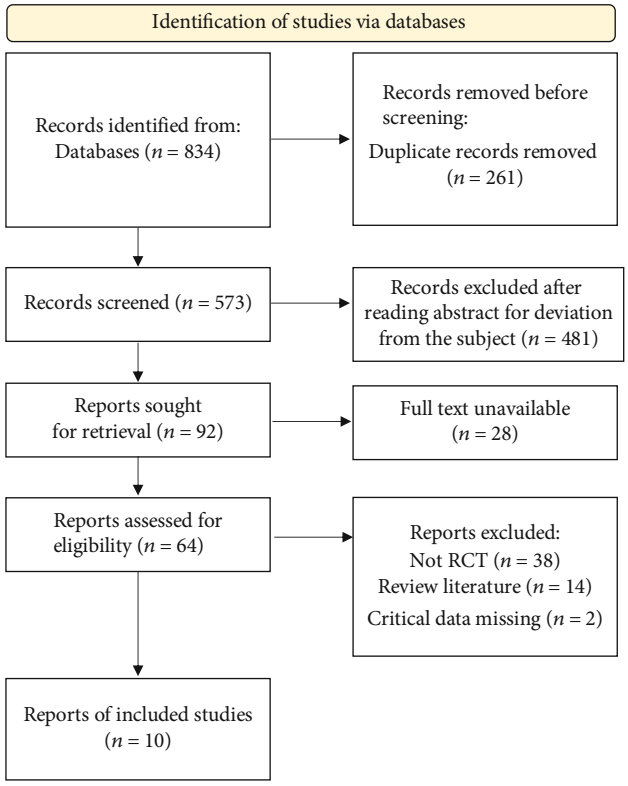

Figure 1: Document screening flow chart. RCT: randomized controlled trial.

3.3. Effect of HSS on 24 h Urine Volume. The 24 h urine volume of patients in the HSS + furosemide group and the furosemide group was compared in 10 literature. The heterogeneity test results ($P = 0.58$, $I^2 = 0\%$) indicated no heterogeneity among the literature, and the fixed effect model was used. The 24 h urine volume in the HSS + furosemide group was higher than that in the furosemide group (MD = 497.29, 95% CI [457.61, 536.96], $P < 0.00001$), as shown in Figure 4.

3.4. Effect of HSS on Serum Creatinine. The serum creatinine levels of the HSS + furosemide group and the furosemide group were compared in 10 literature. The heterogeneity test results ($P < 0.00001$, $I^2 = 81\%$) indicated heterogeneity among the literature, and the random effect model was used. Serum creatinine in the HSS + furosemide group was lower than that in the furosemide group (MD = −0.45, 95% CI [-0.51, -0.39], $P < 0.00001$), as shown in Figure 5.

3.5. Effect of HSS on Weight Loss. The weight loss of the HSS + furosemide group and the furosemide group was compared in 10 literature. The heterogeneity test results ($P = 0.42$, $I^2 = 2\%$) indicated no heterogeneity among the literature, and the fixed effect model was used. The weight loss in the HSS + furosemide group was higher than that in the furosemide group (MD = 1.83, 95% CI [1.51, 2.15], $P < 0.00001$), as shown in Figure 6.

3.6. Publication Bias Assessment. Egger test showed no publication bias in readmission rate, mortality, 24 h urine volume, serum creatinine, and weight loss ($P > 0.05$).

4. Discussion

Our meta-analysis showed that HSS combined with furosemide could increase 24 h urine volume and reduce body weight and serum creatinine level in patients with acute heart failure. Patients treated with HSS combined with furosemide had a lower readmission rate and mortality than patients treated with furosemide alone.

Wan et al. [28] showed that HSS combined with furosemide could reduce the micturition volume and shorten the hospitalization time of patients with moderate and severe heart failure. Patients were followed up for 36 months and found that the readmission rate and mortality in the HSS + furosemide group were lower than those in the furosemide group. In addition, the treatment cost of the HSS + furosemide group was lower than that of the furosemide group. Licata et al. [19] showed that both HSS + furosemide and furosemide could more robustly increase the urine output of patients as well as the effect of HSSs combined with furosemide. Furthermore, HSS combined with furosemide could increase the serum sodium level, but furosemide had the opposite effect. While furosemide could increase the serum creatinine level, this phenomenon was not observed in the HSS + furosemide group. Both treatments increased serum uric acid levels. Their study [19] followed the patients for 31 months. They found that the readmission rate of patients treated with furosemide alone was higher, and the condition at readmission was worse than that at first admission. The mortality of patients treated with HSS + furosemide was lower than that of patients treated with furosemide. The literature published by Paterna et al. [27] in 2000 confirmed the feasibility of the clinical application of HSS + furosemide. In that study, HSS + furosemide could benefit patients in hemodynamics. The hospitalization time of the HSS + furosemide group was shorter than that of the furosemide group. The weight loss of the HSS + furosemide group was more significant. In addition, HSS could protect the renal function of patients with heart failure and reduce the grade of heart failure. This effect could be sustained for a long time. In the literature published in 2005, Paterna et al. [25] pointed out that the daily urine output and sodium output of patients in the HSS combined treatment group increased compared to patients treated with furosemide alone. Both treatment regimens reduced the level of BNP in patients. However, the BNP level decreased faster and more significantly in the HSS + furosemide group. Therefore, HSS combined therapy has shown advantages in shortening hospitalization time and reducing the readmission rate. Paterna et al. [26] also pointed out in the literature published in 2011 that the use of HSS could benefit patients with refractory heart failure for a long time. Compared with furosemide, HSS + furosemide could reduce the hospitalization time of patients. Paterna et al. [26] followed up the patients for 57 months. During the follow-up, they found that the readmission rate and mortality of patients in the HSS

Table 1: Basic characteristics of literature and risk assessment of bias.

Author	Year	No. of patients HSS+ furosemide	No. of patients Furosemide	Outcomes	Risk of basis
Issa et al. [21]	2013	20	12	Urine output, length of stay, readmission rate, hospitalization cost, mortality, readmission time	Uncertain
Licata et al. [19]	2003	53	54	Urine output, serum creatinine, readmission rate, mortality, body weight	Uncertain
Okuhara et al. [22]	2014	22	22	Urine output, brain natriuretic peptide, natriuretic capacity, length of hospital stay, readmission rate, mortality	Low
Parrinello et al. [23]	2012	66	67	Length of hospital stay, readmission, and mortality	Uncertain
Parrinello et al. [24]	2011	122	126	Urine volume, serum creatinine, readmission rate, length of hospital stay, natriuretic capacity, body weight, mortality	Uncertain
Paterna et al. [25]	2005	30	30	Brain natriuretic peptide, body weight, urine volume, serum creatinine	Uncertain
Paterna et al. [26]	2011	48	46	Serum creatinine, body weight, length of stay, readmission rate	Uncertain
Paterna et al. [27]	2000	881	890	Urine volume, serum creatinine, body weight, readmission rate, mortality	Uncertain
Wan et al. [28]	2017	132	132	Urine volume, serum creatinine, body weight, brain natriuretic peptide	Uncertain
Yayla et al. [20]	2015	14	14	Urine volume, serum creatinine, body weight	Low

Note: HSS: hypertonic saline solution.

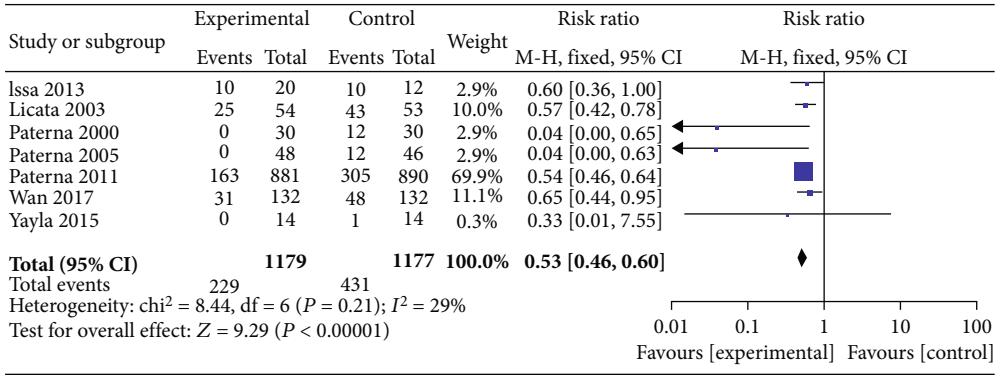

Figure 2: Comparison of readmission rate between the HSS + furosemide group and the furosemide group. HSS: hypertonic saline solution.

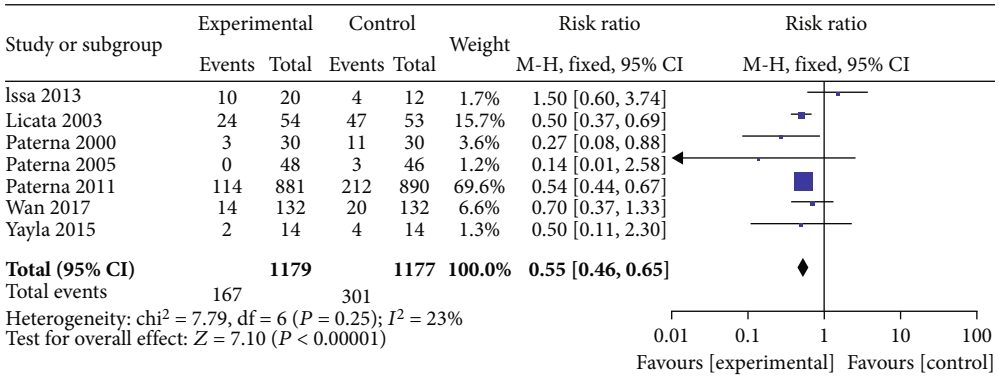

Figure 3: Comparison of mortality between the HSS + furosemide group and the furosemide group. HSS: hypertonic saline solution.

+ furosemide group were lower than those in the furosemide group. Serum creatinine and urea nitrogen in the furosemide group were significantly higher than in the HSS + furosemide group. Parrinello et al. [23] pointed out that HSS could reduce clinical symptoms, improve renal function, and shorten the hospital stay of patients. HSS decreased serum

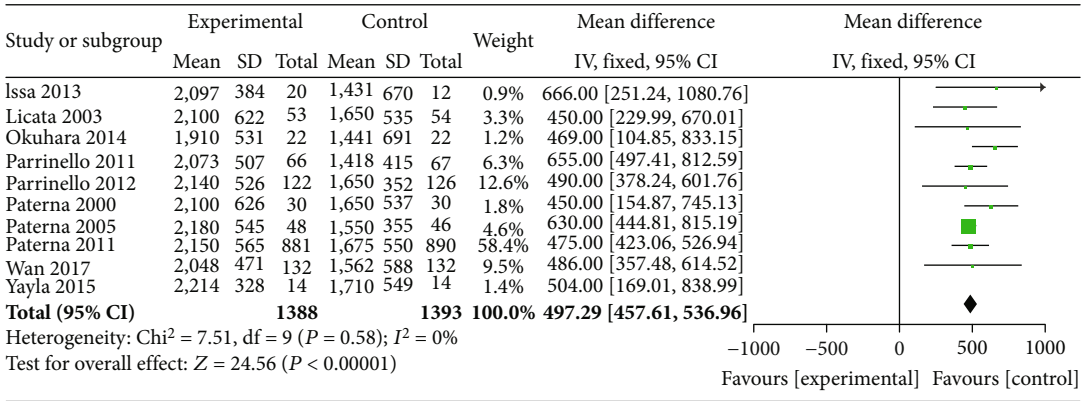

Figure 4: Comparison of 24 h urine volume between the HSS + furosemide group and the furosemide group. HSS: hypertonic saline solution.

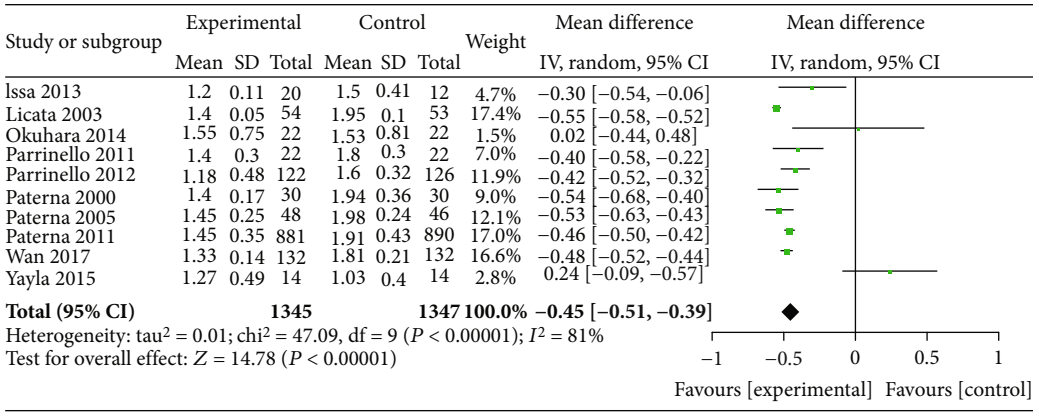

Figure 5: Comparison of serum creatinine levels between the HSS + furosemide group and the furosemide group. HSS: hypertonic saline solution.

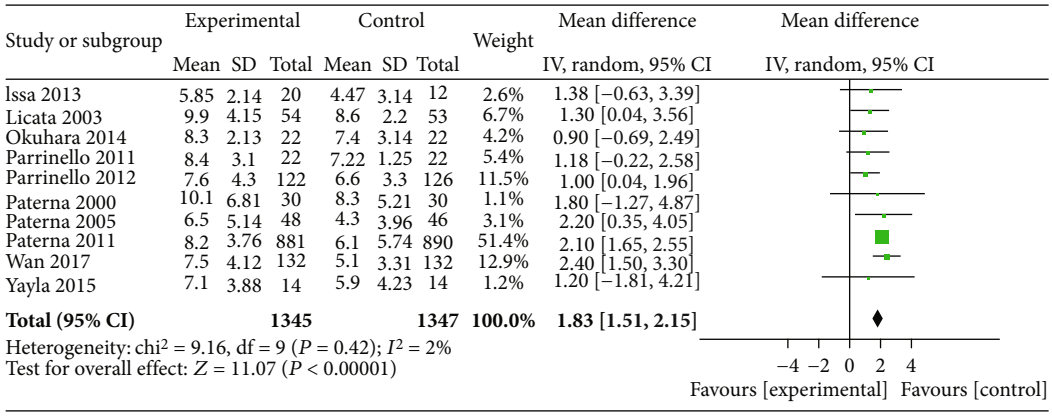

Figure 6: Comparison of weight loss between the HSS + furosemide group and the furosemide group. HSS: hypertonic saline solution.

troponin level and pulmonary capillary wedge pressure (PCWP). The study also noted that HSS did not cause myocardial damage. HSS could improve cardiac function, especially in diastolic volume and ejection fraction. Yayla et al. [20] pointed out that the efficacy of combined use of HSS and simple use of furosemide in patients was similar. There was no significant difference in serum creatinine level, body weight, and urine output between the two treatment regimens. The combined use of HSS could shorten the hospitalization time of patients. Okuhara et al. indicated that the 24 h urine volume and creatinine clearance rate of the HSS + furosemide group were greater than those of the control group, thus improving renal function. Parrinello et al. [24] illustrated that the 24 h urine output and sodium output of

the HSS + furosemide group were higher than those of the furosemide group. Therefore, HSS combined with furosemide could significantly improve the renal function of patients. Both treatments can reduce PCWP, but HSS combined with furosemide is more effective. The study also indicated that BNP was positively correlated with PCWP. Issa et al. [21] studied and compared the levels of biomarkers of renal function in the HSS + furosemide group and furosemide group. They suggested that HSS + furosemide could significantly improve patients' renal function.

This study has some limitations. First, there was a risk of bias in the literature included in the analysis, which might affect the results. And there were differences in research objects and intervention measures in various literature, which might be the source of heterogeneity. Secondly, the outcome indicators included in our analysis were limited, and we could not comprehensively evaluate the efficacy of HSS combined with furosemide in patients with acute heart failure. Third, the results obtained by subgroup analysis according to age, gender, and severity of heart failure are more clinically instructive. However, we were limited by literature information and were unable to perform such subgroup analyses. Fourth, this study failed to retrieve relevant studies in recent years, and the literature included in the analysis was outdated, which may have a certain impact on the results.

In conclusion, despite the heterogeneity and bias in our study, the combination of HSS with furosemide is promising in patients with acute heart failure. However, further research is still needed to confirm.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Zuoqing Li and ZuanJin Wang contributed equally to this work.

Acknowledgments

The project was supported by the Chengmai County People's Hospital.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 6234858, 10 pages
https://doi.org/10.1155/2022/6234858

Research Article

Effectiveness and Safety of Saccharomyces Boulardii for the Treatment of Acute Gastroenteritis in the Pediatric Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Received 9 August 2022; Revised 8 September 2022; Accepted 8 September 2022; Published 20 September 2022

Academic Editor: Xi Lou

Objective. To explore the efficacy and safety of Saccharomyces boulardii for the treatment of acute gastroenteritis in children aged under 5. *Methods*. Two independent researchers retrieved literature from PubMed, OVID, Embase, ScienceDirect, and other databases, followed by extracting indicators of the primary endpoints. Cochrane Q test and I^2 statistics were used to evaluate interstudy heterogeneity. The relative risk (RR) and mean difference (MD) of related indicators were calculated and combined using the random- or fixed-effect model, as appropriate. Furthermore, the funnel plot and Egger's test were used to evaluate the publication bias. A two-sided $P < 0.05$ denoted statistical significance. *Results*. 10 articles were included in this meta-analysis, with a total of 1282 children having acute gastroenteritis. The use of Saccharomyces boulardii in children with acute gastroenteritis could effectively shorten diarrhea duration (MD = 19.70, 95% CI: -24.87, 14.52) and reduce the length of hospital stay (MD = −0.91, 95% CI: -1.28, -0.54). Compared with the control group, the RR of continued diarrhea was significantly lower in the treatment group after 1 day treatment (RR = −0.31, 95% CI: 0.59, 0.03) and 3 days treatment (RR = 0.52, 95% CI: 0.41, 0.66). In addition, treatment with Saccharomyces boulardii reduced the average number of diarrhea after 3 days of treatment by about 1.03 (MD = −1.03, 95% CI: -1.53, -0.53). There were no adverse drug reactions in both groups. *Conclusion*. The use of probiotic Saccharomyces boulardii can significantly improve the symptoms of diarrhea in children with acute gastroenteritis and reduce the duration of diarrhea symptoms and the time of hospitalization. Meanwhile, the RR of continued diarrhea in children after 1 and 3 days of Saccharomyces boulardii treatment and the frequency of diarrhea after 3 days of Saccharomyces boulardii treatment were decreased. It is also safe and does not increase the incidence of adverse drug reactions.

1. Introduction

Acute gastroenteritis is a gastrointestinal mucosal inflammation characterized by diarrhea, vomiting, nausea, and abdominal pain. Pediatric gastroenteritis is mainly caused by norovirus and rotavirus [1, 2]. Although acute gastroenteritis in children is a self-limiting disease and oral rehydration therapy (ORT) can significantly shorten the course of the disease [3–5], there are still clinical challenges in the treatment of children with dehydration and vomiting symptoms in terms of ORT therapy failure and hospitalization [2]. Some studies have shown that not using ORT therapy or failure of ORT therapy significantly increases the risk of dehydration, electrolyte imbalance, intravenous infusion, and hospitalization in children with acute gastroenteritis, especially younger children [6]. Although acute gastroenteritis is treatable and preventable, it is still one of the major factors leading to the "death burden" in children aged 5 years and under. Death in children with acute gastroenteritis are most commonly related to severe dehydration [7].

A large number of children worldwide suffer from acute gastroenteritis every year, of which approximately 150000-250000 died [8]. It is estimated that the incidence of acute gastroenteritis in children under 5 years of age in developing countries is about 3-5 cases per person per year [9, 10]. The incidence of acute gastroenteritis-related death in children under 5 years is about 200 thousand [11] in developing countries, whereas it is about once per person per year in developed countries [12].

Several clinical guidelines suggest that probiotics with promising efficacy and safety should be used as adjuvant treatment for liquid therapy of acute gastroenteritis [13–15]. Although Listeria rhamnosus and Saccharomyces boulardii were the two most used probiotics in clinical practice and recommended by the guidelines, the literature on Listeria rhamnosus is insufficient, and their efficacy in the treatment of acute gastroenteritis remains controversial, which is probably related to inconsistent study conclusions and methodological defects. Increasing randomized controlled trials have shown that Saccharomyces boulardii can effectively shorten the duration of diarrhea in patients with acute gastroenteritis [16]. Therefore, this study explored the safety and effectiveness of Saccharomyces boulardii in treating children with acute gastroenteritis through systematic review and meta-analysis to provide more evidence for the role of probiotics for pediatric acute gastroenteritis and the prevention of dehydration and electrolyte disorders.

2. Methods

2.1. Literature Search. This study used Medical Subject Headings (MESH) as search terms in PubMed, Embase, ScienceDirect, OVID, and other databases for literature retrieval. The search keywords were ("Infant"[Mesh Terms] OR "children" OR "pediatrics" OR "adolescent") AND ("Probiotics"[Mesh Terms] OR "Saccharomyces boulardii") AND ("diarrhea" OR "vomiting" OR "Dehydration" OR "diarrhea∗" OR "emesis" OR "gastroenteritis").

2.2. Literature Screening. The inclusion criteria were: (1) placebo-controlled randomized controlled trial (RCT); (2) children with confirmed acute gastroenteritis as the study population; (3) children aged under 5; (4) Saccharomyces boulardii used for treatment; (5) study main endpoints included at least one of the following six categories: duration of diarrhea, length of hospital stay, stopping diarrhea within 1 day, stopping diarrhea within 3 days, the number of diarrhea after treatment, and the occurrence of adverse drug reaction events.

Literature exclusion criteria: (1) study population limited to a special population, such as people with immune deficiency or those with concomitant gastrointestinal diseases, such as necrotizing colitis, Crohn's disease; (2) studies with subject overlap; (3) sample size of the interventional group or control group less than 20; (4) nonoriginal articles, such as comments, academic conferences, reviews, and case reports. No restrictions of the pathogens that cause acute gastroenteritis were applied in this study.

2.3. Document Data Sorting and Evaluation. The following data were screened and extracted from the literature by Fu and Li (Table 1): study type (open trial or double-blind trial), number of subjects in the control group and the interventional group, demographic characteristics, duration of diarrhea, duration of hospitalization, continuous diarrhea for 1 day after treatment, continuous diarrhea for 3 days after treatment, diarrhea frequency, and incidence of adverse drug reactions. Study quality was evaluated with the Newcastle Ottawa Scale (NOS), with scores below 5, 5-7 and ≥ 8 denoted low-, medium-, and high-quality publications. Controversies between the 2 investigators were settled by discussion and consultation with the third researcher.

2.4. Statistical Methods. The STATA17.0 (SE) software was employed for statistical analysis. The observed primary clinical endpoint for categorical and continuous variables were expressed by relative risk (RR) and mean ± standard deviation, respectively. The random- and fixed-effect model were used in the presence of significant ($I^2 > 50\%$) and nonsignificant interstudy heterogeneity, respectively. Interstudy heterogeneity was assessed by the Cochran's Q test. In the absence of interstudy heterogeneity ($P > 0.05$ and $I^2 < 50\%$), the fixed-effect model was used. Otherwise, the random-effect model was used. The funnel plot, Egger's and Begg's tests were utilized to evaluate publication biases. A two-sided P value less than 0.05 denoted statistical significance.

3. Results

3.1. Search Results and Literature Characteristics. A total of 188 relevant literatures were generated, of which 10 studies were included in the meta-analysis according to the established inclusion and exclusion criteria. The detailed process of literature retrieval and screening was presented in Figure 1. All the included literatures were clinical RCTs that included 1282 children in total. Among the 10 studies, 8 reported diarrhea duration in children with acute gastroenteritis after the use of Saccharomyces boulardii, 5 reported hospitalization time, 4 evaluated the diarrhea frequency on the third day after treatment, 6 reported the diarrhea lasting for one day after treatment, and 7 reported persistent diarrhea for 3 days after treatment. According to the risk-of-bias assessment proposed by Cochrane, only 3 included publications described the grouping concealment and blind method of randomized grouping, which was considered to have a low risk of bias, and the rest of the literature had a moderate- to high-risk of bias. NOS scores ranged from 4 to 8, including 3 high-quality, 4 medium-quality, and 3 low-quality literature.

3.2. Duration of Diarrhea. A total of 1051 children in 8 studies were included for the evaluation of diarrhea duration. The heterogeneity test results were $H^2 = 6.99$, $I^2 = 85.70\%$, $P < 0.001$, indicating a high degree of heterogeneity. Therefore, the random-effect model based on the restricted maximum likelihood method was used to combine the mean difference. Meta-analysis (Figure 2) showed that compared

Table 1: Characteristics of 12 included literatures.

Author	Study design	Sample size		Age range	Duration of diarrhea (h)		Duration of hospitalization (days)		Persistency of diarrhea on day 1		Persistency of diarrhea on day 3		Diarrhea frequency on day 3		Adverse event	
		Intervention	Control		Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Das et al. [17]	RCT	30	30	3 months to 5 years	60(51-67)	89(68-95)	3.18 ± 0.58	3.8 ± 0.71	3	10	1	4	NA	NA	NA	NA
Riaz et al. [18]	RCT	54	54	3 months to 5 years	49.55(25.82-73.27)	66.34(27.07,95.81)	NA	NA	13	21	10	15	15.28 ± 11.71	15.92 ± 13.43	NA	NA
Dinleyici et al. [19]	RCT	220	143	4 months to 4 years	60.4 (37.3-83.5)	78.4(57.5-99.3)	4.6 ± 1.72	6.12 ± 1.71	200	130	69	82	NA	NA	NA	NA
Billoo et al. [20]	RCT	50	50	2 months to 12 years	82(45.3-99.2)	92(81.3-112.1)	NA	NA	10	9	3	5	2.8 ± 3.05	4.4 ± 3.05	NA	NA
Cetina-sauri et al. [21]	RCT	65	65	9 months to 20 months	NA	NA	NA	NA	10	19	8	14	2.53 ± 1.78	3.63 ± 2.53	NA	NA
Hafeez et al. [22]	RCT	50	51	3 months to 60 months	NA	NA	NA	NA	NA	NA	NA	NA	4.29 ± 3.07	5.73 ± 3.07	NA	NA
Villarruel et al. [23]	RCT	44	44	3 months to 2 years	147.84(48-312)	112.8(48-240)	NA	NA	22	30	9	23	NA	NA	NA	NA
Kurugöl et al. [24]	RCT	100	100	3 months to 7 years	112.8(50.4-172.8)	132(55.2-208.8)	2.9 ± 1.2	3.9 ± 1.5	18	38	8	24	NA	NA	NA	NA
Grandy et al. [25]	RCT	25	27	1 months to 23 months	58(18-92)	84.5(23.4-112.4)	3.16 ± 1	3.72 ± 2.43	NA	NA	NA	NA	NA	NA	NA	NA
Bhat et al. [26]	RCT	40	40	6 months to 5 years	41.68 ± 10.84	57.65 ± 26.31	2.72 ± 0.42	3.37 ± 1.1	NA	NA	NA	NA	2.6 ± 1.28	3 ± 2.5	NA	NA

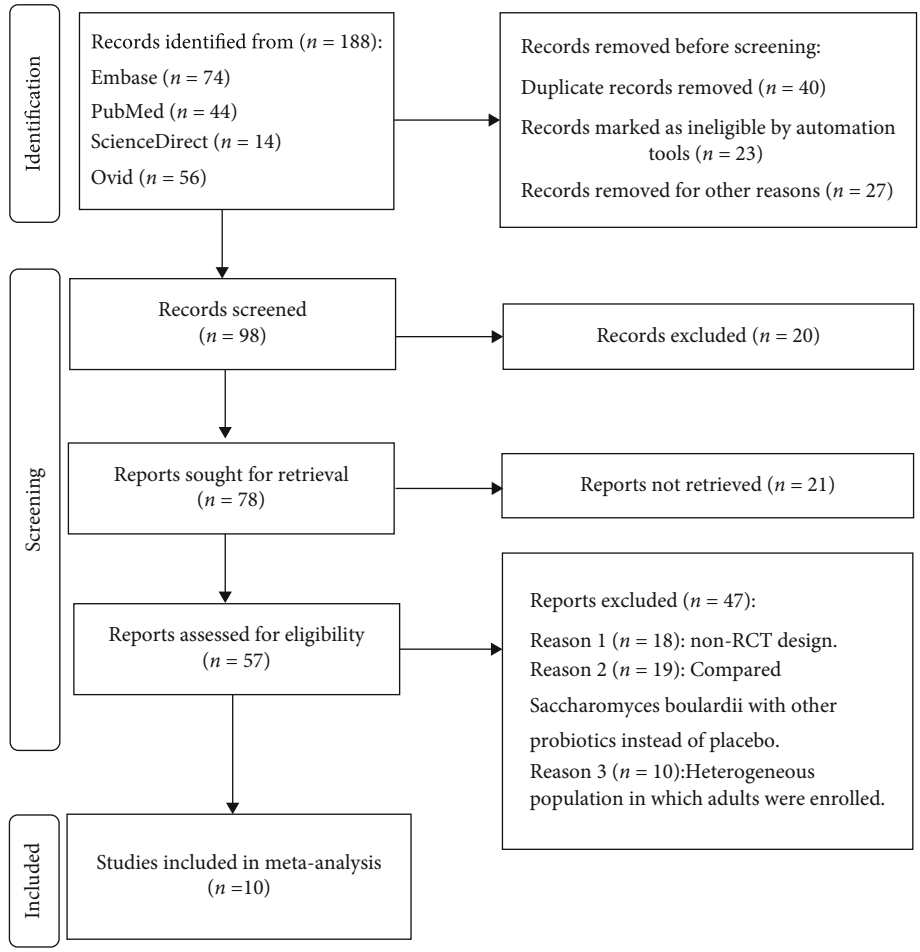

Figure 1: Prism flow chart. Process of screening for literature inclusion and exclusion.

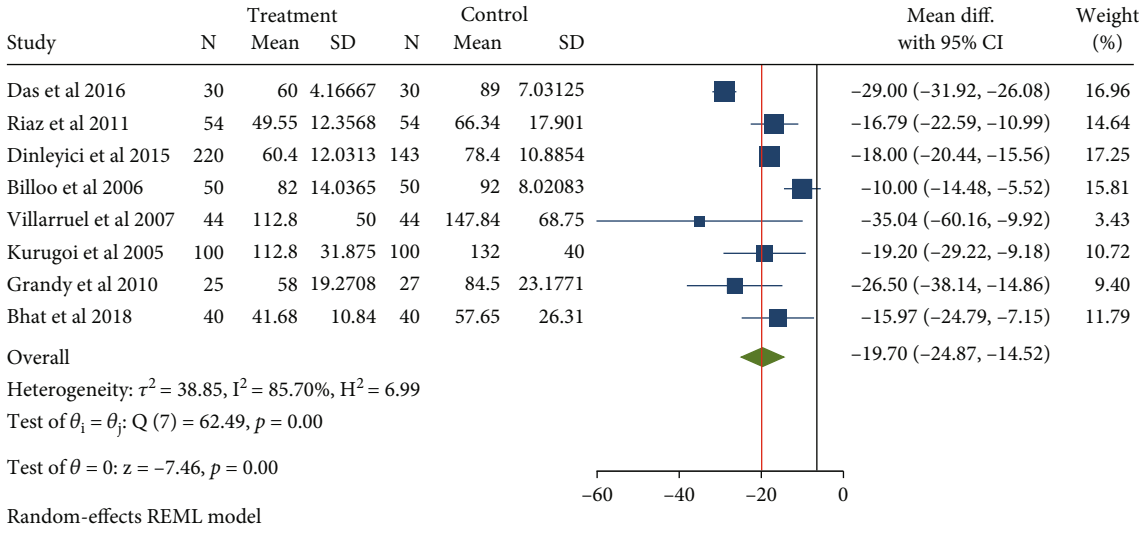

Figure 2: Forest map of the duration of acute gastroenteritis diarrhea in children treated with Saccharomyces boulardii.

with placebo, the use of Saccharomyces boulardii significantly reduced the duration of diarrhea in children with acute gastroenteritis (Mean difference = 19.70, 95% CI: -24.87, 14.52, $P < 0.001$). The funnel plot showed points on both sides in an inverted funnel shape, and two studies were outside the confidence interval. Eegg's test that was performed on the included studies indicated absence of obvious publication bias ($Z = 0.50$, $P = 0.617$, Figure 3).

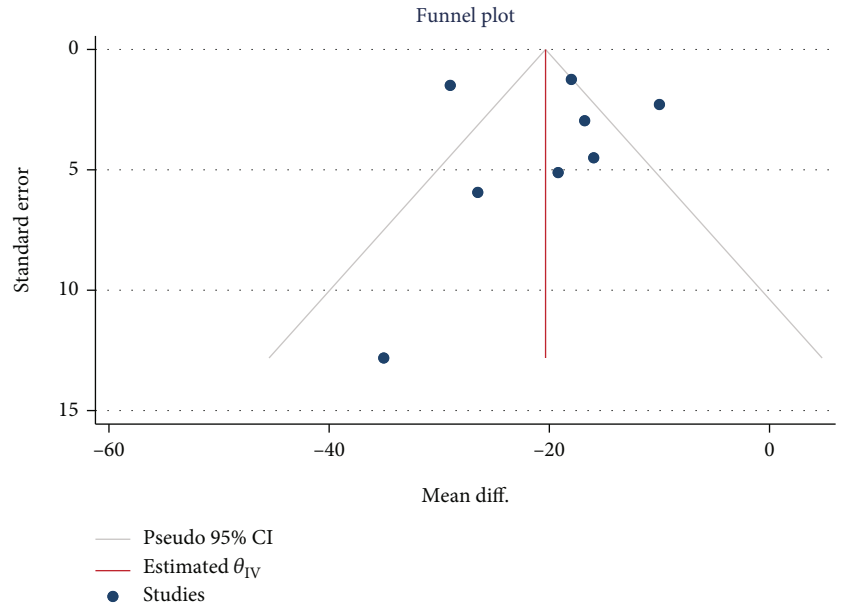

Figure 3: Funnel chart of the duration of acute gastroenteritis diarrhea in children treated with Saccharomyces boulardii.

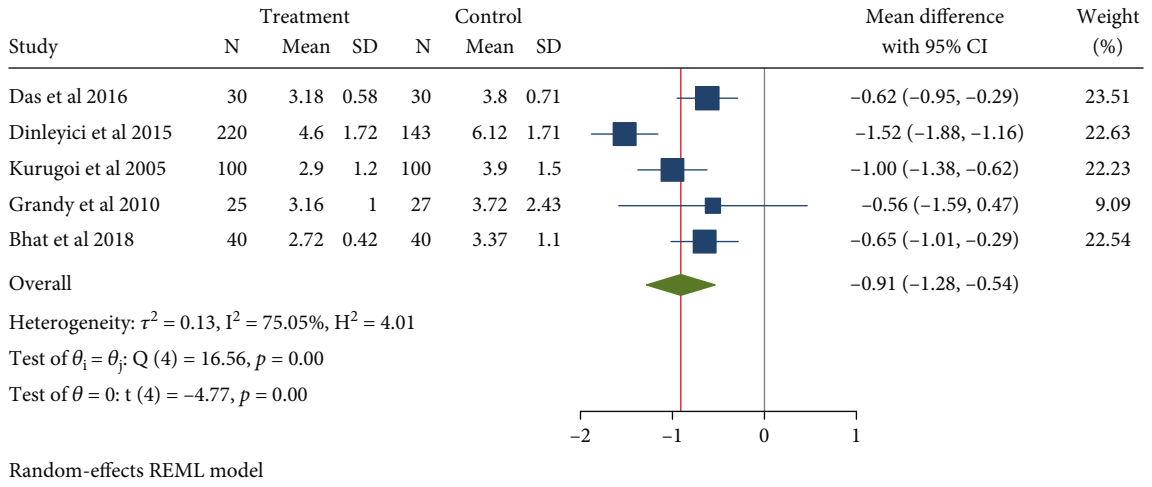

Figure 4: Forest chart of hospitalization time in children with acute gastroenteritis treated with Saccharomyces boulardii.

3.3. Length of Hospital Stay. A total of 755 children from 5 literatures were included. Moderate heterogeneity ($H^2 = 4.01$, $I^2 = 75.05\%$, $P < 0.001$) was noted, for which the random-effect model was used. Compared with the control group, the use of Saccharomyces boulardii significantly reduced length of hospitalization in children with acute gastroenteritis by about 0.91 days (Mean difference = −0.91, 95% CI: -1.28, -0.54, $P < 0.001$, Figure 4). The funnel plot and Eegg's test indicated no obvious publication bias ($Z = -1.86$, $P = 0.108$, Figure 5).

3.4. Diarrhea for 1 Day after Treatment. A total of 1049 subjects from 7 studies were included. The random-effect model was used since the interstudy heterogeneity was modest ($H^2 = 2.84$, $I^2 = 64.85\%$, $P < 0.005$). The result (Figure 6) indicated that Saccharomyces boulardii significantly reduced the risk of persistent diarrhea within 1 day after treatment in children with acute gastroenteritis (RR = 0.70, 95% CI: 0.49, 1.00, $P = 0.01$). The funnel plot shows that the points are distributed on both sides, within the confidence interval, in an inverted funnel shape, but one study is outside the confidence interval. No obvious publication bias was suggested by the Eegg's test ($Z = -0.9$, $P = 0.548$, Figure 7).

3.5. Diarrhea Lasting for 3 Days after Treatment. Seven studies with 1049 children in total were used for meta-analysis. Minimal heterogeneity was noted ($H^2 = 1.00$, $I^2 = 0.00\%$, $P = 0.77$), for which the fixed-model was utilized. The results of the meta-analysis showed that compared with the control group, the use of Saccharomyces boulardii could reduce the risk of 3-day continuous diarrhea in children with acute gastroenteritis after treatment (RR = 0.52, 95% CI: 0.41, 0.66, $P < 0.001$), as shown in Figure 8. No publication bias was found by the funnel chart (Figure 9).

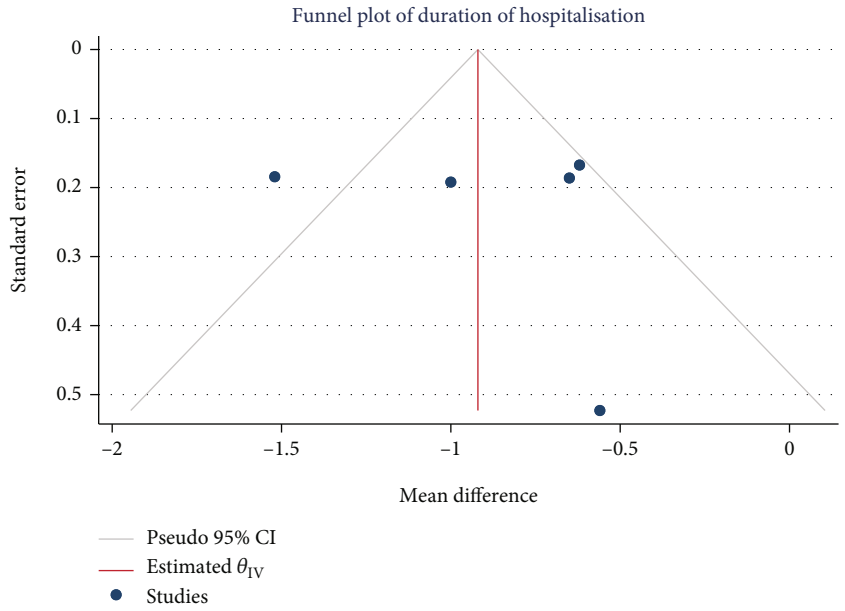

Figure 5: Funnel chart of hospitalization time in children with acute gastroenteritis treated with Saccharomyces boulardii.

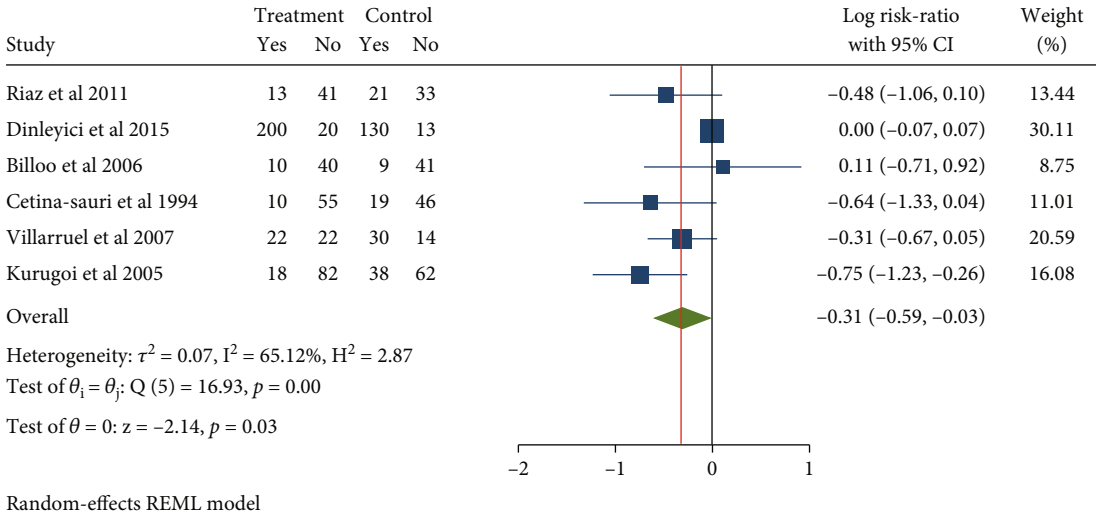

Figure 6: Forest chart of continuous diarrhea for 1 day in children with acute gastroenteritis treated with Saccharomyces boulardii.

3.6. Diarrhea Frequency after Treatment (the Third Day). A total of 519 patients in 5 studies with minimal interstudy heterogeneity ($H^2 = 1.09$, $I^2 = 7.87\%$, $P = 0.49$) were meta-analyzed with the fixed-effect model. The results showed that Saccharomyces boulardii significantly reduced the frequency of diarrhea in children with acute gastroenteritis after treatment by about 1.03 times (Mean difference = −1.03, 95% CI: -1.53, -0.53, $P < 0.001$, Figure 10). The funnel chart (Figure 11) suggested no publication bias.

4. Discussion

Probiotics refer to the microbiota that can colonize and survive in the host and play a beneficial role in health [27]. In recent years, the role of probiotics in health promotion, health protection, disease treatment, and regulation of intestinal flora has attracted increasing attention [28, 29]. In vitro and animal model experiments have shown that probiotics can exert their biological role by competing with pathogenic bacteria for nutrition and binding sites, producing antibacterial substances, providing nutrients for colonic epithelial cells, and reducing intestinal permeability [30, 31]. Other mechanisms related to treating acute gastroenteritis in children included altered gene expression of epithelial cells, increased activity of phagocytes and natural killer cells, and elevated level of immunoglobulin A in saliva and feces [30, 31]. Emerging evidence support that probiotics can also regulate human immune responses, in which the dendritic cells

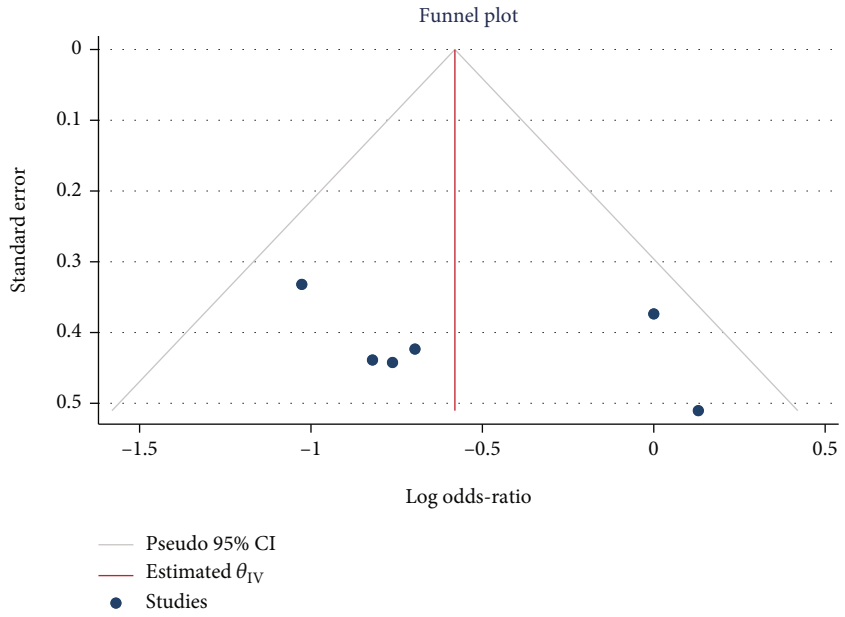

Figure 7: Funnel chart of continuous diarrhea for 1 day in children with acute gastroenteritis treated with Saccharomyces boulardii.

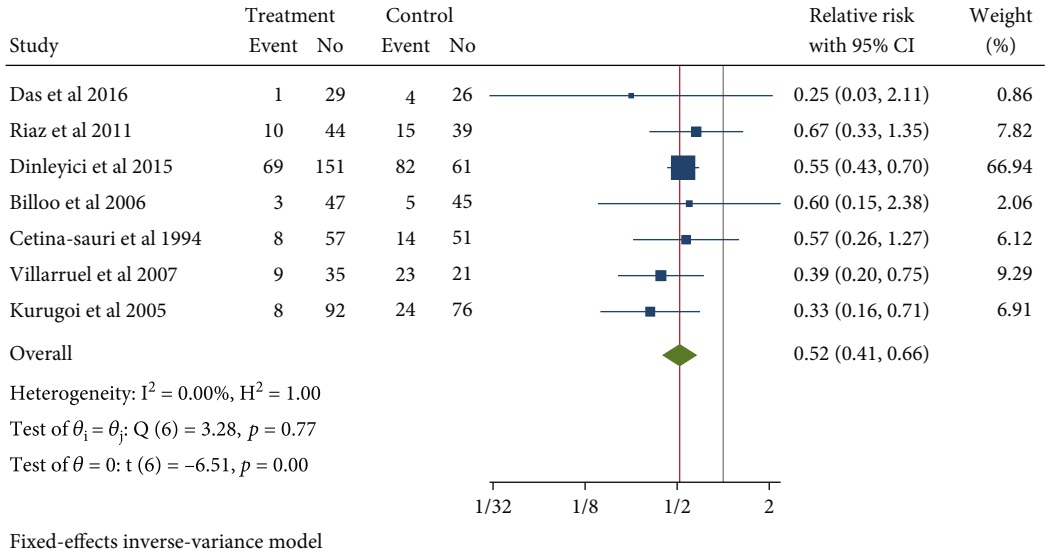

Figure 8: Forest chart of diarrhea for 3 days in children with acute gastroenteritis treated with Saccharomyces boulardii.

and toll-like receptor molecules played a pivotal role. These cells or molecules regulate the production of endogenous immune peptides by receiving structural lipopolysaccharides, glycopeptide molecules, and CpG DNA from probiotics and conducting biological conversion on them [32]. Specifically, Saccharomyces boulardii produced 54 KD protease that can hydrolyze clostridium difficile endotoxin and their corresponding binding sites on intestinal cells, and stimulated production of specific IgG and IgA in the meantime. In addition, some studies have found that probiotics can stimulate the production of anti-inflammatory factors (e.g., interleukin [IL]-10 and IL-4) and inhibit proinflammatory factors tumor necrosis factor- a and interferon- γ, thus promoting the digestive tract mucosa to produce specific anti-rotavirus secretory IgA and regulating the mucosal immune response to pathogens [33].

In a 2010 Cochrane meta-analysis [34], Allen et al. showed that the use of probiotics could reduce the diarrhea time of children with acute gastroenteritis (-25 h, 95% CI: -16 h, -34 h); the proportion of diarrhea lasting four days or more (RR 0.41, 95%ci: 0.32, 0.53) was comparable with the results of this study. Szajewska et al. found through meta-analysis that Lactobacillus rhamnosus could also shorten the diarrhea time of children with acute gastroenteritis by about 1.05 days (95% CI: -1.7, -0.4), and this effect was more significant in the high-dose group. Of note, the

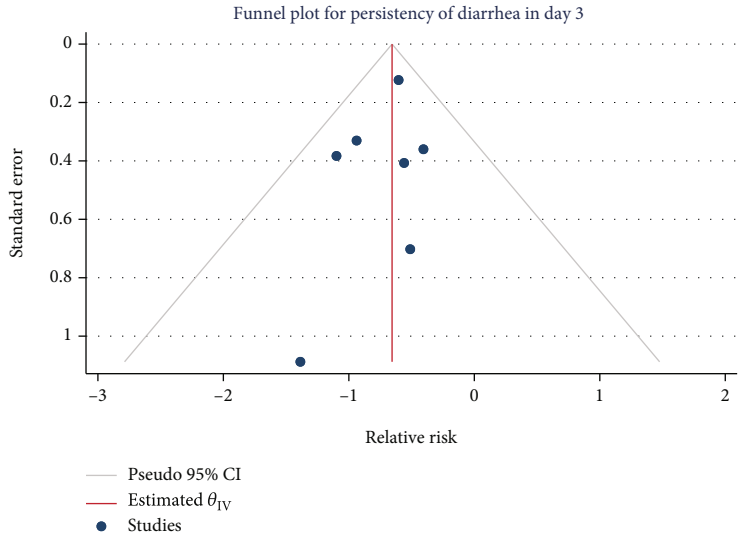

Figure 9: Funnel chart of the observation results of Saccharomyces boulardii on the 3-day continuous diarrhea after the treatment of acute gastroenteritis in children.

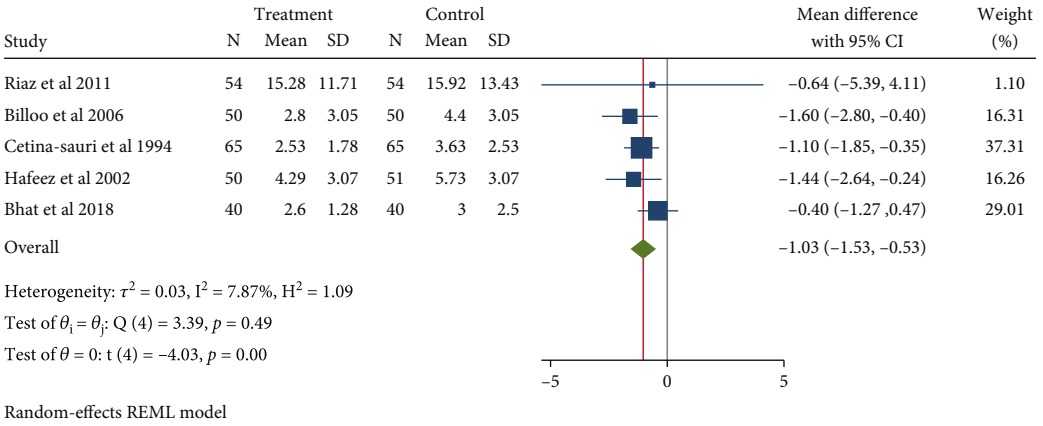

Figure 10: Forest chart of diarrhea frequency on the third day after treatment in children with acute gastroenteritis treated with Saccharomyces boulardii.

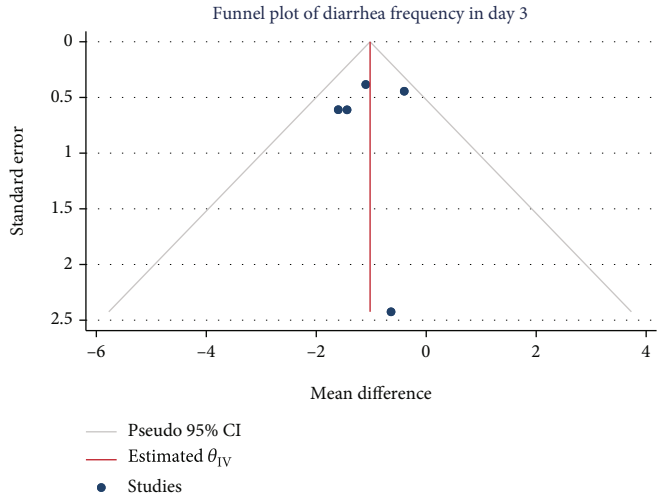

Figure 11: Funnel chart of diarrhea frequency on the third day after treatment in children with acute gastroenteritis treated with Saccharomyces boulardii.

main population of this study was Caucasians. Considering the differences in common colonized flora in the gastrointestinal tract between Chinese and Western population, the conclusions of this study might not be extrapolated to the Chinese population [35]. Previous meta-analyses indicated positive effects of probiotics for treating acute gastroenteritis in children. This evidence-based medical evidence has prompted many institutions to recommend promoting the daily use of probiotics in pediatric inpatients [36]. However, some scholars still believe that the evidence for the widespread use of probiotics in patients with acute gastroenteritis is still weak, especially in outpatients [37]. Furthermore, methodological defects of the RCTs included in the above meta-analysis was also a concern. For example, although 63 literatures were included in the meta-analysis by Allen et al., only 10 met all the methodological requirement for RCTs.

This study suffers from several limitations: (1) Although all the included literature in this study was of medium- or high-quality, the risk of bias, including the use of grouping concealment, randomization, and the selection of blind methods, can not be eliminated. Some literature did not use intention-to-treat analysis, leading to the partial deletion of the final data set; (2) Not all the included RCTs provided the calculation process of sample size. Hence, it was unclear whether the research results had sufficient statistical power to prove their reliability; (3) The wide confidence interval of some endpoint indexes increased the uncertainty of statistical inference; (4) Only 10 literature were included in this paper, and some outcome indicators were less than 10. It is difficult to distinguish the degree of symmetry in the funnel plot evaluation of publication offset, so we combined Egger's and Begg's tests for evaluation. (5) Extensive rotavirus vaccination in some developed countries might lead to changes in the epidemiology of acute gastroenteritis, since rotavirus-associated acute gastroenteritis has been demonstrated to benefit most from probiotics. A subgroup analysis of different disease prototypes was unfeasible in this study since few reported the etiology of acute gastroenteritis; (6) Criteria and clinical practices for hospitalization in children with acute gastroenteritis may differ and introduce bias to this study.

In conclusion, this study showed that the use of Saccharomyces boulardii in children with acute gastroenteritis can significantly shorten the time of hospitalization and diarrhea, and no adverse drug reactions have been observed. It provides some theoretical support for the treatment of acute gastroenteritis in children.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Hongbo Fu and Jinrong Li contributed equally to this work.

Acknowledgments

The study was supported by Haikou Maternal and Child Health Hospital.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 1126616, 8 pages
https://doi.org/10.1155/2022/1126616

Research Article

The Association of Sperm DNA Fragment and Assisted Reproductive Outcomes: A Meta-Analysis

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Received 3 May 2022; Revised 26 July 2022; Accepted 16 August 2022; Published 14 September 2022

Academic Editor: Xi Lou

Objective. To analyze the effect of sperm DNA fragmentation index (DFI) on the outcomes of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). *Methods*. Literature search was conducted on English databases PubMed, Cochrane, and Embase to obtain eligible studies. *Results*. A total of 11 cohort studies were included and analyzed using the random effects model. The results illustrated that the IVF fertilization rate (RR = 0.94, 95% CI: 0.77-1.14, $P = 0.61$), pregnancy rate (RR = 0.83, 95% CI: 0.57-1.21, $P = 0.32$), and live birth rate (RR = 0.53, 95% CI: 0.16-1.80, $P = 0.31$) in the high DFI group were statistically insignificant with those in the low FI group. The correlations between DFI and ICSI fertilization rate (RR = 0.79, 95% CI: 0.52-1.18, $P = 0.25$), pregnancy rate (RR = 0.89, 95% CI: 0.74-1.06, $P = 0.18$), and live birth rate (RR = 0.89, 95% CI: 0.70-1.14, $P = 0.36$) were also not statistically significant. *Conclusion*. This study has observed no significant correlation between sperm DFI and assisted reproductive outcomes. Multicenter large-sample clinical trials are required to conclusively determine the impact of DNA damage on the clinical outcomes of assisted reproduction.

1. Introduction

Infertility is a worldwide health problem that has an incidence of about 7%-15% [1]. In recent years, with the continuous development of medical technology, assisted reproductive technology (ART), including intrauterine artificial insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI), has brought new options to infertile couples. Among the causes of infertility symptoms, male factors such as oligospermia, low sperm motility, and abnormal sperm morphology lead to approximately the same rate of infertility as female factors such as endometriosis and blocked fallopian tubes [2]. In particular, merging data have shown that male sperm disorders were drastically associated with clinical outcomes in ART [2].

As the carrier of human genetic material, sperm DNA plays a crucial role in human reproduction and survival by transferring genetic material to offspring completely. Since sperm has no repair mechanisms, DNA damage is present in almost all sperms. Whether sperm DNA damage has an adverse impact on reproductive outcomes is a question of particular clinical concern [3]. Studies have shown that the integrity of sperm DNA has a significant correlation with the decline of female natural pregnancy rate and male infertility [4]. At present, the pregnancy rate of IVF and intracytoplasmic sperm injection is low. Therefore, it is increasingly necessary to develop techniques to accurately diagnose sperm damage and predict the impact on the clinical results of assisted reproduction [5]. With the continuous development and improvement of sperm detection technology, emerging methods to detect the integrity of sperm chromatin have been established, including comet assay, sperm chromatin diffusion assay (SCD), terminal transferase-mediated dUTP terminal labelling (TUNEL), sperm chromatin structure analysis

(SCSA), and acridine orange test. Currently, the SCSA is considered the "gold standard" for sperm DNA integrity detection.

Therefore, this study is aimed at exploring the impact of sperm DNA fragment index on assisted reproduction through literature retrieval and meta-analysis. The detection method of sperm integrity is limited to "gold standard" chromatin structure analysis.

2. Methods

2.1. Bibliography Retrieval. The English databases PubMed, Cochrane, and Embase were searched from January 2000 to March 2022. The search method was medical subject headings combined with free words. The search items included "in-vitro fertilization OR IVF OR intracytoplasmic sperm injection OR ICSI OR assisted reproductive technique OR ART" AND "Sperm DNA damage OR sperm DNA fragmentation OR DNA fragmentation index OR DFI" AND "sperm chromatin structure assay OR SCSA."

2.2. Literature Screening. The following are the inclusion criteria: (1) subjects with normal ovarian reserve function receiving IVF or ICSI; (2) stratification of patients into the low- and high-DFI groups; (3) outcome measures including at least one of the following: IVF/ICSI fertilization rate, pregnancy rate, or live birth rate; (4) prospective or retrospective cohort study; and (5) DFI detection by SCSA.

The following are the exclusion criteria: (1) DFI not detected by SCSA; (2) ART other than IVF or ICSI; (3) news reports, expert opinions, critical literature, and abstracts; (4) republished literature; (5) incomplete data information or insufficient literature available for data analysis; (6) DIF threshold not clearly defined; and (7) unavailable full text.

2.3. Document Data Extraction. Two researchers conducted literature search and screened potentially eligible studies according to the inclusion/exclusion criteria. The following relevant data were extracted, including title, publication date, author's name, research type, study population, intervention measures, outcome measures, research methods, and subject characteristics. Any disagreements were resolved by discussion and arbitration by another independent senior author.

2.4. Literature Quality Evaluation. The NHLBI-NIH guidelines (http://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) were applied to evaluate the quality of the included studies. The quality assessment tool contained 14 questions with an answer of "yes/no" for each item. On a scale of 14 points, higher score indicated better quality. Two researchers independently evaluated the quality of the included literature before cross-checking. Discrepancies were settled by consulting a third researcher.

2.5. Statistical Method. The Cochrane software RevMan5.4 was utilized for data analysis. The categorical data were compared using the relative risk (RR) coefficient with 95% confidence interval. Interstudy heterogeneity was evaluated using the chi-square test and the I^2 statistic, with $I^2 > 50\%$ denoting significant heterogeneity. The RR was calculated with the fixed or random effects model depending on the heterogeneity assessment. Egger's test and funnel plot were consulted to estimate possible publication bias. A two-sided P value < 0.05 denoted statistical significance.

3. Results

3.1. Literature Search Results. 2132 relevant literatures were obtained through database retrieval in this study. After exclusion of duplicate publications, the study title and abstracts were screened for eligibility. Finally, a total of 12 publications were finally included in this meta-analysis. The specific screening process and results are shown in Figure 1.

3.2. Characteristics and Quality Evaluation. The basic information of the 12 included English literatures [6–17] is shown in Table 1. All these were cohort studies published between 2005 and 2020, of which 4 were retrospective, 5 were prospective, and 3 were bidirectional cohort studies. Five articles reported using both ICSI and IVT, whereas 5 and 1 publication employed only ICSI and IVT, respectively. The other 6 papers studied both ICSI and IVT techniques. The DFI threshold defined varied across studies, with an overall range of 15% -30%. A total of 5, 7, and 3 studies reported IVT fertilization rate, pregnancy rate, and live birth rate, respectively. There were 5, 10, and 3 articles reported ICSI fertilization rate, pregnancy rate, and live birth rate, respectively. The total score of NHLBI-NIH were 8-10 points, with only 1 scored 5 points. The scoring results are shown in Table 1. The quality of the included literature was evaluated to be high.

3.3. Meta-analysis Results

3.3.1. Correlation between DFI and IVF Clinical Outcomes. Patients were divided into the high- and low-DFI groups, using the boundary value as the DFI threshold. The heterogeneity assessment of the IVF fertilization rate, pregnancy rate, and live birth rate was $I^2 = 55\%$, 73%, and 76%, respectively. Significant heterogeneity was noted, for which the random effects model was applied. The results of the meta-analysis showed that the IVF fertilization rate in the high DFI group was statistically insignificant with that in the low DFI group (RR = 0.94, 95% CI: 0.77-1.14, $Z = 0.51$, $P = 0.61$), as shown in Figure 2. Similarly, the IVF pregnancy rate in both groups was also insignificant (RR = 0.74, 95% CI: 0.50-1.12; $Z = 1.47$, $P = 0.14$) (Figure 3). The IVF live yield in the high DFI group was also insignificant with that in the low DFI group (RR = 0.53, 95% CI: 0.16-1.80; $Z = 1.01$, $P = 0.31$) (Figure 4). However, the IVF pregnancy rate and live birth rate in the high DFI group were significantly lower than those in the DFI when the fixed effects model was used.

3.3.2. Correlation between DFI and ICSI Clinical Results. No significant differences with regard to ICSI fertilization rate, pregnancy rate, and live birth rate were noted between the high- and low- DFI groups. The correlation between DFI

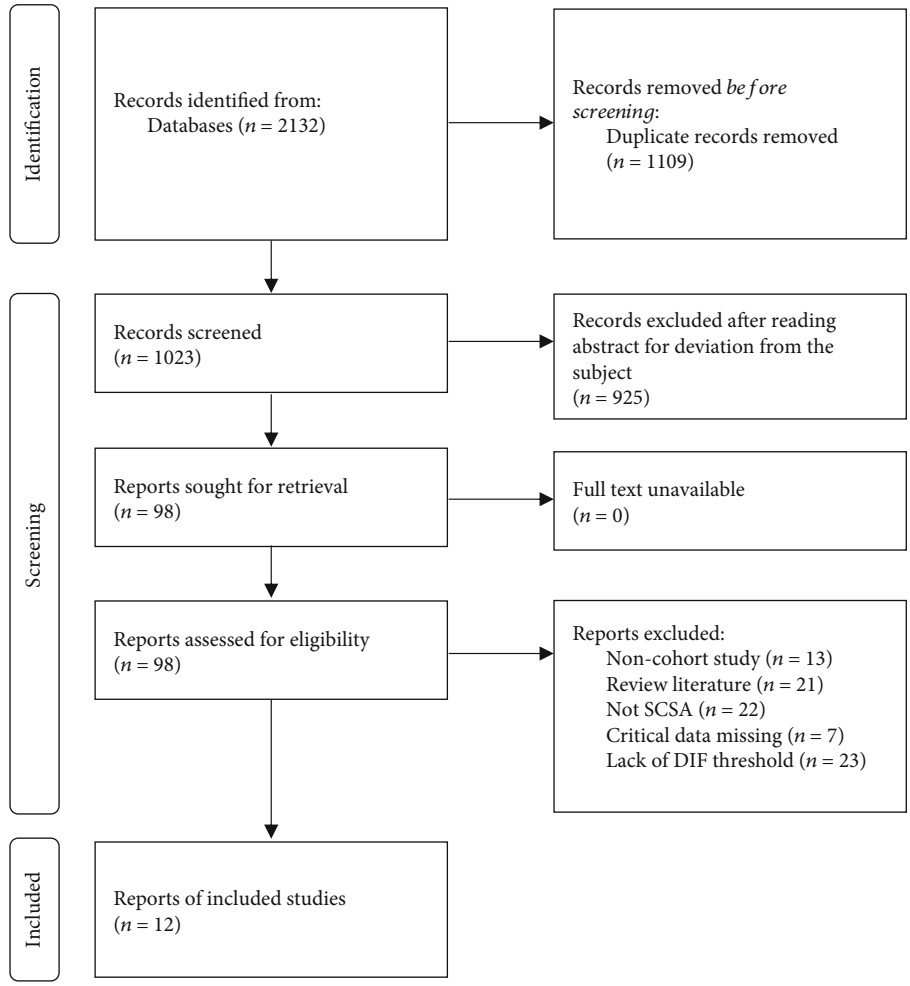

Figure 1: Document screening process and results.

Table 1: Basic characteristics of included literature.

Author/year	Research type	ART	DFI detection method	DFI threshold	Outcome indicators	Quality score
Bungum [9]	Cohort study	ICSI and IVF	SCSA	27%	①②③④⑤⑥	8
Zini [16]	Cohort study	ICSI	SCSA	15% and 30%	⑤	8
Boe-Hansen [6]	Retrospective cohort study	ICSI and IVF	SCSA	27%	④⑤	6
Bungum [8]	Prospective cohort study	ICSI and IVF	SCSA	30%	①②③④⑤⑥	8
Miciński [12]	Prospective cohort study	ICSI	SCSA	15%	⑤	5
Speyer [14]	Cohort study	ICSI and IVF	SCSA	30%IVF 19% ICSI	①②④⑤	8
Niu [13]	Prospective cohort study	IVF	SCSA	27%	①②③	8
Bradley [7]	Retrospective cohort study	ICSI	SCSA	29%	④⑤⑥	9
Gat [10]	Retrospective cohort study	ICSI	SCSA	<15% and>30%	⑤	8
Yang [15]	Retrospective cohort study	ICSI and IVF	SCSA	15% and 30%	②⑤	8
Green [11]	Prospective cohort study	ICSI	SCSA	15%	①②	10
Jiang [17]	Prospective cohort study	ICSI and IVF	SCSA	30%	①⑤	8

① IVF fertilization rate, ② IVF pregnancy rate, ③ IVF live birth rate, ④ ICSI fertilization rate, ⑤ ICSI pregnancy rate, and ⑥ ICSI live birth rate.

and ICSI fertilization rate, pregnancy rate, and live birth rate were RR = 0.79 (95% CI: 0.52-1.18, $P = 0.25$, Figure 5), RR = 0.90 (95% CI: 0.76-1.07, $P = 0.24$, Figure 6), and RR = 0.89 (95% CI: 0.70-1.14, $P = 0.36$, Figure 7), respectively.

3.3.3. Publication Bias Analysis. Funnel plots were drawn for the study groups with ≥5 included literatures. The results showed that the included literatures were distributed symmetrically around the combined effect RR value, suggesting no

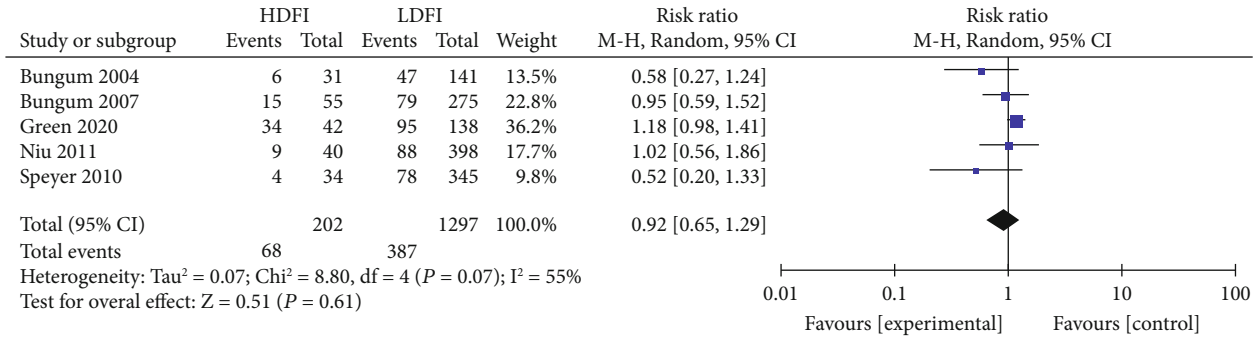

Figure 2: Correlation between DFI and IVF fertilization rate.

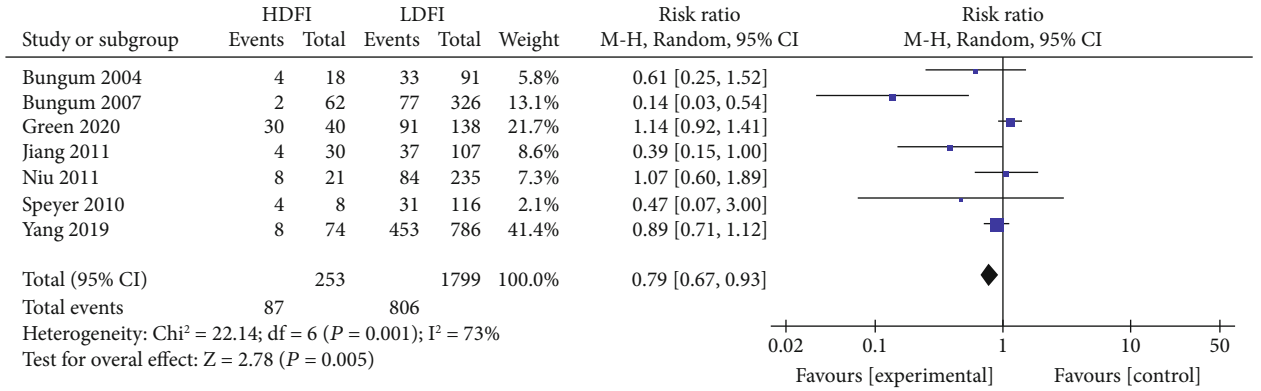

Figure 3: Correlation between DFI and IVF pregnancy rate.

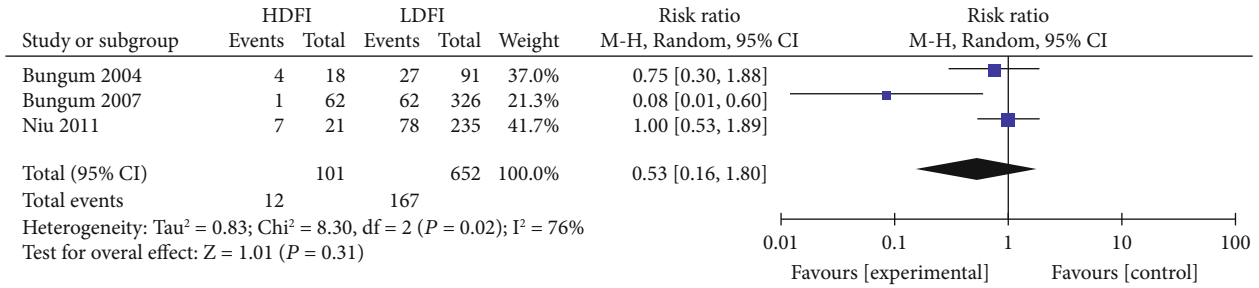

Figure 4: Correlation between DFI and IVF live birth rate.

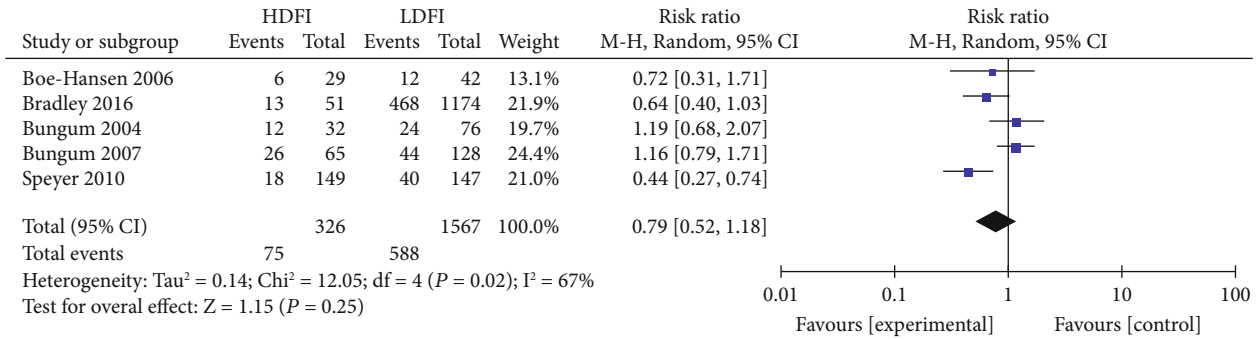

Figure 5: Correlation between DFI and ICSI fertilization rate.

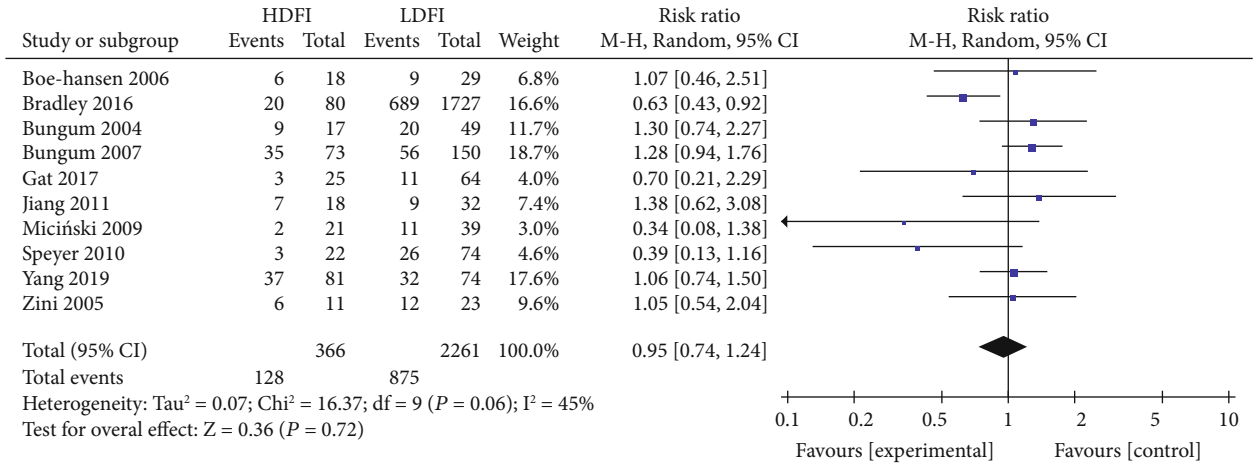

Figure 6: Correlation between DFI and ICSI pregnancy rate.

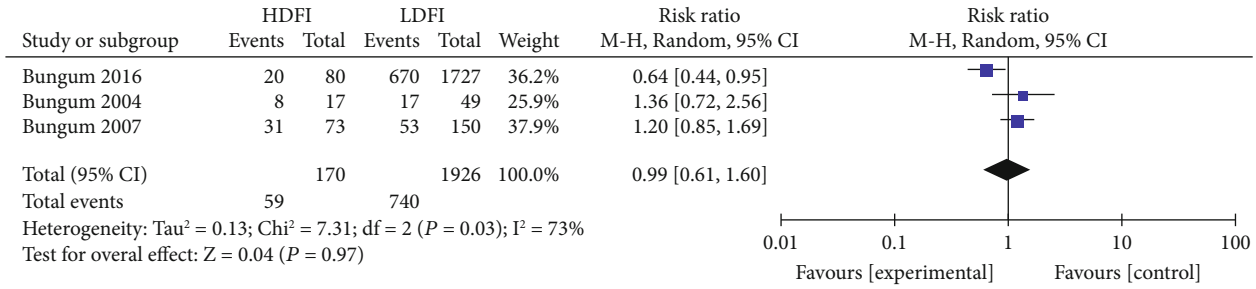

Figure 7: Correlation between DFI and ICSI live birth rate.

significant publication bias ($P > 0.05$), as shown in Figures 8–11. Similarly, Egger's test performed for groups with <5 included articles also showed no publication bias ($P > 0.05$).

4. Discussion

Currently, studies that analyzed the relationship between sperm DNA damage and clinical outcomes following IVF and intracytoplasmic sperm injection reported inconsistent findings. There is still ongoing controversy regarding the impact of DNA loss on ART results. Some studies [18, 19] have suggested that sperm DNA integrity affects the success rate of clinical pregnancy by influencing fertilization and embryonic development. A retrospective cohort study conducted by Boe-Hansen et al. [6] in 2006 showed that the clinical pregnancy rate in IVF decreased in the presence of severe DNA damage. In comparison, other studies [20, 21] reported no correlation between DFI and IVF outcomes. For instance, studies by Niu et al. [13] have demonstrated that the DFI index had no significant influences on IVF fertilization rate, clinical pregnancy rate, or delivery rate, and high DNA fragmentation was only related to low embryo quality. Although a high degree of DNA fragmentation does not necessarily affect fertilization rates, once the embryonic genome is activated, the consequences of damaged paternal DNA can manifest possibly triggering apoptosis, leading to early postimplantation miscarriage [22]. DFI values in some spontaneous abortion groups seem to support this hypothesis, but there is some debate about the effect of DFI on ICIS. Some scientists believe that sperm DNA integrity will affect the clinical outcome of ICIS. Miciński et al. [12] indicated that sperm DNA fragmentation might be related to the pregnancy rate after ICSI. Speyer et al. [14] observed that when DNA fragmentation increased, the fertilization rate in the ICSI cycle would decrease correspondingly. Moreover, unfavorable clinical outcomes in terms of fertilization rate, pregnancy rate, and live birth rate in patients with high levels of sperm DNA fragmentation were also reported [7]. Others, however, have suggested that DNA integrity had no impact on the clinical outcome of ICIS. For example, the retrospective cohort study conducted by Yang et al. [15] in 2019 illustrated no significant differences in fertilization, embryo quality, pregnancy rate, or abortion in ICSI related to DNA damage. The prospective cohort study conducted by Green et al. [11] in 2020 also reached a similar conclusion. Despite numerous studies discussing the relationship between DFI and pregnancy rates [23–25], sperm chromatin testing as part of the assessment of male fertility potential is still not widely accepted. The reasons for this are many, chiefly the lack of standardized protocols for reproducible results and the fact that thresholds in many trials have not been validated. Furthermore, the limitations of our understanding of the underlying nature of DFI and the lack of sufficient data demonstrate the relationship between DFI and reproductive outcomes after IVF and/or ICSI.

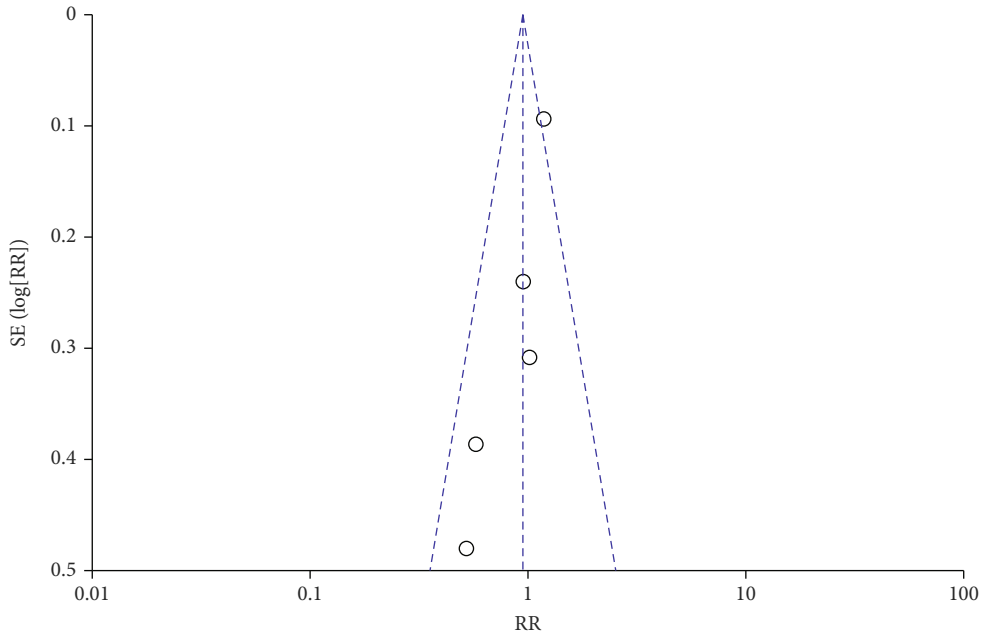

Figure 8: Funnel diagram of the correlation between DFI and IVF fertilization rate.

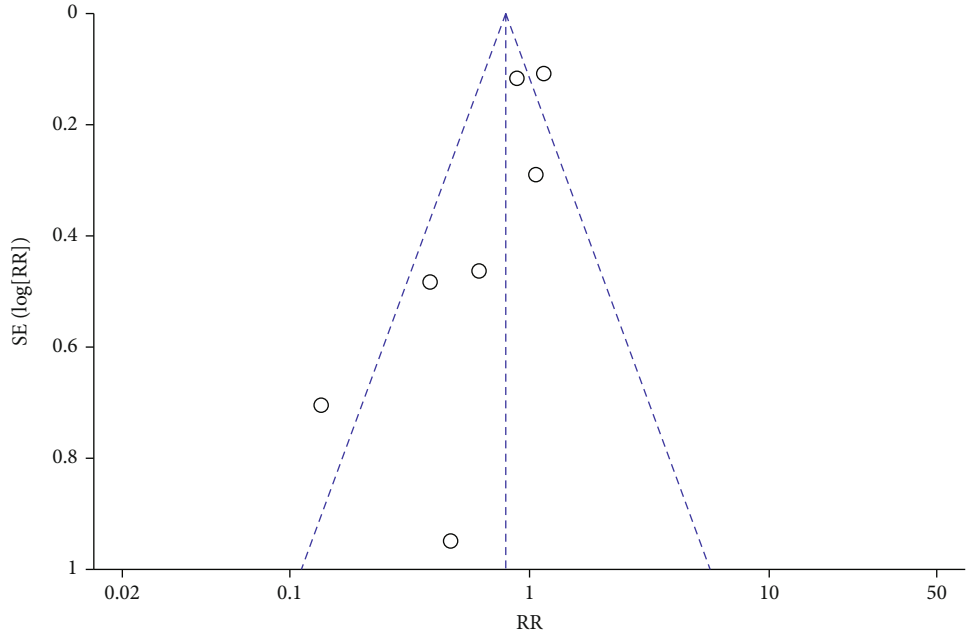

Figure 9: Funnel diagram of the correlation between DFI and IVF pregnancy rate.

The 12 literatures were included in this meta-analysis. The overall quality is high, and the selectivity bias is limited. At present, SCSA is considered to be the "gold standard" for sperm DNA integrity detection, which was adopted as the criteria for inclusion. The heterogeneity test results of the included studies showed heterogeneity in parameters except for the ICSI pregnancy rate, for which the fixed effects model was used for analysis. The meta-analysis results illustrated that the IVF fertilization rate, pregnancy rate, and live birth rate of high DIF were statistically insignificant with those in the IVF group. Differences regarding IVF fertilization rate, pregnancy rate, and live birth rate in the ICSI group were also insignificant. Therefore, this study showed that sperm DNA fragments did not significantly correlate with IVF/ICSI fertilization rate, pregnancy rate, and live birth rate.

This study suffered from several limitations. First, because the included literature included men and women with assisted reproductive age between 30 and 35 years of age, age-considered subgroup analyses were not considered. Secondly, the fact that only studies using SCSA for DFI

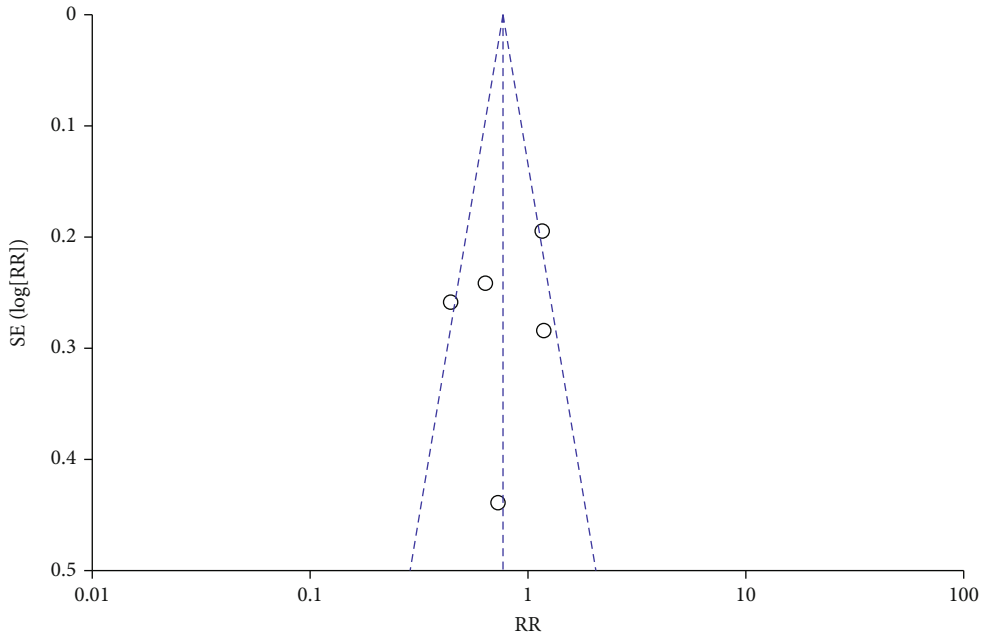

Figure 10: Funnel diagram of the correlation between DFI and ICSI fertilization rate.

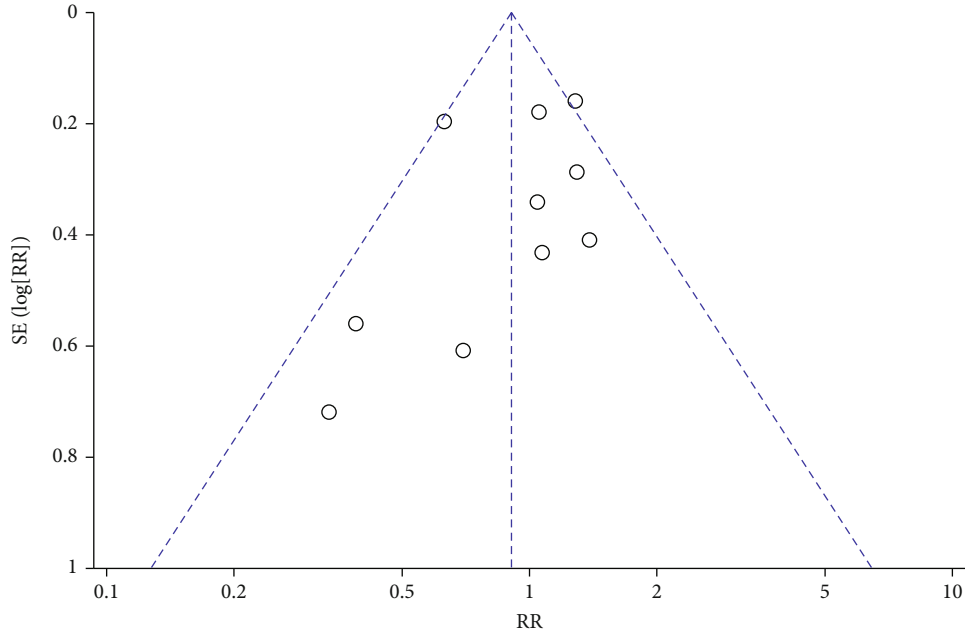

Figure 11: Funnel diagram of a correlation between DFI and ICSI pregnancy rate.

detection was included may introduce biases that might not reflect the impact of the overall DNA fragment index on assisted reproductive outcomes. This study concluded that no differences were observed in sperm DFI in assisted reproductive outcomes. Although the threshold between high DFI and low DFI is concentrated at 15%-30%, this range is relatively large, and multiple groups of DFI can be analyzed. In addition, SCD and TUNEL are other methods to detect sperm chromatin integrity.

In conclusion, consistent with the newly released guidelines related to DNA fragment detection [26], this study observed no significant correlation between sperm DFI and assisted reproductive outcomes. Multicenter and large sample clinical trials should to be carried out to conclusively determine the impact of DNA damage on assisted reproductive outcomes.

Data Availability

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

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Yue Chen and Wei Li contributed equally to this work.

Acknowledgments

This work was supported by the Liaoning Province Science and Technology Project (No. 2021JH2/10300085).

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 9178302, 10 pages
https://doi.org/10.1155/2022/9178302

Research Article

Moth-Flame Optimization for Early Prediction of Heart Diseases

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Received 15 June 2022; Revised 16 July 2022; Accepted 18 August 2022; Published 12 September 2022

Academic Editor: Xi Lou

Heart disease is among the leading causes of mortality globally. Predicting cardiovascular disease is a major difficulty in clinical data analysis. AI has been demonstrated to be powerful in deciding and anticipating an enormous measure of information created by the health domain. We provide a unique method for finding essential traits employing machine learning approaches in this paper, which enhances the effectiveness of identifying heart diseases. Decision tree (DT), support vector machine (SVM), artificial neural network (ANN), and K-nearest neighbor (KNN) are the classification techniques used to create the proposed system. Ensemble stacking integrates the four classification models to create a single best-fit predictive model using logistic regression. Many explorations have been directed at the identification of cardiac infection; however, the exactness of the outcomes is poor. Accordingly, to further enhance the efficiency, Moth-Flame Optimization (MFO) algorithm is proposed. The feature selection strategies are used to improve the classification accuracy while shortening the execution time of the classification system. Medical data are used to assess the probability of heart disease based on BP, age, gender, chest ache, cholesterol, blood sugar, and other variables. Results revealed that the proposed system excelled other existing models, obtaining 99% accuracy in the Cleveland dataset.

1. Introduction

Heart disease refers to a group of illnesses that affect people's hearts and veins. The symptoms of cardiac disease differ from person to person [1]. Cardiac disease alludes to a bunch of issues characterized by side effects, for example, hypertension, stroke, respiratory failure, and arrhythmia. The trouble for medical services suppliers is to give top notch care at a reasonable cost. Inadequate outcomes may result from an inaccurate clinical diagnosis and poor therapy. Detecting and diagnosing cardiovascular illness is a never-ending task that can be accomplished by a skilled practitioner with significant experience and understanding [2]. Decision support systems (DSSs) may be used by healthcare organizations to cut costs [3]. Patient records, various disease diagnoses, resource management, and other aspects of healthcare are common.

There has been a lot of work put into establishing remote monitoring gadgets and processes for diagnosing patients. Device exhaustion, then again, has been viewed as a hindrance to adherence [4]. Commercially accessible technologies have been exhibited to conquer this boundary by lessening the necessity for human contact [5], and the precision of action trackers has been shown to be adequate for health workers [6]. Clinical records are continually being produced, processed, and evaluated as a result of the advent of information technology systems. Clinical reports contain data that could be utilized to develop new healthcare services around the world, addressing issues such as social and economic status. Clinical reports, for example, contain a variety of numerical data, medical descriptions, images, etc. All of which can be used to create content-based services to help patients and doctors.

Rapid cardiovascular disease diagnosis of high-risk patients and faster detection using a prediction system has been widely proposed to reduce mortality rates and improve selection for future diagnosis and interventions [7]. A decision support system (DSS) framework may be utilized to assist clinicians in assessing the chance of cardiovascular problems and providing suitable medicines to further prevent the occurrence. Moreover, several studies have indicated that adopting a DSS can enhance preventive services, treatment planning, and better decision-making [8]. An expert DSS based on machine learning (ML) model and metaheuristics approach is used to efficiently identify heart disease.

The ML prescient models need legitimate information for preparing and testing. ML is now being utilized in hospitals to aid in the organization of administrative procedures, the planning and management of infectious diseases, and the customization of medical treatments [9]. Besides, the machine is presently utilized in an assortment of heart-related disciplines, as well as the improvement of new medical operations, the control of patient information and records, and the therapy of persistent illnesses [10, 11].

Supervised method [12] is an ML approach that predicts future data by mapping data flow based on labeled training information. The goal of this approach is aimed at creating a model and then improving the machine's performance as it is exposed to new data. Unsupervised learning technique is an ML method in which the system is given an unlabeled dataset and is required to uncover relationships within the data. Unsupervised learning is aimed at grouping data together and detecting existing patterns. Reinforcement learning algorithm uses trial and error to uncover the pattern or relationship within the data. An agent who makes decisions, the environment in which the agent interacts, and the actions that the agent must complete are the three key components involved. This algorithm's purpose is to discover the optimum policy based on experience to make reliable decisions.

Data mining and machine learning (ML) approaches minimize computer costs and time. One use of ML is the detection of medical disorders and therapies to enhance a patient's quality of life. Heart disease is commonly thought to be a condition that only affects the elderly; nevertheless, it is growing more common in people of all ages.

Information preprocessing is expected for information standardization to further develop ML models' expectation capacities. Preprocessing techniques such as noisy data removal and normalization are carried out. Model performance is also improved by feature extraction and selection strategies. Feature selection is performed using Moth-Flame Optimization technique and feature extraction using principal component analysis. Furthermore, classification is performed using four models, namely, DT, SVM, ANN, and KNN. Ensemble stacking is performed to combine the results from four classification models using logistic regression. The proposed system's result is evaluated using several metrics such as accuracy, precision, recall, and F-measure.

The main contributions of this research include the following:

(i) An automated system is designed to classify the dataset using Cleveland dataset

(ii) Feature selection is performed using Moth-Flame Optimization algorithm that helps in removing unwanted features present in the dataset

(iii) Feature extraction is carried out using principal component analysis (PCA) that helps in reducing the dimensionality of the dataset further

(iv) Classification is performed using four different models, and the best results are obtained using the ensemble stacking method

(v) The system outperforms the existing state-of-art systems concerning accuracy, precision, recall, and F-measure

The following shows the breakdown of this intended work. Section 2 goes into detail on the work related to the planned task. Section 3 goes into detail about the proposed framework. The fourth section digs into the specifics of experimental outcomes and performance evaluation. Section 5 discusses the conclusion as well as future efforts.

2. Literature Works

Researchers have proposed several ML-based diagnostic methodologies for HD. ML algorithms [13, 14] have been extensively utilized in a variety of research such as disease recognition and identification [15]. Gudadhe et al. [16] used multilayer perceptron and SVM to create a detection approach for heart disease (HD) categorization, which achieved an efficiency of 81%. Detrano et al. [17] used ML classification techniques to construct the HD classification system, which had 77 percent accuracy.

Al-Makhadmeh and Tolba [18] introduced a deep belief neural network model-based IoT-based heart disease identification system. The collected data was examined for missing values. The writers looked at how the data was distributed. The authors also employed the studentized approach to use normalized data. Deep belief networks and a high-order Boltzmann machine were used to extract features from noiseless data to be used by the model. The researchers achieved a prediction accuracy of 99.03, which can aid in the reduction of heart disease mortality. Ahmed [19] proposed an HD identification algorithm employing IoT architecture with SVM. To forecast heart disease, the patient data was analyzed using an SVM. The researchers claim that their method predicted cardiac disease with 97.53 percent accuracy. Using an IoT device, they acquired heart data and identified HD. This method detected HD in a short period of time, but the accuracy suffered when a large amount of data was used [20].

Guidi et al. [21] helped to create a DSS for heart failure analysis (HF). They investigated the effectiveness of neural networks (NN), SVM, CART-based fuzzy rules, and random forests, among other ML classifiers (RF). The CART model with random forests produced the best results, with an accuracy of 87.6 percent. Parthiban and Srivatsa [22] explored an SVM approach for detecting HD in diabetic patients with an efficiency of 95%.

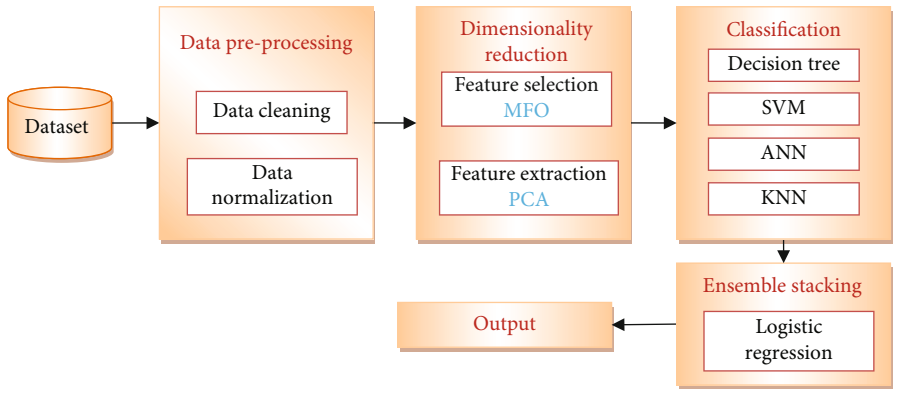

Figure 1: Schematic diagram of proposed system.

Melillo et al. [23] led to the formation of an automated classification model that differentiates between those at low and high risk. The sensitivity and specificity of the classification and regression tree (CART) were calculated to be 93.3 percent and 63.5 percent, respectively. To reduce the number of features, Sewak et al. [24] employed a binary classifier that correctly identified heart disease with a 100% improvement in accuracy. Various techniques are available for feature selection [25, 26]. PCA [27, 28] has been employed as a feature retrieval strategy for categorization in healthcare services in recent research.

Classification is performed using Cleveland dataset [29] to identify if a patient had heart disease or not. The ML algorithms combined with feature extraction have three major goals: (i) to discover the unique features, (ii) evaluate the efficiency of PCA, and (iii) investigate the model that produces better results.

3. Proposed Methodology

This section describes the proposed system and its components in detail. Figure 1 depicts the proposed system's schematic diagram.

3.1. Materials. In this research, the Cleveland dataset is used. There were 303 occurrences and 75 features when this dataset was designed. We preprocessed the dataset in this research, and six samples were excluded due to missing values in this dataset.

3.2. Data Preprocessing. Data preparation is a crucial stage in ML that enhances the quality of the data and makes it easier to extract useful knowledge from big data. Data preprocessing is a method of organizing and managing unprocessed data to prepare it for the development and training of ML models. Data cleaning is the process of eliminating erroneous, missing, and inconsistent data from databases as well as restoring missing data. After 6 samples with missing values are discarded, the remaining samples are processed. The absence and the presence of HD are portrayed by a solitary result marked with two classes. After missing values are eliminated, the data should be normalized well within the range from 0 to 1 to make evaluating heart disease trends easier. The studentized residual methodology is a standard deviation computation-based normalizing method [30]. To standardize the data for HD prediction, several data distributions and regression analysis are employed.

3.3. Dimensionality Reduction. The process of lowering the variables analyzed is known as dimensionality reduction [31]. It is employed to retrieve hidden characteristics within the unprocessed without sacrificing the integrity. This work incorporates 2 methods: the Moth-Flame Optimization (MFO) [32] for feature selection and the principal component analysis (PCA) for feature extraction [33].

3.3.1. Feature Selection by Moth-Flame Optimization (MFO) Algorithm. MFO is an optimization approach focused on moths' use of transverse orientation to travel at night. Moths may fly greater ranges in a linear fashion by keeping a constant alignment towards the Moon. When moths come into touch with ambient light, they strive to maintain the same angle towards the light source, but the close closeness causes them to become entangled in a spiral route.

The MFO method distributes moths to various alternatives in the optimization problem's solution space, within each fitness function. Every moth carries a flame containing the optimal solution the moth has discovered. The moths fly in a circular route around their flames, changing their locations in each iteration as they explore the solution space. In MFO, moth positions are randomly set inside the solution space. The moths' fitness values are calculated. Each moth's best individual location is identified by the flame. The flame identifies the ideal location for every moth. The moths' locations are improved using a spiral movement algorithm nearing their best individual positions highlighted by a flame in the following iteration, and the flames' locations are replaced with new optimum and most consistent locations. Until the termination requirements are reached, the MFO algorithm keeps updating and generating new positions for the moths and flames.

The following is the computing procedure for MFO:

Step 1 (creating the preliminary population). Each moth is considered to occupy a P-dimensional solution space. The

Step 1. Decide on the number of neighbours (K).
Step 2. Determine the Euclidean distance between K neighbours.
Step 3. Using the obtained Euclidean distance, find the K closest neighbours.
Step 4. Count the number of data points in each group among these K neighbours.
Step 5. Assign the new data points to the group among with the greatest number neighbours.
Step 6. We have completed our model.

Algorithm 1: Algorithm of KNN.

Table 1: Cleveland dataset used for the proposed system.

Name	Cleveland
Total # of instances	303
Number of attributes	75
Omitted values	Yes
Dataset type	Multivariate
Attribute type	Categorical, integer, real
Tasks performed	Classification

collection of moths might be written as

$$N = \begin{bmatrix} N_{1,1} & \cdots & N_{1,p} \\ N_{2,1} & \cdots & N_{2,p} \\ \vdots & \ddots & \vdots \\ N_{m,1} & \cdots & N_{m,p} \end{bmatrix}, \quad (1)$$

where m denotes the moth and p denotes the dimensions. The fitness function is given by

$$F = \begin{bmatrix} f_1 \\ f_2 \\ \vdots \\ f_m \end{bmatrix}. \quad (2)$$

Two components of the MFO include flames and their respective fitness functions as shown below:

$$FM = \begin{bmatrix} FM_{1,1} & \cdots & FM_{1,p} \\ FM_{2,1} & \cdots & FM_{2,p} \\ \vdots & \ddots & \vdots \\ FM_{m,1} & \cdots & FM_{m,p} \end{bmatrix}, \quad \text{OF} = \begin{bmatrix} \text{of}_1 \\ \text{of}_2 \\ \vdots \\ \text{of}_m \end{bmatrix}. \quad (3)$$

In MFO, moths seek the optimum solution in each iteration, with flames depicting the optimum solution discovered. Location of the flame is then restructured.

Step 2 (positions of the moths are being updated). MFO employs three functions to setup the moths' random placements (R), optimal solution (S), and stop process (T):

$$\text{MFO} = (R, S, T). \quad (4)$$

To setup the moths' location in the optimal position, any random distribution can be utilized. The R function's implementation can be written as

$$N(A, B) = (\text{up}(A) - \text{lo}(B)) * \text{rand}\ () + \text{lo}(A), \quad (5)$$

where up and lo are arrays that determine the upper limit and lower limit of the function, respectively. The direction of moths in the optimal position is described using a logarithmic function that is susceptible to the conditions listed as follows:

(i) The initial point of the spiral should be the moth

(ii) The location of the flame should represent the spiral's ultimate point

(iii) The spiral's reach should not vary more than the problem space

As a result, the S represents the movement as shown as follows:

$$S(N_A, FM_B) = D_A.e^{ct}.\cos(2\pi t) + FM_B, \quad (6)$$

where c is a constant used to establish the logarithmic shape, t is a random value between 1 and -1, and D_A is the length.

$$D_A = |FM_B - N_A|. \quad (7)$$

The spiral path of the moth encircling the flame assures that the optimal solution is explored and utilized. Each cycle sorts the ideal solution (flames) to keep the moths from being stuck in local optima, and it hovers surrounding its associated flame using OF and OM matrix.

Step 3 (flame update). Equation (8) would be used to reduce the number of flames in the MFO algorithm, resulting in the moths solely circling around the optimal solution in the

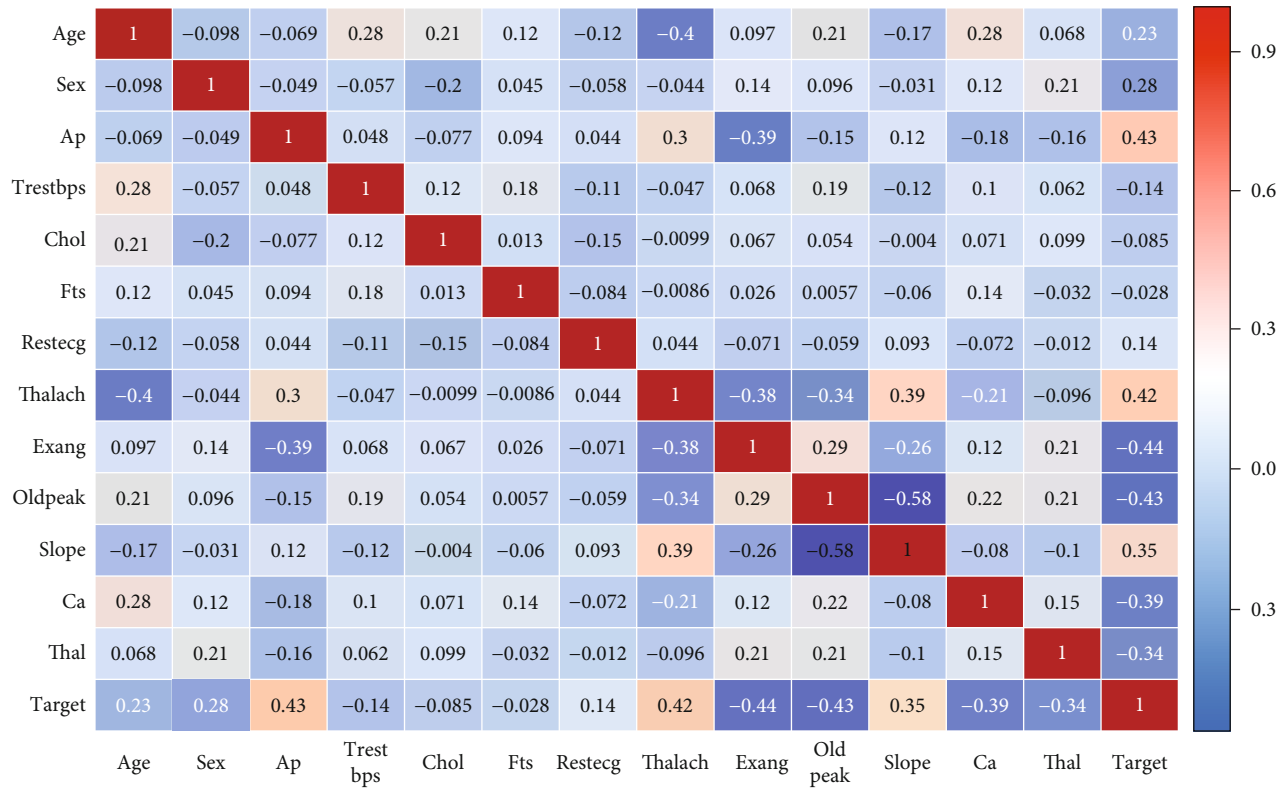

Figure 2: Heat map of Cleveland dataset.

Table 2: Instances in the dataset after preprocessing.

Name	Instances present	With HD	Without HD
Cleveland	283	157 (55%)	126 (45%)

method's final phase.

$$\text{Flame Number} = \text{round}\left(\text{Max} - \text{Cur} * \frac{\text{Max} - \text{Cur}}{\text{Iter}}\right), \quad (8)$$

where Cur stands for the existing number of epochs, Max stands for the highest number of flames, and Iter stands for the number of iterations. The solution space developments are balanced by reducing the number of flames.

Step 4 (termination condition). The termination criterion decides when the algorithm should be stopped. The choice of a good termination criterion is critical for the algorithm's correct convergence. The MFO is frequently terminated based on the number of repetitions, the amount of improved performance, and the length of time it has been running.

3.3.2. Feature Extraction by Principal Component Analysis (PCA). We use the eigenvalue-one criterion to identify the number of meaningful components to keep in the analysis. We were able to keep all components with an eigenvalue larger than 1 as a result of this. As an independent variable, each element accounts for one unit of variation. As a result, components having an eigenvalue larger than one accounted for higher variance compared to individual contributions. Components having eigenvalues less than 1, on the other hand, delivered lesser than the individual and were eliminated.

3.4. Classification. The proposed research's subsequent phase is classification. A class label is forecasted for a particular example of input data in classification, which is a predictive modeling (PM) job in ML. PM design is the method of estimating the feature representation from discrete input parameters to discrete independent variables. The primary purpose is to determine which group the additional knowledge corresponds to. There are four classification algorithms incorporated in the proposed research that includes decision tree, SVM, ANN, and KNN.

3.4.1. Decision Tree (DT). DT is a visual representation of decision taking using an algorithm. A DT is created by asking a yes/no question and then breaking the answer into two parts to lead to another decision. The question is at the node, and the decisions that follow are at the leaves. It may be used to tackle classification and regression problems.

3.4.2. Support Vector Machine (SVM). SVM is a regulated ML methodology that can tackle classification and regression issues. It may also be utilized to address categorization challenges. Each piece of data is represented as a locus in geometry, without the value of each attribute representing the algorithm's value of a single locus. The categorization is then accomplished by determining the hyperplane that

Table 3: Experimental results of preprocessing technique.

S. no	Method	Precision (%)	Recall (%)	*F*-measure (%)	Accuracy (%)
1	No preprocessing	80	80	81	79
2	Noise removal	82	80	86	85
3	Normalization using min-max	86	84	80	87
4	Normalization using *Z*-score	87	85	86	86
5	Combining 2, 3, and 4	90	89	89	91

Table 4: Experimental results of feature selection approach.

S. no	Methodology	Precision (%)	Recall (%)	*F*-measure (%)	Accuracy (%)
1	Genetic algorithm	82	81	76	81
2	Particle swarm optimization	87	86	84	89
3	Moth-Flame Optimization	90	87	87	91

Table 5: Experimental results of feature extraction approach.

S. no	Methodology	Precision (%)	Recall (%)	*F*-measure (%)	Accuracy (%)
1	Linear discriminant analysis (LDA)	81	79	73	80
2	Nonnegative matrix factorization (NMF)	80	83	84	85
3	Principal component analysis (PCA)	90	86	87	90

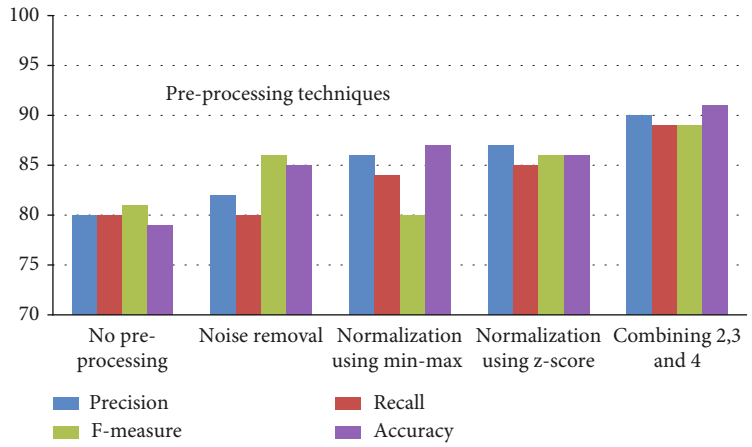

Figure 3: Comparison of preprocessing techniques.

Table 6: Experimental results of classification approach.

S. no	Methodology	Precision (%)	Recall (%)	*F*-measure (%)	Accuracy (%)
1	DT	94	95	98	98
2	SVM	96	98	98	99
3	ANN	98	94	97	98
4	KNN	97	97	98	96
5	Ensemble stacking	98	98	99	99

clearly differentiates the 2 groups. An SVM model in high-dimensional space is simply a representation of different groups in a hyperplane. To decrease the error, SVM will create the hyperplane progressively. The goal of SVM is to divide the datasets into groups such that a maximal marginal hyperplane may be identified (MMH). Using these support vectors, we optimize the classifier's margin. If the support vectors are removed, the location of the hyperplane will change.

3.4.3. Artificial Neural Network (ANN). ANNs are a crude model of how the human brain learns. Neurons, which are in charge of layer generation, make up an ANN. These neurons are also known as tuned factors. The result of each layer is forwarded on to the subsequent layer. Every layer has its own nonlinear activation function, which helps with the process of learning and producing the result. Terminal neurons are another name for the output layer. Each epoch, the

Table 7: Evaluation with other existing studies.

S. no	Approaches	Precision (%)	Recall (%)	*F*-measure (%)	Accuracy (%)
1	Miao et al. [40]	81	71	80	80
2	Naidu and Rajendra [41]	80	85	82	85
3	Shamosollahi et al. [42]	92	90	90	92
4	Hungarian dataset	93	91	95	94
5	Proposed method (Cleveland dataset)	98	98	99	99

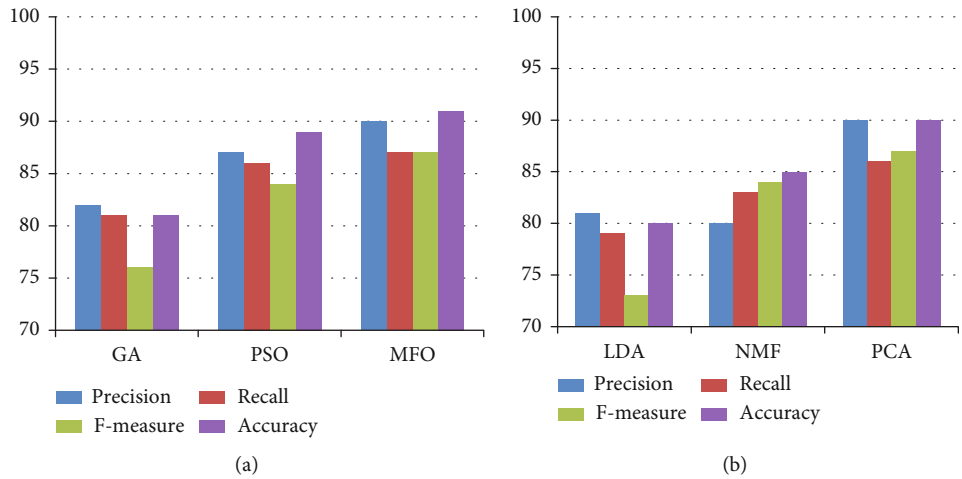

Figure 4: Comparison of (a) feature selection techniques and (b) feature extraction technique.

weights connected to the neurons and responsible for overall prediction are modified. Various optimizers are incorporated to increase the learning process. Every ANN has objective function that decreases as learning progresses. The best weights for which the cost function gives the best outcomes are then used.

3.4.4. K-Nearest Neighbor (KNN). KNN is a simplistic, convenient solution for dealing with classification and regression tasks. The KNN technique ensures that the newest scenario and existing scenarios are identical and places the new case in the group that is most close to the original group. KNN is discussed below.

3.5. Ensemble Stacking

3.5.1. Stacking. Ensemble learning is a machine learning terminology in which several models are trained to handle the same problem and then integrated to improve results. The main idea is that by correctly combining weak models, we can get more accurate and/or resilient results. A single method may not be able to deliver the best estimate for a given dataset. ML algorithms have limitations, and it is difficult to create a high-accuracy model. The total precision might be enhanced by developing and combining many models. Integrating the results of each system achieves reduced error while keeping generality. This sort of aggregate may be implemented in a variety of ways. Meta-algorithms are a term used in some textbooks to describe such designs.

Stacking is an ML approach used in ensembles. Using a metalearning strategy, it learns how to merge the predictions from two or more ML algorithms. Stacking has the benefit of integrating the characteristics of many high-performing systems to provide predictions that surpass any single model in composition of a classification or regression task.

3.5.2. Logistic Regression. A method for evaluating the probability of a finite result given independent variables is known as logistic regression. A binary outcome is incorporated in the majority common logistic regression methods. To model scenarios with more than 2 distinct outcomes, multinomial logistic regression can be employed. Logistic regression is a powerful statistical method for determining if a fresh data matches well inside a group. Because cyber security components, like threat detection, are categorization issues, logistic regression is a useful analysis technique.

4. Results and Discussion

The Cleveland dataset is used to run the proposed architecture. It performs classification using the following steps, namely, preprocessing, feature selection using MFO, feature extraction using PCA, and classification using decision tree, SVM, ANN, and KNN, followed by ensemble staking using logistic regression. The proposed system achieves higher accuracy with reduced computation.

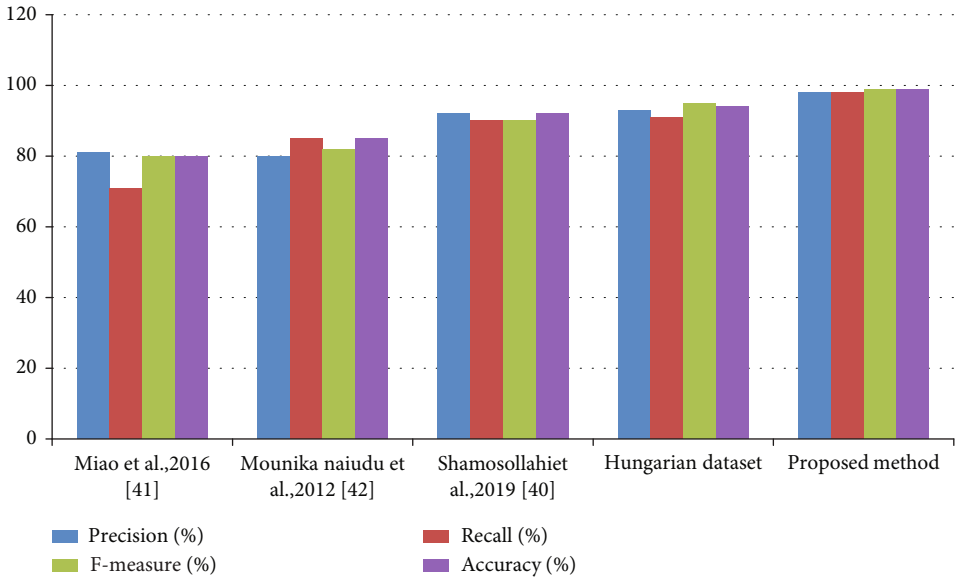

Figure 5: Comparison of various state-of-art methods.

Table 1 shows the description of Cleveland dataset. A heat map helps in visualizing the data present in the dataset. Figure 2 represents the heat map for Cleveland dataset. Table 2 represents the instances in the dataset after preprocessing.

For the proposed research, the datasets are divided into two halves: (1) a training part with 70% of the information and (2) a testing part with 30% of the information. Four performance metrics, namely, accuracy, precision, recall, and F-measure, are considered in the proposed research. The accuracy rate is obtained through dividing the number of accurate classifications by the total number of classes in the dataset. It is represented in

$$\text{Accuracy} = \frac{\text{Num of correct classes identified}}{\text{Total Num of classes}}. \quad (9)$$

Precision, recall, and F-measure are estimated using the following equations:

$$\text{Precision} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}} \times 100, \quad (10)$$

$$\text{Recall} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}} \times 100, \quad (11)$$

$$\text{F-Measure} = 2 \times \frac{\text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \times 100. \quad (12)$$

Accuracy, precision, recall, and F-measure should improve over period. Table 3 shows the research findings without preprocessing and with preprocessing technique like noise removal by removing missing values, normalization using min-max, normalization using Z-score, and combined results. Various metaheuristic algorithms are applied for various applications [34–39]. Table 4 displays the results of experimentation using several feature selection strategies such as the genetic algorithm, particle swarm optimization, and Moth-Flame Optimization. The proposed method using MFO achieves the best result when compared with other techniques. Table 5 displays the results of the experiment of several feature extraction strategies, with the PCA employed in the proposed method producing the best results in comparison with other approaches. Figure 3 depicts a comparison of preprocessing methods.

Table 6 shows the experimental classification approaches like DT, SVM, ANN, and KNN. The result after applying ensemble stacking using logistic regression produces the best results than applying individual models. When compared to previous strategies, the current technique employing MFO delivers superior results.

Table 7 shows the result of comparison of the proposed method with various existing techniques. Figure 4 shows the comparison with various feature selection and feature extraction techniques. Figure 5 shows the comparison with several state-of-art methodologies. The recommended strategies produce superior performance in the aspects of accuracy, precision, recall, and F-measure.

5. Conclusions and Future Work

Many lives are saved to healthcare monitoring and prediction technologies, especially when patients are placed distant. The classifier's objective was to determine whether a patient had cardiovascular disease or not. When system resources must be considered, using all functionalities is not possible. In this work, we utilized dimensionality reduction methods to enhance the original collected data. Classification was performed using decision trees, SVM, ANN, and KNN, and ensemble stacking called logistic regression helped in achieving the best results from the various classification models. Our technology may be used to evaluate large volumes of data and discover the risk variables associated with various diseases in a variety of real-world applications or in other medical diagnoses. We intend to test our strategy

on a larger dataset and analyze a different disease using alternative feature selection strategies. Our key limitation is that the limited sample size makes it difficult to generalize these findings to heart disease. In further work, we intend to expand the dataset to which our method will be used and analyze more diseases using various feature selection methods.

Data Availability

The authors confirm that the data supporting the proposed work are taken from publically available datasets.

Conflicts of Interest

The authors ensure that there is no conflict of interest in this proposed work.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 8315519, 10 pages
https://doi.org/10.1155/2022/8315519

Research Article

The Effect of Serum β-Human Chorionic Gonadotropin on Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

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Received 11 July 2022; Revised 20 August 2022; Accepted 26 August 2022; Published 9 September 2022

Academic Editor: Xi Lou

Background. The relationship among elevated serum β-human chorionic gonadotropin (β-hCG), the incidence of pregnancy complications, and adverse pregnancy outcomes has been controversial. Differences in study design, subject bias due to demographic characteristics, and differences in local medical levels could contribute to inconsistent results. *Methods*. Literature searches were performed in PubMed, EMBASE, Medline, Central, China National Knowledge Infrastructure (CNKI), Wanfang, and China Science Digital Library (CSDL) databases. Inclusion criteria were as follows: (1) research subjects were singleton pregnant women; (2) the study is identified as cohort study; (3) the subjects were assigned to the high β-hCG group and control group according to whether the exposure factors increased β-hCG in the second trimester; (4) the observed outcomes include at least pregnancy-induced hypertension (PIH), diabetes (gestational diabetes mellitus, GMD), preterm delivery (PD), and intrauterine growth restriction (IUGR); and (5) the odds ratio (OR) and 95% confidence interval (CI) of exposure factors are calculated based on literature dataset. To determine the risk bias of selected literatures, Newcastle-Ottawa scale was applied. The chi-square test was further used for heterogeneity analysis. If heterogeneity was identified, subgroup analyses were then performed for source investigation. *Results*. A total of 13 literatures were included and analyzed, including 67,355 pregnant women and 5980 pregnant women assigned to the high β-HCG group and 61,375 pregnant women to the control group. The incidence of PIH in the high β-HCG group was higher than that in the control group (OR = 2.11, 95% CI [1.90, 2.35], $Z = 13.85$, $P < 0.00001$). There was no heterogeneity among literatures ($\chi^2 = 8.53$, $P = 0.38$, $I^2 = 6\%$), and thus there is no identified publication bias ($P > 0.05$). The incidence of preterm birth in the high β-HCG group was higher than that in the control group (OR = 2.11, 95% CI [1.90, 2.35], $Z = 13.85$, $P < 0.00001$). The analysis suggested no heterogeneity among included literatures ($\chi^2 = 11.78$, $P = 0.11$, $I^2 = 41\%$) and no publication bias ($P > 0.05$). Higher incidence of abortion was observed in the high β-HCG group compared with the control group (OR = 2.80, 95% CI [1.92, 4.09], $Z = 5.32$, $P < 0.00001$). There was no heterogeneity among literatures ($\chi^2 = 3.43$, $P = 0.33$, $I^2 = 13\%$) and no publication bias ($P > 0.05$). The incidence of gestational diabetes was higher in the high β-HCG group than in the control group (OR = 2.15, 95% CI [1.05, 4.40], $Z = 2.09$, $P = 0.04$). Heterogeneity was identified among literatures ($\chi^2 = 47.01$, $P < 0.00001$, $I^2 = 87\%$). Sensitivity analysis showed that the results were not robust, and there was no publication bias ($P > 0.05$). Compared with control, the incidence of IGUR was higher in the high β-HCG group (OR = 2.70, 95% CI [1.75, 4.19], $Z = 4.45$, $P < 0.0001$) with no heterogeneity among literatures ($\chi^2 = 3.92$, $P = 0.14$, $I^2 = 49\%$) and no publication bias ($P > 0.05$). *Conclusion*. High levels of β-hCG during pregnancy in singleton women are associated with a high incidence of pregnancy complications and adverse pregnancy outcomes. Pregnant women with high levels of β-hCG should be monitored more closely, followed up, and given timely medical interventions to reduce the incidence of pregnancy complications and adverse outcomes.

1. Introduction

Common pregnancy complications and adverse pregnancy outcomes, including pregnancy-induced hypertension (PIH), diabetes mellitus (GMD), preterm delivery (PD), intrauterine growth restriction Intrauterine growth restriction (IUGR), and miscarriage, are important causes of increased maternal and perinatal morbidity and mortality [1–3]. In addition, pregnancy complications and adverse pregnancy outcomes increase family burdens and consumption of social medical resources [4, 5]. Due to the variety in the level of medical technology, prevention of complications during pregnancy and safe delivery remains challenging especially in developing countries. Accurate prediction and comprehensive monitoring and follow-ups could contribute significantly in reducing pregnancy complications and adverse pregnancy outcomes [5].

Previous studies identified serum β-human chorionic gonadotropin (β-hCG) as a key parameter associated with the incidence of pregnancy complications and adverse pregnancy outcomes [6–8]. Serum β-hCG is a glycoprotein secreted by placental trophoblast cells [7, 9, 10]. Embryo formation happens after fertilized egg moves into the uterine cavity and implants in matured woman. During the development of fetus, the placental syncytiotrophoblast produce a large amount of HCG which could be excreted into urine through maternal blood circulation. Serum and urine HCG levels rapidly increase from 1 to 2.5 weeks of gestation, peak at the 8th week of pregnancy, decrease to moderate levels by the 4th month of pregnancy, and remain at the end of pregnancy [11, 12]. Serum β-hCG levels can reflect the functional status of the placenta. When placental ischemia and hypoxia happen, the secretion of β-hCG by trophoblast cells increases [13–15]. Placental function is directly related to the occurrence of various diseases during pregnancy and adverse pregnancy outcomes.

However, the correlation of β-hCG and the incidence of pregnancy complications and adverse pregnancy outcomes have been controversial. Some studies suggested that high levels of β-hCG have no significant correlation with the incidence of IUGR, PIH, PD, and GDM [16]. In contrary, other studies concluded that high levels of β-hCG in the second trimester predict a high incidence of complications during pregnancy and poor pregnancy outcomes [17, 18]. Through our meta-analysis, we discovered that the inconsistent results might be caused by different study design, subject bias due to inconsistent demographic characteristics, and difference in medical levels. This study is aimed at elucidating the correlation of high levels of β-hCG on pregnancy complications and adverse pregnancy outcomes through a meta-analysis.

2. Materials and Methods

2.1. Literature Download. Literature searches were performed in PubMed, EMBASE, Medline, Central, China National Knowledge Infrastructure (CNKI), Wanfang, and China Science Digital Library (CSDL) databases. Searching terminology were as follows: β-human chorionic gonadotropin or β-hCG or hCG or human chorionic gonadotropin and pregnancy and adverse outcomes or complications. The languages of the literature are English and Chinese. The retrieval date was July 1, 2022.

2.2. Literature Screening. Inclusion criteria were as follows: (1) research subjects were singleton pregnant women; (2) the study is identified as cohort study; (3) the subjects were assigned to the high β-hCG group and control group according to whether the exposure factors increased β-hCG in the second trimester; (4) the observed outcomes include at least pregnancy-induced hypertension (PIH), diabetes (gestational diabetes mellitus, GMD), preterm delivery (PD), and intrauterine growth restriction (IUGR); and (5) the odds ratio (OR) and 95% confidence interval (CI) of exposure factors are calculated based on literature dataset.

Exclusion criteria were as follows: (1) repeated reports, (2) animal experiments, (3) inconsistent study types, (4) no control group, (5) inconsistent outcome indicators, and (6) incomplete literature data with authors contacted but data not replenished.

2.3. Data Extraction and Literature Risk Bias Assessment. Literature screening was performed by two researchers jointly. Data including author, title, publication time, study type, study number, number of high β-hCG group, number of control group, number of PIH, number of diabetes mellitus, number of intrauterine development, the number of delays, the number of miscarriages, and the number of premature births were extracted from included literatures. Unavailable datasets were obtained by contacting the authors. Two researchers performed the Newcastle-Ottawa Scale (NOS) to assess the risk of bias in the included studies, including the selectivity, comparability, and exposure factors and outcomes of study methods. NOS score ≥ 6 was classified as low risk of bias, otherwise, high risk of bias. During the process of data extraction and risk of literature bias assessment, if there was disagreement between the researchers, consensus was reached through discussion.

2.4. Statistical Methods. Cochrane software RevMan5.3 was used for statistical analysis in this study. The OR value was calculated by the number of cases and the number of cases in the group. Statistical descriptions of effect sizes were performed using OR values and 95% CIs. Heterogeneity was determined using chi-square test. When the degree of freedom corrected $I^2 > 50\%$ or $P < 0.1$, it was considered that there was heterogeneity among the published literatures. Subgroup analysis was used to explore the root cause of heterogeneity. When heterogeneity could not be eliminated, use a random effects model or review only. When the degree of freedom corrected $I^2 \leq 50\%$ and $P \geq 0.1$, it was considered that there was no heterogeneity among the publications, and a fixed effect model was used. Publication bias was assessed using funnel plots and Egger's test. Two-sided $P < 0.05$ indicates statistical significance.

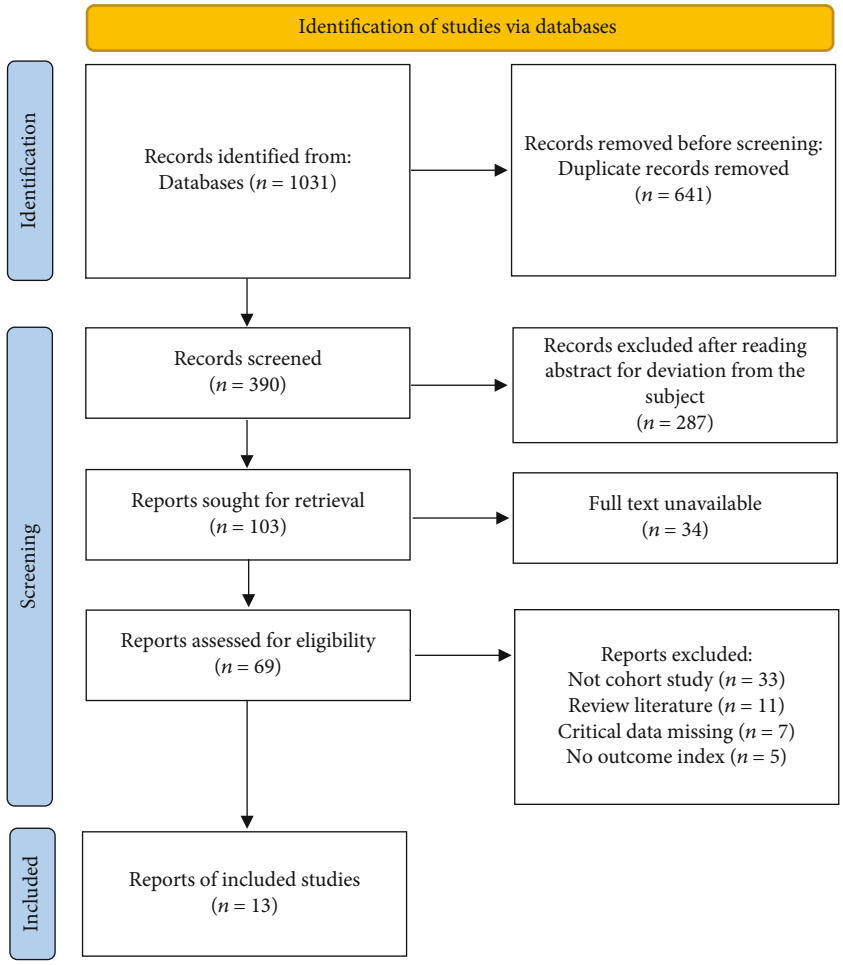

Figure 1: Flowchart of literature screening.

3. Results

3.1. Basic Features of the Included Literature. In this study, a total of 1031 literatures were retrieved from the above databases, 1018 literatures were excluded, and 13 literatures were included for this study [16–28]. The literature screening flowchart was shown in Figure 1. The 13 articles included 67355 pregnant women, among which, 5980 pregnant women were in the high β-hCG group and 61375 pregnant women were in the control group. All included literature information is shown in Table 1. The risk of bias assessment in the literature was shown in Table 2.

3.2. High β-hCG and PIH. A total of 9 studies compared the incidence of PIH between high β-hCG and control groups. No heterogeneity among 9 studies were identified from heterogeneity test ($\chi^2 = 8.53$, $P = 0.38$, $I^2 = 6\%$). Therefore, a fixed-effects model was used for pooling. As shown in Figure 2, the incidence of PIH was suggested to be significantly higher in the high β-hCG group than in the control group (OR = 2.91, 95% CI [2.31, 3.66], $Z = 13.85$, $P < 0.00001$). Egger's test and funnel plot shown in Figure 3 showed that the scatter points were distributed within the confidence interval with a semisymmetrical shape, and no publication bias was found ($P > 0.05$).

3.3. High β-hCG and PD. A total of 8 studies compared the incidence of PD between high β-hCG and control groups. The heterogeneity test confirmed nonheterogeneity among these studies ($\chi^2 = 11.78$, $P = 0.11$, $I^2 = 41\%$). Therefore, a fixed-effects model was used for pooling. Compared to the control group, the analyzed results showed higher incidence of PD in the high β-hCG group (OR = 2.11, 95% CI [1.90, 2.35], $Z = 13.85$, $P < 0.00001$), as shown in Figure 4. Semisymmetrical distribution of scatter points within the confidence interval was observed, as shown in Figure 5, using Egger's test and funnel plot.

3.4. High β-hCG and Abortion. A total of 4 studies compared the incidence of miscarriage between high β-hCG and control groups. There was no heterogeneity among selected 4 studies basing on the heterogeneity test ($\chi^2 = 3.43$, $P = 0.33$, $I^2 = 13\%$). Therefore, a fixed-effects model was used for pooling. The analysis results showed that the incidence of miscarriage in the high β-hCG group was higher than that in the control group (OR = 2.80, 95% CI [1.92, 4.09], $Z = 5.32$, $P < 0.00001$), as shown in Figure 6. The scatter points

Table 1: Basic information of literature.

Author	Year	Study type	No. of patients		Outcomes	Standards of high HCG
			High β-hCG	Control		
Brajenović-Milić et al. [16]	2004	Cohort	121	1386	PIH, PD, abortion, GMD, IUGR	≥2.0 MoM
Cai et al. [19]	2017	Cohort	494	976	PIH, GMD, PD, IUGR	≥2.0 MoM
Ding et al. [20]	2016	Cohort	23	83	PIH	>2.0 MoM
Gonen et al. [21]	1992	Cohort	271	222	IUGR, PIH	>2.5 MoM
Han et al. [22]	2014	Cohort	62	1938	PIH, GMD	≥2.0 MoM
Han et al. [23]	2014	Cohort	55	171	PIH, GMD	>2.0 MoM
Lepage et al. [18]	2003	Cohort	564	1692	PD, PIH, abortion	≥2.0 MoM
Li et al. [24]	2001	Cohort	51	381	PIH	>2.0 MoM
Onderoğlu and Kabukcu [25]	1997	Cohort	81	481	PD	> 2 MoM
Sharony et al. [26]	2017	Cohort	204	120	IUGR, PD	> 3.0 MoM
Sirikunalai et al. [17]	2016	Cohort	2164	10085	PD, abortion	>2.0 MoM
Yaron et al. [27]	1999	Cohort	1850	43715	Abortion, PD	>2.5 MoM
Zeng et al. [28]	2021	Cohort	40	125	PIH, CMD	>2.0 MoM

Note: PIH: pregnancy-induced hypertension; GMD: gestational diabetes mellitus; PD: premature delivery; IUGR: intrauterine growth restriction; β-hCG: β-human chorionic gonadotropin; MoM: multiples of the median.

Table 2: Literature risk of bias assessment.

Study	Selection				Comparability	Exposure			NOS
	Adequate definition of case	Representativeness of the case	Selection of controls	Definition of controls	control for important factor	Ascertainment of exposure	Same method of ascertain for cases and controls	Nonresponse rate	
Brajenović-Milić	*	—	—	*	—	*	*	—	4
Cai	*	*	*	*	*	—	*	*	7
Ding	*	—	*	*	—	*	*	*	6
Gonen	*	—	*	*	—	—	*	*	5
Han (1)	*	*	*	*	*	—	*	*	7
Han (2)	*	—	*	*	—	*	*	*	7
Lepage	*	*	*	*	—	*	*	*	7
Li	*	—	*	*	*	—	*	—	5
Onderoğlu	*	—	*	*	—	*	*	—	5
Sharony	*	*	*	*	—	—	*	*	6
Sirikunalai	*	—	*	*	*	*	*	*	7
Yaron	*	—	*	*	—	—	*	*	5
Zeng	*	*	*	*	*	—	*	*	7

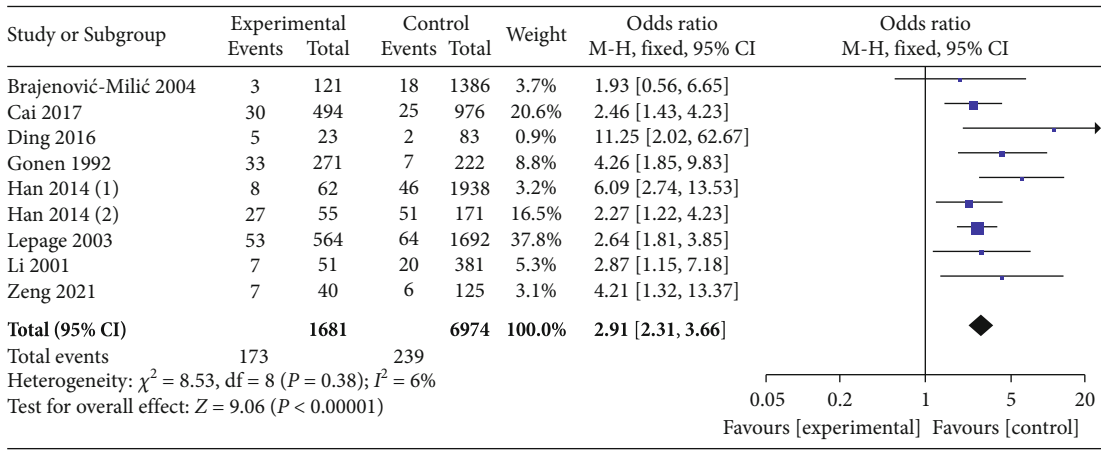

Figure 2: Forest plot: the incidence of pregnancy-induced hypertension in the high β-hCG group and the control group.

fell in range of the confidence interval using Egger's test and funnel plot along with a semisymmetrical shape ($P > 0.05$) as shown in Figure 7.

3.5. High β-hCG and GDM. A total of 7 studies compared the incidence of GDM between high β-hCG and control groups. A heterogeneity was identified among the 7 studies with heterogeneity test ($\chi^2 = 47.01$, $P < 0.00001$, $I^2 = 87\%$). Therefore, a random effects model was used for pooling. The analysis results showed that the incidence of GDM during pregnancy in the high β-hCG group was higher than that in the control group (OR = 2.15, 95% CI [1.05, 4.40], $Z = 2.09$, $P = 0.04$), as shown in Figure 8. Sensitivity analysis showed that the results were not robust, as shown in Table 3. Egger's test and funnel plot showed that the scatter points were distributed within the confidence interval, roughly symmetrical, and there was no publication bias ($P > 0.05$), as shown in Figure 9.

3.6. High β-hCG and IUGR. A total of 3 studies compared the incidence of IUGR between high β-hCG and control groups. The included 3 studies did not exhibit heterogeneity ($\chi^2 = 3.92$, $P = 0.14$, $I^2 = 49\%$). Therefore, a fixed-effects model was used for pooling. The analysis results showed that the incidence of IUGR in the high β-hCG group was higher

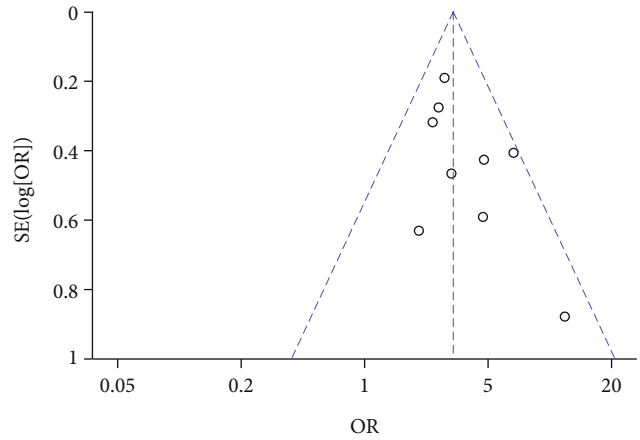

Figure 3: Funnel plot: the incidence of pregnancy-induced hypertension in the high β-hCG group compared with the control group.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95% CI
Brajenović-Milić 2004	5	121	44	1386	1.7%	1.31 [0.51, 3.38]
Cai 2017	36	494	53	976	8.4%	1.37 [0.88, 2.12]
Ding 2016	1	23	1	83	0.1%	3.73 [0.22, 62.00]
Lepage 2003	61	564	80	1962	8.1%	2.85 [2.02, 4.04]
Onderoğlu 1997	14	81	33	481	2.0%	2.84 [1.44, 5.58]
Sharony 2017	32	204	6	120	1.6%	3.53 [1.43, 8.72]
Sirikunalai 2016	281	2164	637	10085	49.9%	2.21 [1.91, 2.57]
Yaron 1999	110	1850	1442	43715	28.1%	1.85 [1.52, 2.26]
Total (95% CI)		**5501**		**58808**	**100.0%**	**2.11 [1.90, 2.35]**
Total events	540		2296			

Heterogeneity: $\chi^2 = 11.78$, df = 7 ($P = 0.11$); $I^2 = 41\%$
Test for overall effect: $Z = 13.85$ ($P < 0.00001$)

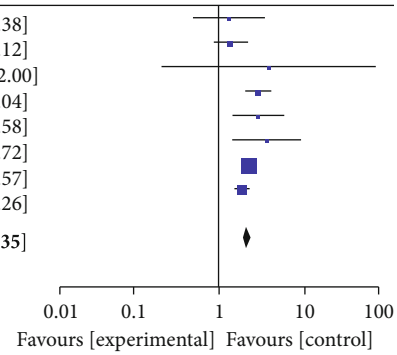

Figure 4: Forest plot: comparison of the incidence of premature delivery in the high β-hCG group and the control group.

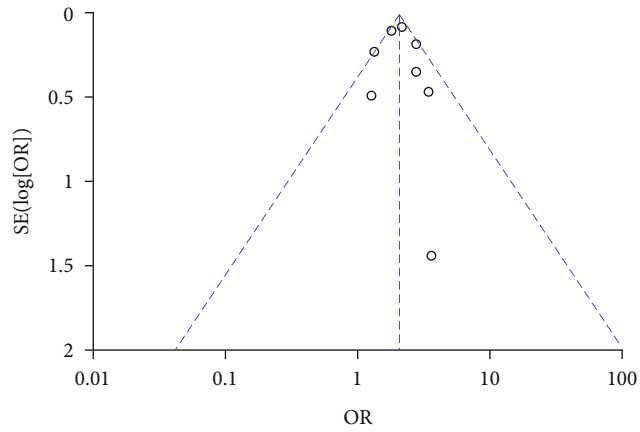

Figure 5: Funnel plot: comparison of the incidence of premature delivery in the high β-hCG group and the control group.

than that in the control group (OR = 2.70, 95% CI [1.75, 4.19], $Z = 4.45$, $P < 0.0001$), as shown in Figure 10. Egger's test and funnel plot showed that the scatter points were distributed semisymmetrically within the confidence interval, and there was no publication bias ($P > 0.05$), as shown in Figure 11.

4. Discussion

Through our comprehensive meta-analysis, we concluded that high levels of β-hCG are risk factors for IUGR, PIH, PD, and miscarriage in singleton pregnancy. In terms of GDM, sensitivity analysis showed that the results were not

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95% CI
Brajenović-Milić 2004	1	121	3	1386	2.1%	3.84 [0.40, 37.22]
Ding 2016	1	23	0	83	0.9%	11.13 [0.44, 282.66]
Lepage 2003	14	564	9	1692	19.4%	4.76 [2.05, 11.06]
Yaron 1999	20	1850	218	43715	77.5%	2.18 [1.38, 3.46]
Total (95% CI)		**2558**		**46876**	**100.0%**	**2.80 [1.92, 4.09]**
Total events	36		230			

Heterogeneity: $\chi^2 = 3.43$, df = 3 ($P = 0.33$); $I^2 = 13\%$
Test for overall effect: $Z = 5.32$ ($P < 0.00001$)

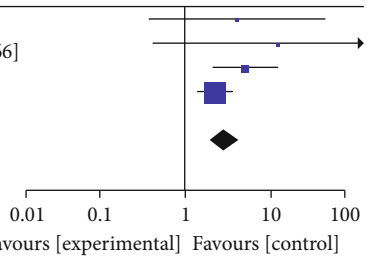

Figure 6: Forest plot: comparison of the incidence of miscarriage in the high β-hCG group and the control group.

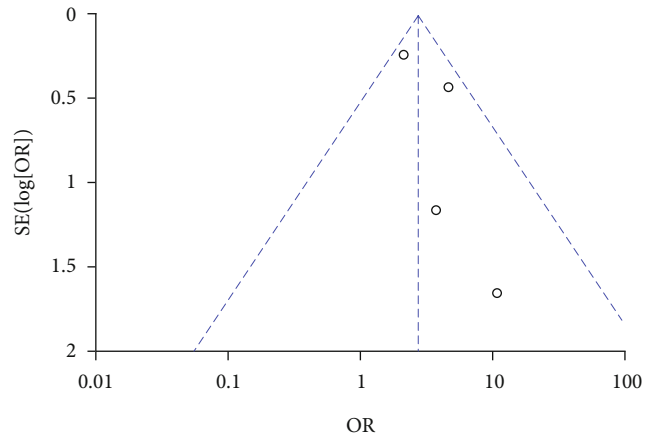

Figure 7: Funnel plot: comparison of the incidence of miscarriage between the high β-hCG group and the control group.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95% CI
Brajenović-Milić 2004	1	121	10	1386	7.5%	1.15 [0.15, 9.03]
Cai 2017	34	494	94	976	18.8%	0.69 [0.46, 1.04]
Ding 2016	5	23	2	83	9.3%	11.25 [2.02, 62.67]
Han 2014 (1)	9	62	64	1983	16.5%	5.09 [2.41, 10.77]
Han 2014 (2)	22	55	36	171	17.2%	2.50 [1.30, 4.80]
Sirikunalai 2016	73	2164	425	10085	19.6%	0.79 [0.62, 1.02]
Zeng 2021	6	40	3	125	11.1%	7.18 [1.71, 30.20]
Total (95% CI)		**2959**		**14809**	**100.0%**	**2.15 [1.05, 4.40]**
Total events	150		634			

Heterogeneity: $\tau^2 = 0.67$, $\chi^2 = 47.04$, df = 6 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: $Z = 2.09$ ($P = 0.04$)

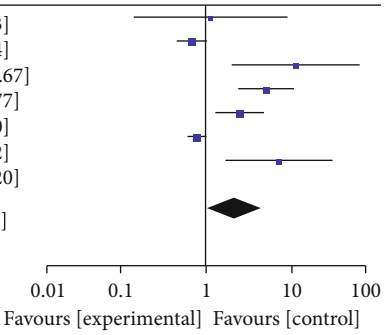

Figure 8: Forest plot: the incidence of gestational diabetes mellitus in the high β-hCG group compared with the control group.

robust. The relationship between high levels of β-hCG and GDM still needs further research to confirm.

High levels of β-hCG in the second trimester predict a high incidence of complications during pregnancy and poor pregnancy outcomes [9]. The possible underlying mechanism is that β-hCG produced by placental trophoblasts can directly reflect placental function, and placental function is directly related to the occurrence of various diseases during pregnancy and adverse pregnancy outcomes [29]. At present, it is believed that GDM, PIH, IUGR, PD, miscarriage, fetal respiratory distress, and stillbirth are all caused by placental pathophysiological changes [29, 30]. Taken all together, the use of β-hCG to predict the occurrence of gestational hypertension has its pathophysiological basis.

Brajenović-Milić et al. [16] studied that elevated β-hCG levels could lead to an increased incidence of preeclampsia; however, elevated β-hCG levels were not identified as an independent risk factor for preeclampsia. There is no significant evidence which suggests that high levels of were associated with the incidence of IUGR, PIH, PD, and GDM. We analyzed that the study was biased in the selection of pregnant women. Pregnant women in the study and control

Table 3: Sensitivity analysis between high β-hCG and GDM.

Eliminate literature	Heterogeneity	OR	P value	Z
Brajenović-Milić et al. [16]	$I^2 = 89\%$, $P < 0.00001$	2.28	0.03	2.13
Cai et al. [19]	$I^2 = 88\%$, $P < 0.00001$	2.92	0.03	2.16
Ding et al. [20]	$I^2 = 87\%$, $P < 0.00001$	1.79	0.11	1.61
Han et al. [22]	$I^2 = 82\%$, $P < 0.00001$	1.69	0.12	1.54
Han et al. [23]	$I^2 = 87\%$, $P < 0.00001$	2.10	0.07	1.81
Sirikunalai et al. [17]	$I^2 = 86\%$, $P < 0.00001$	2.87	0.04	2.09
Zeng et al. [28]	$I^2 = 87\%$, $P < 0.00001$	1.83	0.10	1.63

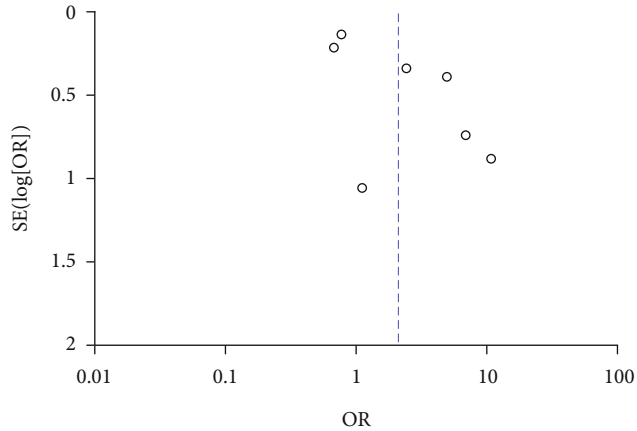

Figure 9: Funnel plot: incidence of gestational diabetes mellitus in the high β-hCG group compared to the control group.

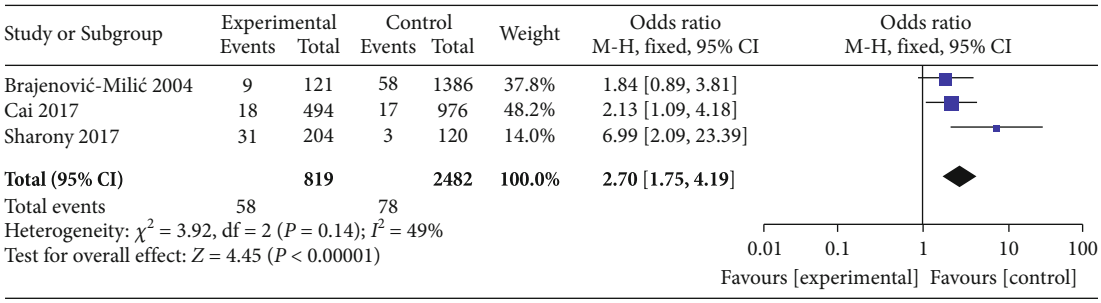

Figure 10: Forest plot: comparison of the incidence of intrauterine growth restriction in the high β-hCG group and the control group.

groups were poorly balanced with respect to baseline data. Sirikunalai et al. [17] suggested that low or high β-hCG levels will increase the risk of complications and adverse outcomes for pregnant women. However, this conclusion only fitted in the second trimester. Lepage et al. [18] showed that in singleton pregnant women, high β-hCG levels were associated with a high incidence of pregnancy complications. In multiple pregnancies, the conclusion remains consistent. Sharony et al. [26] found a strong correlation between high levels of β-hCG and the incidence of IUGR and PD. However, the morbidities of several other complications, including preeclampsia, placental abruption, and prenatal death, were associated with extremely high levels of beta-hCG, suggesting that pregnant women with high levels of beta-hCG should be counseled and monitored in extreme case. Cai et al. [19] found that there was no significant difference in the incidence of gestational hypertension, fetal distress, and placental abruption between pregnant women aged ≥35 years and the elevated β-hCG group compared with the normal group. The increase of serum β-hCG level in the second trimester is closely related to the occurrence of adverse pregnancy outcomes, and it has certain clinical significance in predicting adverse pregnancy outcomes in obstetrics in combination with maternal age. Ding et al. [20] found that the incidence of gestational diabetes mellitus, gestational hypertension, oligohydramnios, and neonatal asphyxia in pregnant women with high serum β-hCG levels was significantly higher than those in women with normal levels. In addition, the same

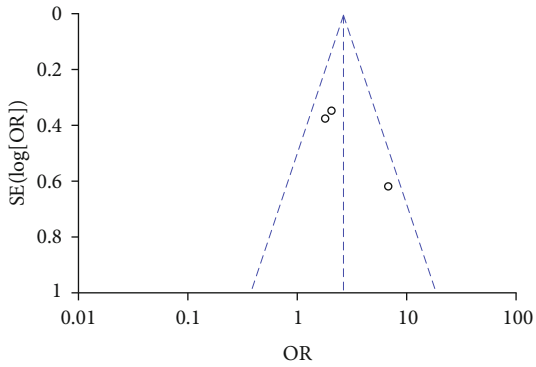

Figure 11: Funnel plot: the incidence of intrauterine growth restriction in the high β-hCG group compared with the control group.

trend was not observed in the low β-hCG group and the normal group.

With the comprehensive meta-analysis, this study does exhibit some limitations. First of all, all included studies have inconsistent criteria for the definition of high β-hCG, which may affect the robustness of the results. Second, there is heterogeneity among studies in the relationship between β-hCG and GDM incidence; however, the root cause of heterogeneity was not identified. Thirdly, we did not explore the effect of very high or low levels of β-hCG on the incidence of pregnancy complications and adverse pregnancy outcomes. Ghasemi-Tehrani et al. [31] found that low levels of β-hCG has no significant effect on the incidence of complications including PD, PIH, miscarriage, and IUGR. Another study [32] pointed out that very high levels of β-hCG increase the risk of adverse outcomes in pregnant women, including stillbirth, small-for-gestational-age infants, and complete moles. Finally, we were not able to age-stratify pregnant women for more instructive results.

In conclusion, high levels of β-hCG during pregnancy in singleton women are associated with a high incidence of pregnancy complications and adverse pregnancy outcomes. Pregnant women with high levels of β-hCG should be monitored more closely, followed up, and given timely medical interventions to reduce the incidence of pregnancy complications and adverse outcomes.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

The authors Ju Huang and Yuying Liu contributed equally to this work.

Acknowledgments

The study was supported by the People's Hospital of Wanning, Hainan.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 4671419, 7 pages
https://doi.org/10.1155/2022/4671419

Research Article

Effect of Endurance Training in COPD Patients Undergoing Pulmonary Rehabilitation: A Meta-Analysis

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Received 24 June 2022; Accepted 20 August 2022; Published 7 September 2022

Academic Editor: Xi Lou

Background. The efficacy of endurance training (ET) on patients with chronic obstructive pulmonary disease (COPD) has been controversial. This study was aimed at meta-analyzing the effect of ET in COPD patients undergoing pulmonary rehabilitation. *Methods*. The literature retrieval was performed in databases to screen relevant literature. Inclusion criteria were as follows: (1) subjects—COPD patients; (2) inclusion of interventional and control groups; (3) intervention measures—the interventional group received whole-body ET and other lung rehabilitation training, while the control group did not receive intervention or other lung rehabilitation training; (4) outcome indicators which included at least one of the following—6MWD, modified Medical Research Council questionnaire (mMRC), and COPD Assessment Test (CAT); and (5) study type—randomized controlled trials (RCTs). The Cochrane risk-of-bias tool was used to assess the risk of bias. The chi-square test was used to evaluate the magnitude of heterogeneity. Subgroup analysis was used to explore the source of heterogeneity. A funnel plot and Egger's test were used to evaluate publication bias. *Results*. The 6MWD in the ET group was significantly higher than that in the control group (MD = 47.20, 95% CI [28.60, 65.79], $P < 0.00001$). Significant heterogeneity ($P < 0.00001$, $I^2 = 76\%$) without publication bias ($P > 0.05$) was noted. Subgroup analysis showed that the 6MWD of the ET group was significantly larger than that of the control group without heterogeneity ($P = 0.63$, $I^2 = 0\%$; $P = 0.59$, $I^2 = 0\%$) in both the no training subgroup (MD = 79.26, 95% CI [72.69, 85.82], $P < 0.00001$) and other rehabilitation training group (MD = 23.64, 95% CI [6.70, 40.57], $P = 0.006$). The mMRC score (MD = −0.72, 95% CI [-1.09, -0.34], $P = 0.002$) and CAT (MD = −6.07, 95% CI [-7.28, -4.87], $P < 0.00001$) of the ET group were significantly lower than those of the control group. There was no heterogeneity ($P = 0.32$, $I^2 = 15\%$; $P = 0.16$, $I^2 = 41\%$). *Conclusion*. ET can improve patients' motor function and reduce dyspnea. ET might be incorporated as an important part of lung rehabilitation training.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow restriction. Exposure to tobacco smoke and air pollutants has been found to be responsible for the abnormalities found in the airway and/or alveolus [1–4]. Epidemiological studies showed that COPD has already become the 3rd most common cause of mortality worldwide [5–7]. It is expected that the global burden of COPD may continue to increase in the coming decades due to the aggravation of air pollution and the aging population [8–10]. Moreover, COPD is associated with decreased exercise endurance that may adversely affect patients' quality of life [11, 12].

Lung rehabilitation is the most effective nondrug treatment for COPD [13] that has been suggested to be a component of the standard treatment for COPD [14, 15]. The comprehensive pulmonary rehabilitation program includes patient assessment, exercise training, education, nutritional

intervention, and psychosocial support. In 2007, the lung rehabilitation guidelines of the American Association of Chest Physicians and the American Heart and Lung Rehabilitation Association proposed exercise training as the cornerstone of lung rehabilitation (level of evidence 1A) [16]. Furthermore, endurance training (ET), which is usually carried out in the form of walking, climbing stairs, running, and cycling [17], is an important part of exercise training [18].

The effect of ET on COPD patients has been controversial. Some studies [19] pointed out that ET could alleviate symptoms of dyspnea and enhance patient exercise capacity. However, ET has also been found to be of no benefits for COPD patients [20]. Previous meta-analyses [21] concluded that upper limb ET could not improve lung function but increase 6-minute walking distance (6MWD). However, the study was limited to upper limb ET and failed to clarify the source of heterogeneity. Therefore, heterogeneity occurs due to a lack of strict screening criteria to control the intervention measures. We conducted a meta-analysis to explore the impact of ET in COPD patients undergoing pulmonary rehabilitation.

2. Methods

2.1. Retrieval Strategy. Literature retrieval was performed using electronic databases, including PubMed, Embase, the Cochrane Library, Web of Science, China Biology Medicine disc (CBMdisc), China National Knowledge Infrastructure (CNKI), and Wanfang from inception to June 2022 without restrictions on language. In addition, the references in the included literature were also reviewed and screened to expand potentially eligible literature. The retrieval strategy adopted a combination of Medical Subject Headings words and free words. Search terms included (chronic obstructive lung disease OR COPD) AND (endurance training or cycling or walking or limb training).

2.2. Literature Screening. Inclusion criteria were as follows: (1) subjects—COPD patients; (2) inclusion of interventional and control groups; (3) intervention measures—the interventional group received whole-body ET and other lung rehabilitation training, while the control group did not receive intervention or other lung rehabilitation training; (4) outcome indicators which included at least one of the following: 6MWD, modified Medical Research Council questionnaire (mMRC), and COPD Assessment Test (CAT); and (5) study type—randomized controlled trials (RCTs).

Exclusion criteria were as follows: (1) duplicate publications, (2) non-RCT, (3) inconsistent intervention measures, and (4) key data that were missing and could not be supplemented by contacting the author.

2.3. Literature Screening and Data Extraction. The two authors independently screened the literature and extracted and cross-checked the data. In case of any disagreement, an agreement was reached by discussion or consultation with the corresponding author. The data extracted mainly included the following: (1) the basic information included in the study, including the research topic, the first author, the publication time, and the published journal; (2) baseline characteristics, including the sample size of each group, patient age and sex, and others; (3) interventions; and (4) outcome indicators and outcome measurement data. Missing data could be supplemented by contacting the author.

2.4. Assessment of Risk of Bias. Two researchers independently evaluated the risk of bias using the Cochrane risk-of-bias tool for RCT. Any disputes were resolved by seeking the opinion of the corresponding author.

2.5. Statistical Analysis. RevMan 5.3 software was used for meta-analysis. Mean difference (MD) with 95% confidence interval (CI) was calculated. The interstudy heterogeneity was analyzed by the chi^2 test (the inspection level was $\alpha = 0.1$), and the combination of I^2 was used to quantitatively analyze the size of heterogeneity. In the presence of $I^2 \leq 50\%$ and $P \geq 0.1$, mild heterogeneity was considered and the fixed effects model was used for meta-analysis. Otherwise, the random effects model was adopted. Subgroup analysis was used to explore the source of heterogeneity. Publication bias was assessed using the funnel plot and Egger's test. Two-sided $P < 0.05$ denoted statistical significance.

3. Results

3.1. Characteristics of Included Literature. A total of 2361 articles were retrieved, among which 14 RCTs with a total of 816 patients with COPD were finally included [19, 20, 22–33]. The screening process is shown in Figure 1. The basic information of literature and risk of bias assessment are shown in Table 1.

3.2. Comparison of 6MWD between the ET Group and Control Group. A total of 11 articles compared 6MWD between the ET group and the control group. The random effects model ($\text{chi}^2 = 42.53$, $P < 0.00001$, $I^2 = 76\%$) suggested that 6MWD in the ET group was significantly larger than that in the control group (MD = 47.20, 95% CI [28.60, 65.79], $P < 0.00001$), as shown in Figure 2. The funnel chart (Figure 3) showed no publication bias among the literature ($P > 0.05$).

Subgroup analysis (Figure 4) according to the different intervention methods of the control group was then performed by dividing the publications into the no training subgroup and other rehabilitation training subgroup. In the no training subgroup, the 6MWD in the ET group was significantly larger than that in the control group (MD = 79.26, 95% CI [72.69, 85.82], $P < 0.00001$), and there was no interstudy heterogeneity ($\text{chi}^2 = 0.92$, $P = 0.63$, $I^2 = 0\%$). In the other rehabilitation training subgroup, 6MWD in the ET group was also significantly larger than that in the control group (MD = 23.64, 95% CI [6.70, 40.57], $P = 0.006$) without interstudy heterogeneity ($\text{chi}^2 = 5.60$, $P = 0.59$, $I^2 = 0\%$).

3.3. Comparison of mMRC Scores between the ET Group and Control Group. Comparisons between the mMRC scores of the ET group and control group were performed by pooling

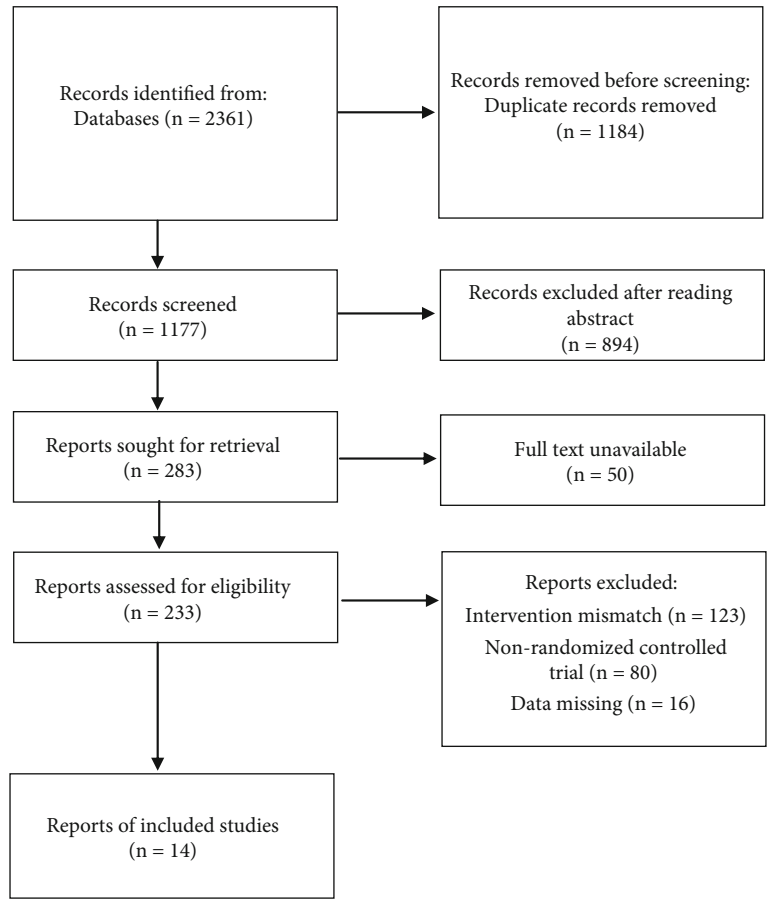

Figure 1: Document screening flow chart.

Table 1: Literature review and risk bias assessment.

Author	Year	Language	No. of patients		Outcomes	Risk of basis
			ET	Control		
Breyer [29]	2010	English	30	30	6MWD	Low risk
Domaszewska [28]	2022	English	20	12	mMRC	Uncertain
Duan [19]	2016	Chinese	46	40	6MWD; CAT	High risk
Hernández [22]	2000	English	20	17	6MWD; mMRC	Uncertain
Jin [32]	2016	Chinese	48	38	6MWD; mMRC; CAT	High risk
Karagiannis [25]	2021	English	18	18	mMRC; CAT	Uncertain
Li [31]	2015	Chinese	50	50	6MWD; CAT	High risk
McKeough [23]	2012	English	16	14	mMRC	Uncertain
Moezy [27]	2018	English	14	16	6MWD	Low risk
Wang [30]	2015	Chinese	23	23	6MWD	Uncertain
Wootton [20]	2017	English	77	44	6MWD	Uncertain
Wootton [24]	2014	English	62	39	6MWD	Uncertain
Zambom-Ferraresi [26]	2015	English	14	8	6MWD	Low risk
Zhang [33]	2012	Chinese	19	10	6MWD	Uncertain

6MWD: 6-minute walking distance; mMRC: modified Medical Research Council questionnaire; CAT: COPD Assessment Test; ET: endurance training.

data from 5 documents. No heterogeneity ($chi^2 = 4.73$, $P = 0.32$, $I^2 = 15\%$) was noted. The mMRC score of the ET group was significantly lower than that of the control group (MD = −0.72, 95% CI [-1.09, -0.34], $P = 0.002$), as shown in Figure 5. The funnel plot (Figure 6) indicated no publication bias.

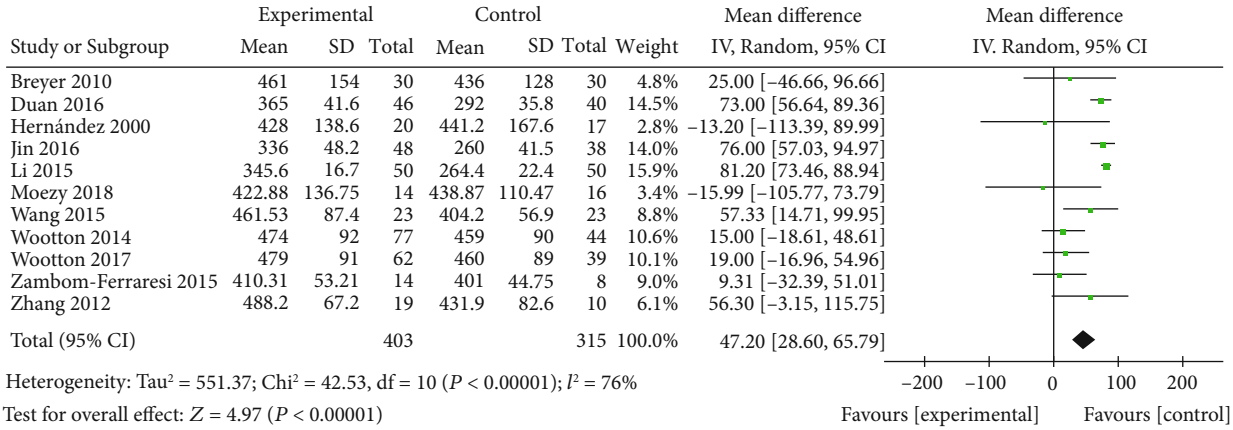

Figure 2: Forest map: comparison of 6MWD between the ET group and control group. 6MWD: 6-minute walking distance; ET: endurance training.

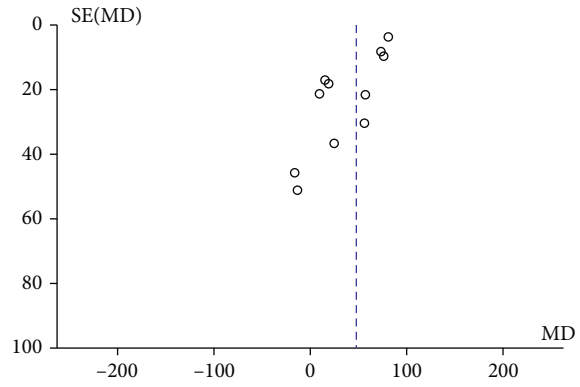

Figure 3: Funnel plot that compares 6MWD between the ET group and control group. 6MWD: 6-minute walking distance; ET: endurance training.

3.4. Comparison of CAT Scores between the ET Group and Control Group. CAT scores of the ET group and control group were compared in 4 literature. Meta-analysis (Figure 7) using the fixed effects model ($chi^2 = 5.11$, $P = 0.16$, $I^2 = 41\%$) showed that the CAT score of the ET group was significantly lower than that of the control group (MD = −6.07, 95% CI [-7.28, -4.87], $P < 0.00001$). No publication bias was found (Figure 8).

4. Discussion

Our meta-analysis showed that 6MWD in the ET group was significantly higher than that in the control group, whereas the mMRC score and CAT score were significantly lower than those in the control group. The results indicated that ET could improve motor function and reduce dyspnea in COPD patients. It should be noted, however, that there was interstudy heterogeneity in terms of 6MWD analyzed by the random effects model. In the subgroup analysis, we then eliminated the heterogeneity by using a fixed effects model, which showed consistent result with overall analysis.

Domaszewska et al. [28] suggested that ET might be related to the levels of prooxidants and antioxidants in COPD patients. They compared the maximal oxygen uptake, pulmonary function parameters, blood concentration of biomarkers of oxidative stress, and antioxidant between the ET group and control group. The results indicated that ET could improve the maximal oxygen uptake and lung function in COPD patients. Meanwhile, ET does not induce oxidative stress and oxidant imbalance in COPD patients. McKeough et al. [23] have shown that ET can significantly increase the endurance exercise time and exercise ability of COPD patients. ET combined with strength training can significantly alleviate dyspnea and the rate of perceived exertion in COPD patients. They believed that ET combined with strength training might be suitable for COPD patients receiving community rehabilitation training. Zambom-Ferraresi and colleagues [26] compared the effects of resistance training alone and resistance training combined with ET on COPD patients. The results showed that resistance training alone and ET combined with resistance training had similar effects on 6MWD and quality of life in COPD patients. However, ET was noted to increase patient muscle strength and improve patient endurance performance. They observed reduced heart rate and serum lactate levels but comparable quality of life in patients receiving ET. Furthermore, strength training with upper limb ET has also been demonstrated to significantly improve the quality of life and muscle strength than strength training alone [25]. However, both methods have similar effects in reducing CAT scores. Upper limb ET showed no advantage in reducing dyspnea symptoms. In a study that assessed ET in COPD patients by walking down the slope, improved lung function and quality of life were shown [27]. Compared with the control group, the ET was associated with significantly longer distance on 6MWD and improved motor ability that could antagonize skeletal muscle adverse reactions caused by COPD. Ground walking training could benefit COPD patients, especially in improving lung function and quality of life, as indicated by the fact that patients who received ground walking training had milder symptoms of dyspnea than those who received routine training [24]. However, this finding was disputed in another study that noted no such phenomenon [20]. Although simple walking training could

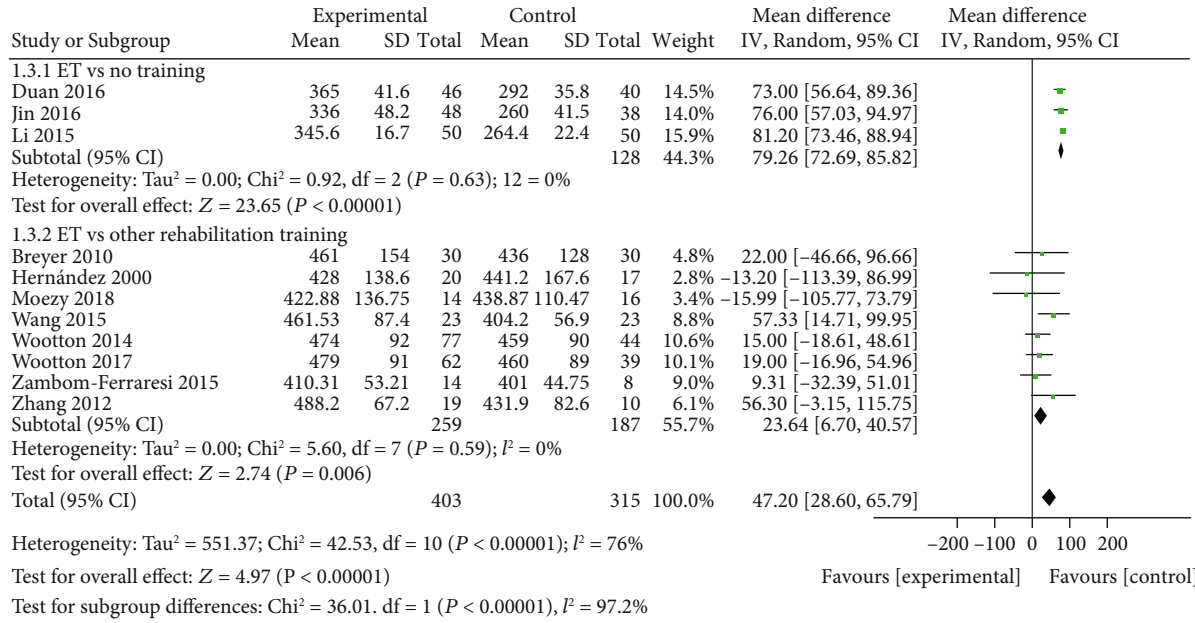

Figure 4: Subgroup analysis forest map: comparison of 6MWD between the ET group and control group. 6MWD: 6-minute walking distance; ET: endurance training.

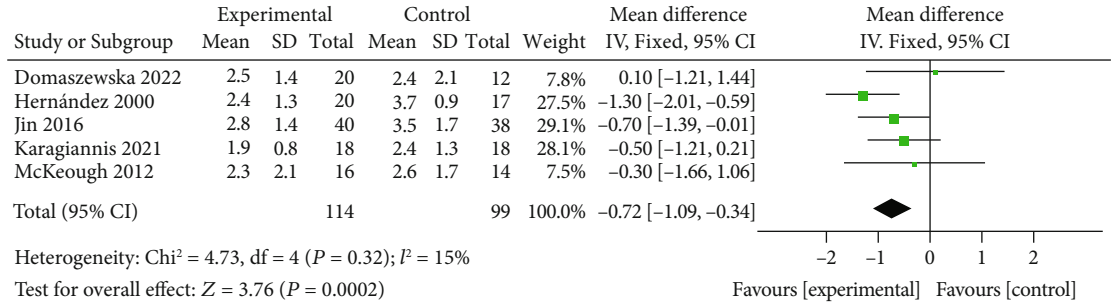

Figure 5: Forest map: comparison of MMRC between the ET group and control group. mMRC: modified Medical Research Council questionnaire; CAT: COPD Assessment Test; ET: endurance training.

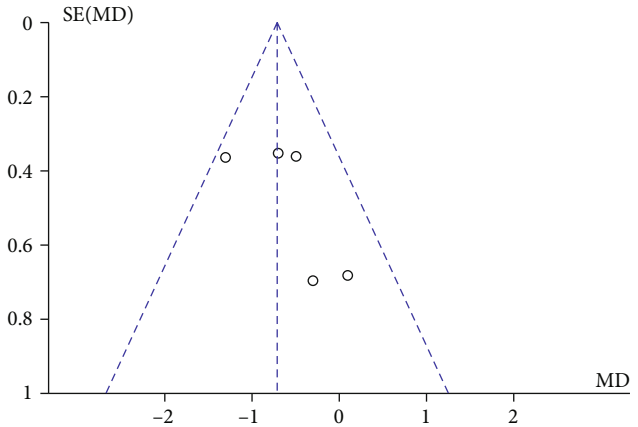

Figure 6: Funnel plot that compares MMRC between the ET group and control group. mMRC: modified Medical Research Council questionnaire; CAT: COPD Assessment Test; ET: endurance training.

reduce the sedentary time, it had no clinical significance for COPD patients. However, no reasons were explained for the discrepancy between their two studies. Our analysis showed that the difference might be related to the inconsistency of training time and intensity. The work by Breyer et al. [29] showed that Nordic walking for 3 months was feasible in different stages of COPD and could significantly improve patients' standing time, reduce sedentary time, and increase 6MWD, all of which were absent in the control group. The curative effect of Nordic walking still existed 9 months after training. Hernández et al. [22] suggested that the shuttle walk test could improve patients' dyspnea and their quality of life, but it had no significant effect on pulmonary function. Jin et al. [32] found that the CAT score in the ET group decreased from 23.4 to 15.6, and the 6MWD increased from 238.0 m to 386.0 m. The score of mMRC decreased from 3.3 to 2.8, which was significantly better than that of the control group. Quantitative walking exercise training can effectively improve the activity tolerance and quality of life for patients

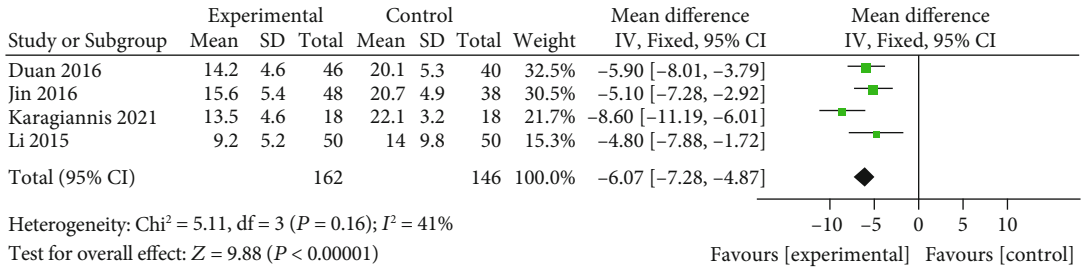

Figure 7: Forest map: comparison of CAT between the ET group and control group. CAT: COPD Assessment Test; ET: endurance training.

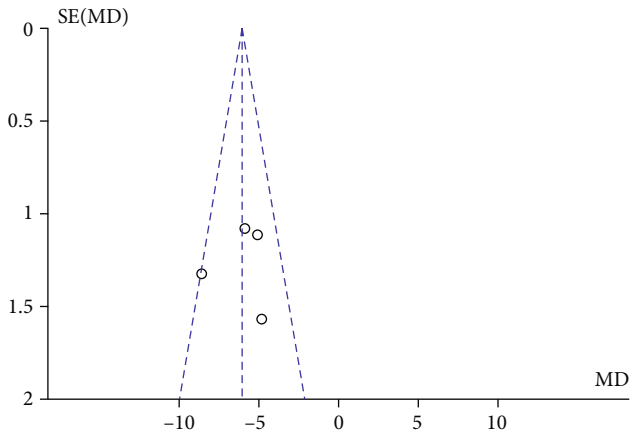

Figure 8: Funnel plot comparing CAT between the ET group and control group. CAT: COPD Assessment Test; ET: endurance training.

with moderate and severe COPD. Wang et al. [30] showed that 5000-step arm swing exercise could not change the pulmonary function but could significantly improve the quality of life in COPD patients. Li et al. [31] showed that the pulmonary function, 6MWD, and CAT scores were improved after exercise in both groups compared with baseline. However, the improvement was more prominent in the interventional group. Duan et al. [19] showed that patients in the ET group could benefit from the CAT score and 6MWD. In addition, walking training can also reduce the number of acute exacerbations. Zhang et al. [33] have shown that high-intensity exercise training of lower limbs can improve the exercise endurance and ventilation function of patients with stable COPD during exercise, but it has no significant effect on static lung function.

Our research suffers from several limitations. First, the observed high risk of bias in some included publications might confound study results. Second, the intervention methods, training cycle, and frequency in each literature were inconsistent. Different training intensity might have different effects on COPD patients. Third, most literature lacked long-term follow-up data, and we could not clarify the duration of endurance training efficacy. Finally, the changes of 6MWD, mMRC, and CAT scores might also be related to demographics and study design. However, due to the lack of relevant information in the literature, we were unable to elucidate their relationships.

In conclusion, ET can improve patients' motor function and reduce dyspnea. ET might be incorporated as an important part of lung rehabilitation training [19, 20, 22–33].

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Yingying Li and Weiwei Wu contributed equally to this work.

Acknowledgments

The study was supported by the Hainan Provincial Health Industry Research Project (No. 20A200498).

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 3605369, 15 pages
https://doi.org/10.1155/2022/3605369

Research Article

A Simple Nomogram for Predicting Osteoarthritis Severity in Patients with Knee Osteoarthritis

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Received 23 June 2022; Revised 9 August 2022; Accepted 20 August 2022; Published 2 September 2022

Academic Editor: Xi Lou

Objective. To explore the influencing factors of knee osteoarthritis (KOA) severity and establish a KOA nomogram model. *Methods*. Inpatient data collected in the Department of Joint Surgery, Chengde Medical University Affiliated Hospital from January 2020 to January 2022 were used as the training cohort. Patients with knee osteoarthritis who were admitted to the Third Hospital of Hebei Medical University from February 2022 to May 2022 were taken as the external validation group of the model. In the training group, the least absolute shrinkage and selection operator (LASSO) method was used to screen the factors of KOA severity to determine the best prediction index. Then, after combining the significant factors from the LASSO and multivariate logistic regressions, a prediction model was established. All potential prediction factors were included in the KOA severity prediction model, and the corresponding nomogram was drawn. The consistency index (C-index), area under the receiver operating characteristic (ROC) curve (AUC), GiViTi calibration band, net classification improvement (NRI) index, and integrated discrimination improvement (IDI) index evaluation of a model predicted KOA severity. Decision curve analysis (DCA) and clinical influence curves were used to study the model's potential clinical value. The validation group also used the above evaluation indexes to measure the diagnostic efficiency of the model. Spearman correlation was used to investigate the relationship between nomogram-related markers and osteoarthritis severity. *Results*. The total sample included 572 patients with knee osteoarthritis, including 400 patients in the training cohort and 172 patients in the validation cohort. The nomogram's predictive factors were age, pulse, absolute value of lymphocytes, mean corpuscular haemoglobin concentration (MCHC), and blood urea nitrogen (BUN). The C-index and AUC of the model were 0.802. The GiViTi calibration band ($P = 0.065$), NRI (0.091), and IDI (0.033) showed that the modified model can distinguish between severe KOA and nonsevere KOA. DCA showed that the KOA severity nomogram has clinical application value with threshold probabilities between 0.01 and 0.78. The external verification results also show the stability and diagnosis of the model. Age, pulse, MCHC, and BUN are correlated with osteoarthritis severity. *Conclusions*. A nomogram model for predicting KOA severity was established for the first time that can visually identify patients with severe KOA and is novel for indirectly evaluating KOA severity by nonimaging means.

1. Introduction

Knee osteoarthritis (KOA) is the most common musculoskeletal disease in people over 60 years old, and with the ageing of the population and the prevalence of obesity, the incidence of KOA is on the rise [1, 2]. The incidence of KOA is also on the rise among young people and physically active people [3, 4].

In particular, approximately 10% of people over 55 years old in the world experience KOA pain and incapacitation,

Table 1: Demographics and clinical characteristics of 400 patients with knee osteoarthritis in the training cohort.

Variables	Total ($n = 400$)	KL 1-3 ($n = 206$)	KL 4 ($n = 194$)	P
Sex, n (%)				0.19
Female	290 (72)	143 (69)	147 (76)	
Male	110 (28)	63 (31)	47 (24)	
Age, median (Q1, Q3)	64 (58, 69)	60 (54.25, 65)	66 (63, 71)	<0.001
Height, median (Q1, Q3)	160 (158, 167)	162 (158, 168)	160 (158, 165)	0.147
Weight, median (Q1, Q3)	70 (60, 75)	70 (62, 80)	69 (60, 75)	0.061
Physical illnesses, *n* (%)				<0.001
No	152 (38)	96 (47)	56 (29)	
Yes	248 (62)	110 (53)	138 (71)	
Temperature, median (Q1, Q3)	36.4 (36.2, 36.6)	36.3 (36.2, 36.6)	36.4 (36.2, 36.5)	0.635
Pulse, median (Q1, Q3)	80 (74, 88)	80 (72, 87)	82 (74.5, 90)	0.004
Breathing rate, *n* (%)				0.77
16	34 (8)	16 (8)	18 (9)	
18	256 (64)	135 (66)	121 (62)	
20	110 (28)	55 (27)	55 (28)	
Systolic pressure, median (Q1, Q3)	141 (130, 157)	138 (128, 150)	146 (132.25, 160)	0.003
Diastolic pressure, mean ± SD	83.05 ± 11.83	82.71 ± 12.06	83.41 ± 11.61	0.555
C-reactive protein, median (Q1, Q3)	1.68 (0.81, 3.95)	1.68 (0.83, 3.62)	1.74 (0.8, 4.3)	0.462
White blood cell count, median (Q1, Q3)	5.64 (4.75, 6.49)	5.64 (4.79, 6.42)	5.65 (4.72, 6.64)	0.807
Red blood cell count, median (Q1, Q3)	4.33 (4.09, 4.65)	4.39 (4.13, 4.71)	4.24 (3.99, 4.56)	<0.001
Haemoglobin, median (Q1, Q3)	132 (123, 142)	134 (127, 144)	128 (120.25, 138)	<0.001
Haematocrit, median (Q1, Q3)	40 (37.9, 42.73)	40.65 (38.52, 43.18)	39.4 (37.25, 42.08)	<0.001
Platelet count, mean ± SD	225.93 ± 54.4	224.91 ± 52.99	227 ± 55.97	0.702
Neutrophil ratio, mean ± SD	58.04 ± 8.96	57.21 ± 9.15	58.91 ± 8.69	0.057
Lymphocyte percentage, mean ± SD	31.36 ± 7.9	32.29 ± 8.05	30.38 ± 7.63	0.015
Monocyte percentage, median (Q1, Q3)	7.4 (6.4, 8.6)	7.3 (6.4, 8.6)	7.5 (6.5, 8.78)	0.285
Percentage of eosinophils, median (Q1, Q3)	2 (1.2, 3.1)	2.05 (1.2, 3)	2 (1.2, 3.1)	0.937
Percentage of basophils, median (Q1, Q3)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.337
Absolute value of neutrophils, median (Q1, Q3)	3.16 (2.59, 3.93)	3.1 (2.63, 3.75)	3.34 (2.55, 4.09)	0.184
Absolute value of lymphocytes, median (Q1, Q3)	1.71 (1.38, 2.12)	1.78 (1.43, 2.17)	1.67 (1.35, 2.05)	0.043
Absolute value of monocytes, median (Q1, Q3)	0.42 (0.34, 0.5)	0.41 (0.34, 0.49)	0.42 (0.34, 0.51)	0.236
Absolute value of eosinophils, median (Q1, Q3)	0.11 (0.07, 0.17)	0.11 (0.07, 0.17)	0.11 (0.06, 0.18)	0.845
Absolute value of basophils, median (Q1, Q3)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.486
Average volume of red blood cells, median (Q1, Q3)	92.8 (89.8, 95.7)	92.5 (90.23, 94.97)	93.05 (89.5, 96)	0.382
Average haemoglobin content, median (Q1, Q3)	30.6 (29.58, 31.6)	30.9 (29.8, 31.8)	30.45 (29.2, 31.4)	0.011
Mean corpuscular haemoglobin concentration(MCHC), median (Q1, Q3)	329 (322, 336)	332 (324.25, 338)	325.5 (320, 333)	<0.001
Coefficient of the variation of red blood cell distribution width, median (Q1, Q3)	12.6 (12.1, 13.1)	12.5 (12, 13)	12.6 (12.12, 13.2)	0.003
Red blood cell distribution width -SD value, median (Q1, Q3)	42.9 (41, 44.9)	42.2 (40.8, 44.4)	43.45 (41.73, 45.5)	<0.001
Average volume of platelets, median (Q1, Q3)	10.3 (9.7, 11)	10.3 (9.6, 11)	10.3 (9.9, 11)	0.258
Distribution width of platelets, median (Q1, Q3)	11.7 (10.6, 13.4)	11.7 (10.5, 13.4)	11.7 (10.8, 13.35)	0.537
Ratio of large platelets, median (Q1, Q3)	27.25 (22.4, 33.32)	27.25 (21.83, 33.27)	27.2 (23.58, 33.25)	0.377
Thrombocytocrit, median (Q1, Q3)	0.23 (0.2, 0.26)	0.23 (0.2, 0.26)	0.24 (0.2, 0.27)	0.505
Total protein, median (Q1, Q3)	68.1 (64.65, 71.6)	67.95 (65.2, 71.75)	68.15 (63.9, 71.38)	0.53
Albumin, median (Q1, Q3)	38.8 (37, 40.73)	39.2 (37.4, 41.08)	38.4 (36.6, 40.48)	0.006
Total bilirubin, median (Q1, Q3)	11.77 (9.44, 14.66)	12.41 (9.72, 14.98)	11.22 (9.13, 14)	0.034

Table 1: Continued.

Variables	Total ($n = 400$)	KL 1-3 ($n = 206$)	KL 4 ($n = 194$)	P
Prealbumin, median (Q1, Q3)	250.45 (213.75, 287.82)	254.1 (216.4, 291.65)	241.7 (208.62, 284.35)	0.093
Alanine aminotransferase, median (Q1, Q3)	15 (11.2, 21.38)	15.4 (11.25, 21.28)	14.1 (11.12, 21.48)	0.244
Aspartate aminotransferase, median (Q1, Q3)	19.1 (16.28, 23.4)	19.35 (16.83, 23.4)	18.9 (16.1, 23.37)	0.542
Gamma glutamyltransferase, median (Q1, Q3)	22.05 (15.9, 34.45)	21.75 (15.72, 33.6)	22.55 (16.52, 35.55)	0.496
Direct bilirubin, median (Q1, Q3)	3.3 (2.5, 4.2)	3.5 (2.5, 4.38)	3.2 (2.4, 4)	0.151
Alkaline phosphatase, median (Q1, Q3)	82.2 (69.7, 98.1)	76.85 (67.53, 91.95)	86.55 (72.9, 103.6)	<0.001
Blood glucose, median (Q1, Q3)	4.99 (4.55, 5.65)	4.96 (4.58, 5.57)	5.02 (4.52, 5.83)	0.922
Total cholesterol, median (Q1, Q3)	4.63 (4.12, 5.35)	4.62 (4.16, 5.43)	4.64 (4.05, 5.3)	0.366
Triglyceride, median (Q1, Q3)	1.4 (1.05, 2.01)	1.38 (1.04, 1.97)	1.41 (1.11, 2.07)	0.373
High-density lipoprotein cholesterol, median (Q1, Q3)	1.21 (1.04, 1.4)	1.23 (1.04, 1.44)	1.17 (1.02, 1.36)	0.207
Apolipoprotein A1, median (Q1, Q3)	1.19 (1.08, 1.33)	1.21 (1.07, 1.37)	1.18 (1.08, 1.3)	0.493
Apolipoprotein B, median (Q1, Q3)	0.88 (0.76, 1.04)	0.89 (0.76, 1.03)	0.88 (0.75, 1.05)	0.952
Low-density lipoprotein cholesterol, median (Q1, Q3)	2.83 (2.46, 3.27)	2.83 (2.48, 3.28)	2.83 (2.4, 3.26)	0.562
Potassium, median (Q1, Q3)	3.68 (3.45, 3.89)	3.74 (3.46, 3.92)	3.63 (3.44, 3.81)	0.026
Sodium, median (Q1, Q3)	141 (139, 142)	140 (139, 141)	141 (139, 142)	0.019
Chlorine, median (Q1, Q3)	106 (105, 108)	106 (105, 108)	106 (105, 108)	0.439
Calcium, mean ± SD	2.26 ± 0.1	2.27 ± 0.1	2.25 ± 0.1	0.193
Phosphorus, median (Q1, Q3)	1.12 (1, 1.26)	1.11 (1, 1.24)	1.12 (0.99, 1.28)	0.777
Magnesium, median (Q1, Q3)	0.88 (0.83, 0.91)	0.87 (0.82, 0.9)	0.88 (0.83, 0.92)	0.344
α-Hydroxybutyrate dehydrogenase, median (Q1, Q3)	152 (135, 172.25)	147 (131, 169)	154.5 (138, 174.75)	0.004
Lactic dehydrogenase, median (Q1, Q3)	178 (157, 200.25)	172.5 (152, 198)	183 (163, 203)	0.006
Creatine kinase, median (Q1, Q3)	63.5 (48.68, 85.1)	63.5 (49.92, 83.38)	63.55 (47.12, 87.68)	0.721
Creatine kinase isoenzyme, median (Q1, Q3)	12 (9.75, 15)	12 (9, 15)	12 (10, 15)	0.571
Blood urea nitrogen (BUN), median (Q1, Q3)	5.36 (4.48, 6.42)	5.12 (4.3, 5.94)	5.64 (4.7, 6.83)	< 0.001
Creatinine, median (Q1, Q3)	56.7 (50.35, 66.3)	56.95 (50.2, 67.22)	56.4 (50.5, 66.25)	0.98
Uric acid, median (Q1, Q3)	296.25 (248.43, 361.6)	296.6 (250.3, 362.03)	295.45 (245.6, 359.1)	0.928
Bicarbonate, mean ± SD	25.88 ± 2.23	25.83 ± 2.32	25.94 ± 2.13	0.627
β2 microglobulin, median (Q1, Q3)	1.63 (1.44, 1.91)	1.53 (1.39, 1.78)	1.72 (1.53, 2.06)	<0.001
Homocysteine determination, median (Q1, Q3)	13.1 (11.38, 16.5)	12.5 (10.9, 16.28)	13.75 (11.9, 16.6)	0.007
Lipoprotein A, median (Q1, Q3)	13.05 (6.68, 28.23)	11.65 (5.62, 26.82)	14.75 (7.53, 29.23)	0.077
Serum cystatin C determination, median (Q1, Q3)	0.64 (0.55, 0.77)	0.6 (0.52, 0.7)	0.67 (0.59, 0.8)	<0.001
Adenosine deaminase, median (Q1, Q3)	9.85 (8.5, 11.9)	9.55 (8.3, 11.7)	10.1 (8.7, 12.2)	0.079
Serum total bile acid, median (Q1, Q3)	3.5 (2.2, 5.7)	3.45 (2.2, 5.77)	3.6 (2.2, 5.5)	0.918
Estimated glomerular filtration rate, median (Q1, Q3)	98.42 (90.7, 104.56)	101.78 (94.04, 108.55)	95.36 (87.9, 100.53)	<0.001
Fibrinogen, median (Q1, Q3)	2.57 (2.25, 2.96)	2.49 (2.26, 2.94)	2.62 (2.24, 2.96)	0.309
Prothrombin time, median (Q1, Q3)	11.2 (10.8, 11.7)	11.2 (10.8, 11.7)	11.2 (10.8, 11.8)	0.693
Thrombin time, median (Q1, Q3)	17.7 (17.1, 18.5)	17.7 (17.1, 18.6)	17.7 (17.1, 18.3)	0.276
Activity, mean ± SD	93.33 ± 8.61	93.52 ± 8.17	93.12 ± 9.08	0.64
International standardized ratio, median (Q1, Q3)	0.97 (0.94, 1.02)	0.97 (0.94, 1.02)	0.97 (0.93, 1.03)	0.666
Activated partial thromboplastin time, mean ± SD	26.08 ± 2.08	26.14 ± 2.12	26.02 ± 2.04	0.563
Fibrinogen degradation products, median (Q1, Q3)	2.5 (2.5, 2.5)	2.5 (2.5, 2.5)	2.5 (2.5, 2.5)	0.103
Antithrombin III, median (Q1, Q3)	87.7 (81.57, 97.73)	87.75 (81.95, 97.18)	87.7 (81.08, 97.85)	0.935
Erythrocyte sedimentation rate, median (Q1,Q3)	10 (6, 17)	9 (5, 15)	12 (6, 18)	0.004
Blood type ABO, n (%)				0.766
AB	35 (9)	20 (10)	15 (8)	
A	134 (34)	72 (35)	62 (32)	
B	115 (29)	57 (28)	58 (30)	
O	116 (29)	57 (28)	59 (30)	

Table 1: Continued.

Variables	Total ($n = 400$)	KL 1-3 ($n = 206$)	KL 4 ($n = 194$)	P
Blood type Rh, n (%)				1
Negative	2 (0)	1 (0)	1 (1)	
Positive	398 (100)	205 (100)	193 (99)	

making it one of the main causes of disability in the world [5]. According to the data of the third national health and nutrition survey in the United States, the incidence of symptomatic knee osteoarthritis is 12.1% [6]. The prevalence of knee osteoarthritis reported by regional epidemiology in Canada is 10.5%. In addition, China's 2020 research report showed that the number of KOA patients increased from 26.1 million in 1990 to 61.2 million in 2017, and KOA was also the 24th most common cause of disability years in 2017, accounting for 1.08% of all disability years [7].

At present, there is no effective cure for patients with KOA [8]. For a long time, the treatment strategies for KOA have mainly been analgesics and surgery [9–11]. The complications associated with the available treatments pose a huge hidden danger for elderly patients. Nonsteroidal anti-inflammatory drugs are the main drug therapy for osteoarthritis of the knee joint. However, a large number of randomized controlled clinical studies have confirmed that the long-term use of nonsteroidal anti-inflammatory drugs will significantly increase the risk of gastrointestinal bleeding, cardiovascular events, and death [12]. Artificial joint replacement is an important method to treat severe pain and joint deformities in late KOA, but it is not the best choice for patients with a poor economic status or relatively young people because of its high cost and the limited life span of artificial joints. In addition, Beswick et al. reported that nearly 20% of KOA patients still had persistent pain after joint replacement [13]. The proportion of patients having revision surgery within 10 years is as high as 12% [14]. This suggests that it is necessary to explore the factors that affect the severity of knee osteoarthritis to improve the interventions given to patients with early knee osteoarthritis, improve the quality of life of patients, and reduce the social burden.

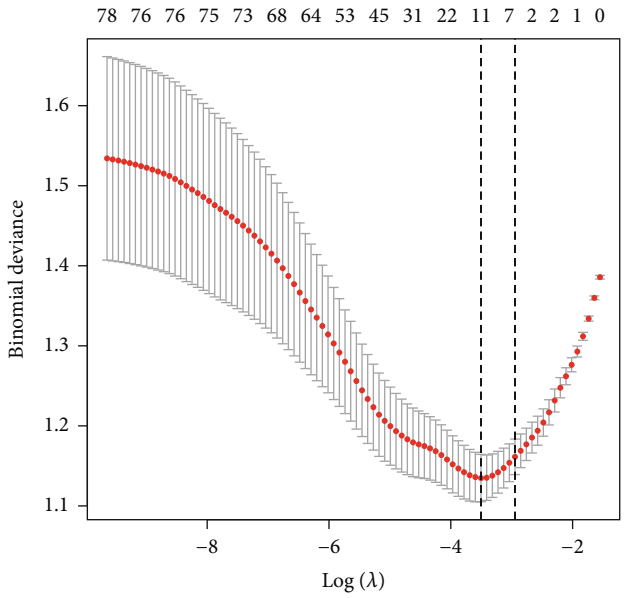
To date, many studies have focused on the treatment, pathogenesis, and biomarkers of KOA [15, 16]. However, there are few reports that have indirectly evaluated the severity of KOA by nonimaging methods [17–21]. Therefore, by analysing the related data of inpatients in the Department of Joint Surgery, Chengde Medical University Affiliated Hospital, this study investigated the influencing factors of KOA severity, thus establishing a nomogram model. It is hoped that the nomogram can provide a more reliable and accurate visual prediction model. At the same time, the data of inpatients in the Department of Joint Surgery of Third Hospital of Hebei Medical University were used to verify the nomogram model externally.

2. Patients and Methods

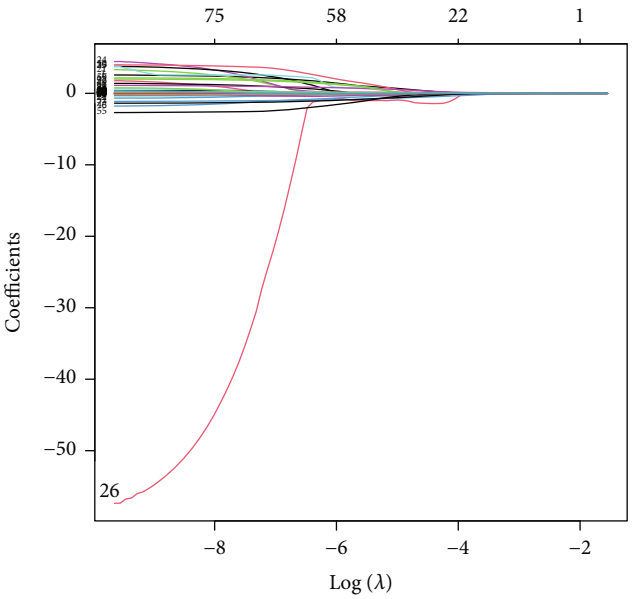
2.1. Data Source. The training cohort retrospectively collected data from a total of 642 patients who were initially diagnosed with KOA in the Department of Joint Surgery, Chengde Medical University Affiliated Hospital from January 2020 to January 2022. A total of 242 patients were excluded due to the lack of clinical data ($n = 108$), combined with osteoarthritis in other joints ($n = 67$), knee replacement, osteotomy and internal fixation for KOA, and knee fracture ($n = 32$), active malignancy ($n = 10$), renal or liver failure ($n = 10$), rheumatic disease ($n = 9$), and active infection ($n = 6$). Finally, the clinical information of 400 KOA patients was collected.

In addition, we selected 256 patients with knee osteoarthritis treated in the Department of Joint Surgery of Third Hospital of Hebei Medical University from February 2022 to May 2022 as the validation cohort. A total of 84 patients were excluded for the following reasons: lack of clinical data ($n = 42$), other joint osteoarthritis ($n = 10$), knee replacement, osteotomy and internal fixation for KOA, and knee fractures ($n = 12$), active malignant tumour ($n = 3$), renal or liver failure ($n = 5$), rheumatic diseases ($n = 6$), and active infection ($n = 6$). Finally, the clinical information of 172 KOA patients was collected.

2.2. Data Collection. All clinical information collected in this study was obtained from the examination information of the patients when they were admitted to the hospital. Clinical information of patients included two parts: demographic characteristics and blood laboratory data. Demographic characteristics included the following: sex, age, height, weight, physical illnesses, temperature, pulse, breathing rate, blood pressure, and Kellgren-Lawrence (KL) grade. Blood laboratory data contains a lot of information as follows: C-reactive protein, white blood cell count, red blood cell count, haemoglobin, haematocrit, platelet count, neutrophil ratio, lymphocyte percentage, monocyte percentage, percentage of eosinophils, percentage of basophils, absolute value of neutrophils, absolute value of lymphocytes, absolute value of monocytes, absolute value of eosinophils, absolute value of basophils, average volume of red blood cells, average haemoglobin content, mean corpuscular haemoglobin concentration (MCHC), coefficient of variation of red blood cell distribution width, red blood cell distribution width -SD value, average volume of platelets, distribution width of platelets, ratio of large platelets, thrombocytocrit, total protein, albumin, total bilirubin, prealbumin, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, direct bilirubin, alkaline phosphatase, blood glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, apolipoprotein A1, apolipoprotein B, low-density lipoprotein cholesterol, potassium, sodium, chlorine, calcium, phosphorus, magnesium, α-hydroxybutyrate dehydrogenase, lactic dehydrogenase, creatinine kinase, creatine kinase isoenzyme, blood

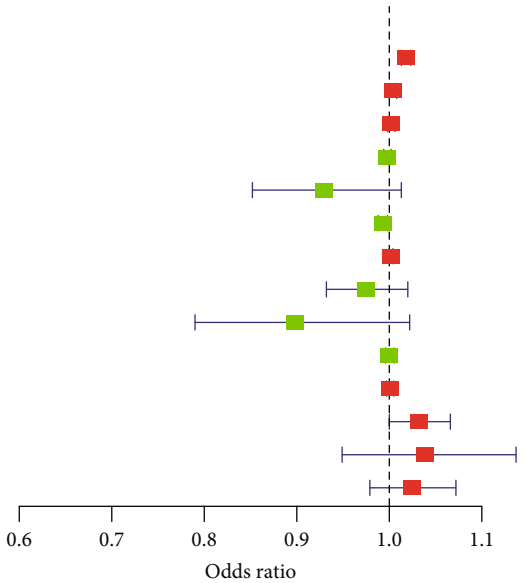


(a)



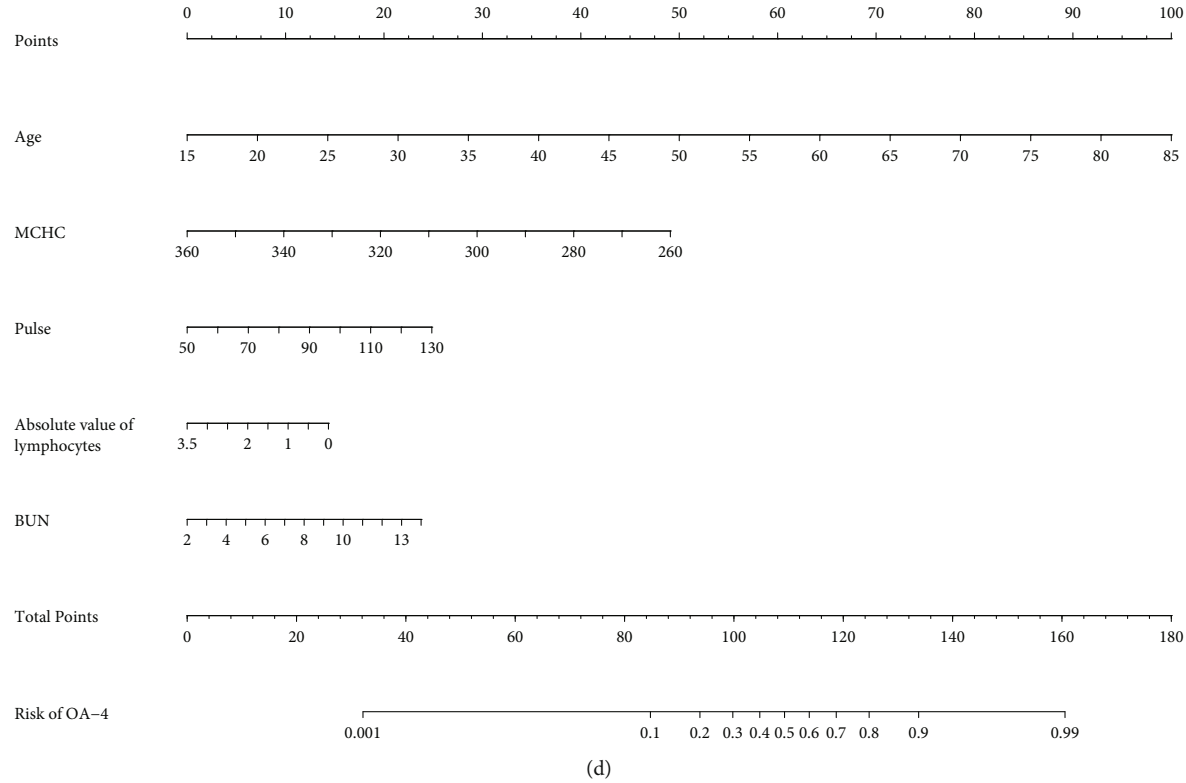
(b)

	p value	Odds ratio (95% CI)
Age	<0.001	1.018(1.013–1.023)
Pulse	0.063	1.004(1.000–1.008)
Diastolic pressure	0.342	1.002(0.998–1.006)
Hemoglobin	0.281	0.998(0.994–1.002)
Absolute value of lymphocytes	0.097	0.929(0.852–1.013)
MCHC	0.004	0.993(0.988–0.998)
Alkaline phosphatase	0.111	1.002(1.000–1.004)
Total cholesterol	0.277	0.975(0.932–1.020)
Potassium	0.105	0.898(0.790–1.022)
α-hydroxybutyrate dehydrogenase	0.826	1.000(0.996–1.005)
Lactate dehydrogenase	0.613	1.001(0.997–1.005)
BUN	0.052	1.032(1.000–1.066)
β 2 microglobulin	0.410	1.039(0.949–1.137)
ABO blood type	0.292	1.025(0.979–1.072)



(c)

Figure 1: Continued.



(d)

Figure 1: Prediction factors for osteoarthritis severity were selected, and an osteoarthritis severity nomogram was developed in patients with knee osteoarthritis in the training cohort. (a, b) Least absolute shrinkage and selection operator (LASSO) coefficient profiles of the 14 prediction factors. (c) Logistic regression analyses of the 5 prediction factors in patients with knee osteoarthritis. (d) Nomogram prediction of osteoarthritis severity in patients with knee osteoarthritis.

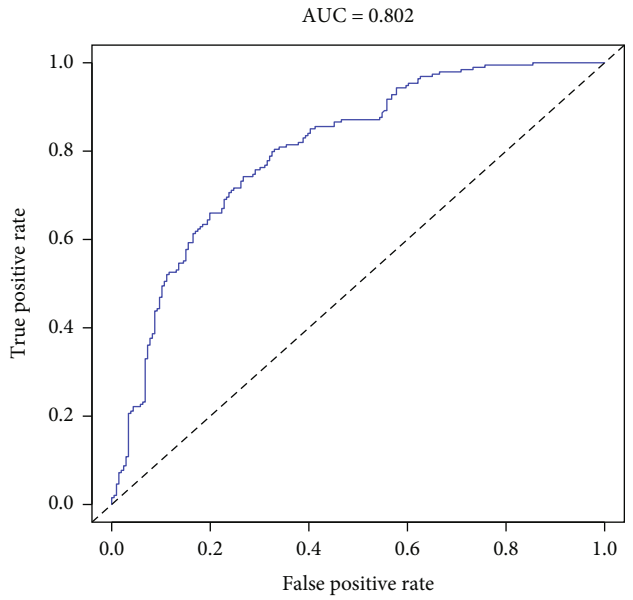
urea nitrogen (BUN), creatinine, uric acid, bicarbonate, β2 microglobulin, homocysteine determination, lipoprotein A, serum cystatin C determination, adenosine deaminase, serum total bile acid, estimated glomerular filtration rate, fibrinogen, prothrombin time, thrombin time, activity, international standardized ratio, activated partial thromboplastin time, fibrinogen degradation products, antithrombin III, erythrocyte sedimentation rate, and blood type.

The KL classification system is often used to classify the severity of osteoarthritis using radiological findings. According to the severity of the imaging changes in the bones and joints and by using the KL classification system, KOA can be divided into grades 0, 1, 2, 3, and 4. If there is a classification difference between the patient's knees, the most serious grade is the grading result of the patient [22]. In our study, grade 4 KOA patients were classified into the severe group, while the others (grade 1, 2, and 3 KOA patients) were classified into the nonsevere group.

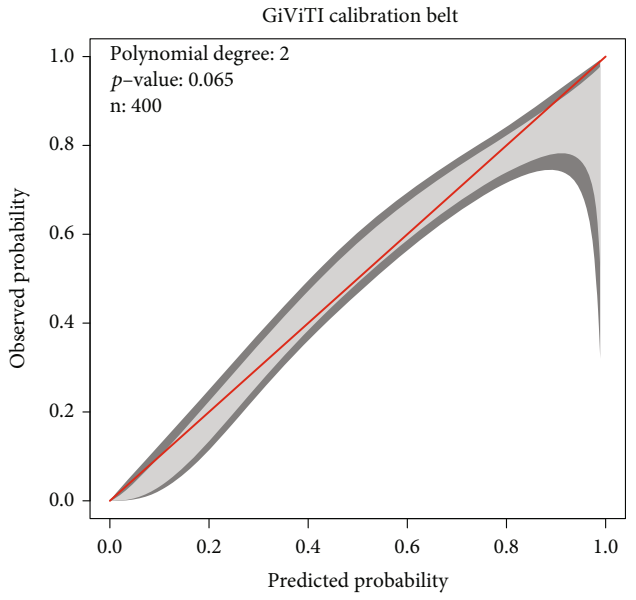
2.3. Construction and Estimation of the Nomogram. Least absolute shrinkage and selection operator (LASSO) methods were used to screen the factors influencing the severity of KOA to determine the best predictive index in the training cohort. Then, by combining the factors obtained by the LASSO regression analysis and multivariate logistic regression analysis, the nomogram of the prediction model was established [10]. $P < 0.05$ indicated that the difference was statistically significant. All potential prediction factors were included in the KOA severity prediction model, and the corresponding nomogram was drawn. Harrell's C statistic was used to calculate the consistency index (C-index) to evaluate the discrimination of the nomogram model. The receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC) and evaluate the value of the index model in predicting KOA severity [23]. The GiViTi calibration band was also utilized to illustrate the distinguishing ability of the prediction model. Net reclassification improvement (NRI) and comprehensive discrimination improvement (IDI) indexes were calculated to evaluate the predictive power of the model. Decision curve analysis (DCA) and clinical influence curves were used to study the potential clinical value of the model [24–26]. It is convenient to predict patients with severe KOA in clinical practice. In this study, "DynNom" of the R package was used to support the dynamic statistical analysis of the nomogram model [27].

The factors of the nomogram included in the training cohort were evaluated in the validation cohort. The evaluation indicators in the validation cohort also included the following: AUC, C-index, GiViTi calibration band, and DCA.

2.4. Statistical Analysis. All data in this study were analysed by the R software (version 4.1.2; https://www.r-project.org/). In this study, the comparison of continuous variables between the two groups is expressed as the mean, standard deviation, and difference. Student's t-test was used for normally distributed data, but the Mann–Whitney U test was

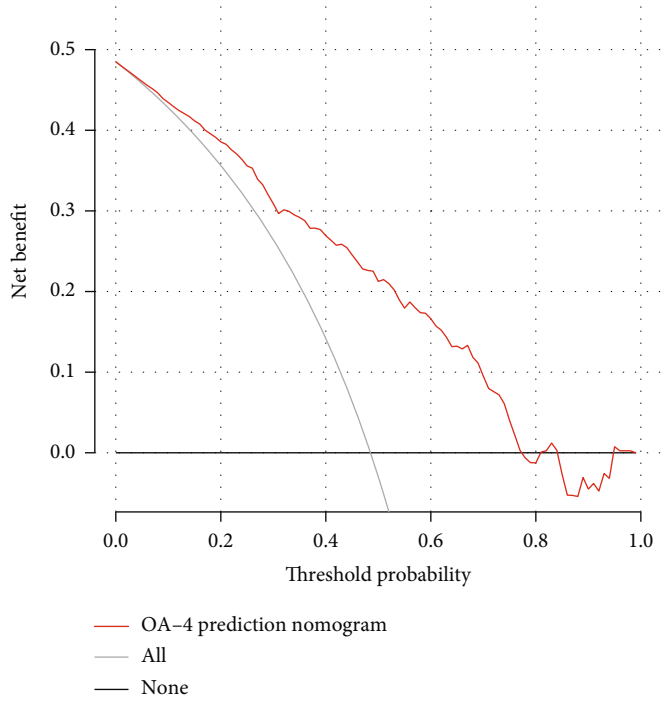


(a)



Confidence level	Under the bisector	Over the bisector
80%	0.00–0.10 0.89–0.99	NEVER
95%	NEVER	NEVER

(b)



(c)

Figure 2: Continued.

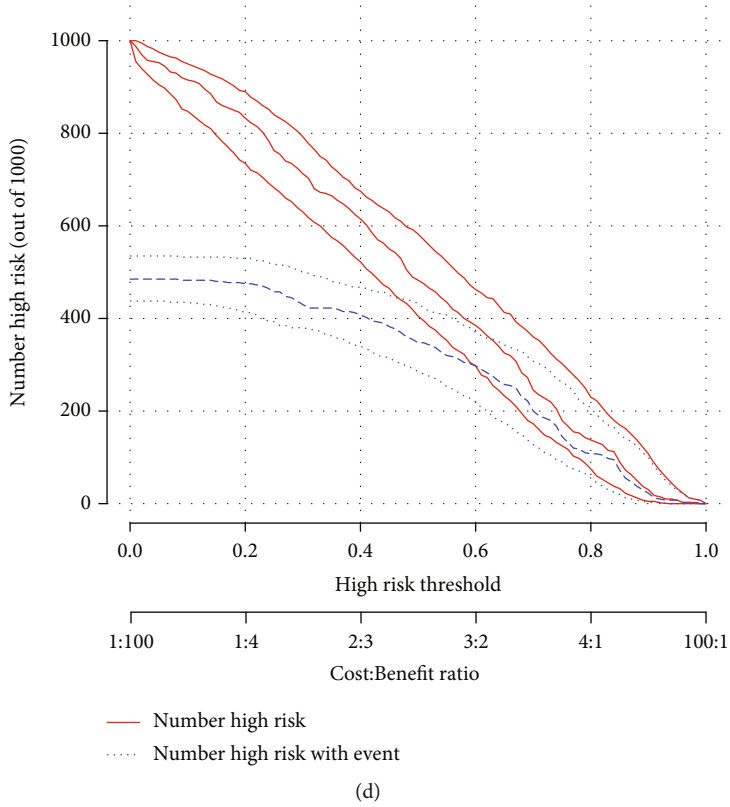


Figure 2: Evaluation of the KOA nomogram and its clinical use in patients with KOA in the training cohort. (a) ROC curve based on the predictive nomogram for osteoarthritis severity. (b) Calibration plots for predicting osteoarthritis severity. (c) Decision curve analysis for the osteoarthritis severity nomogram in patients with knee osteoarthritis. (d) Clinical impact plot for predicting osteoarthritis severity.

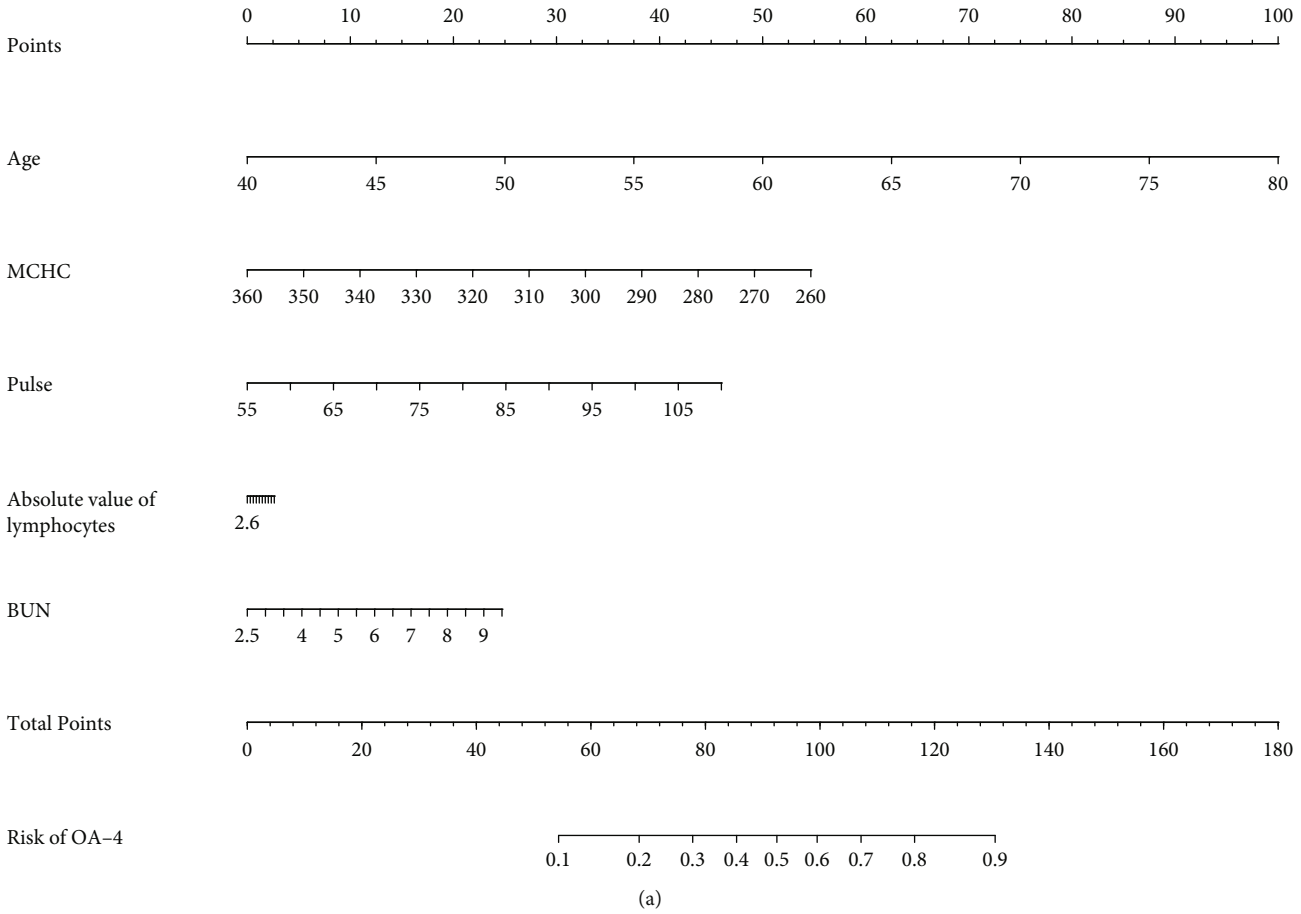
used for nonnormally distributed data. The R package used in the LASSO method is "glmnet." The AUC, C-index, GiViTi calibration band, and DCA adopted the R packages "pROC," "Hmisc," "givitiR," and "rms," respectively. The use of NRI and IDI includes the R packages "nricens" and "PredictABEL." Spearman grade correlation coefficients were calculated to investigate the relationship between nomogram-related markers and osteoarthritis severity by the R software.

3. Results

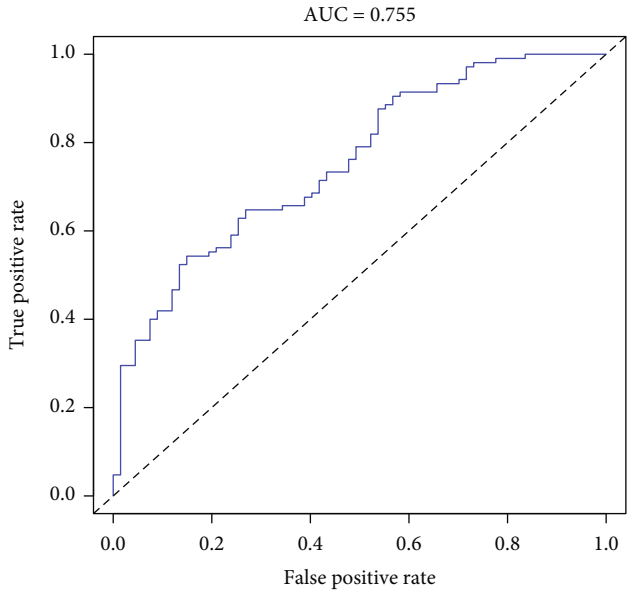
3.1. Characteristics of the KOA Patients. The training cohort included 400 patients (110 males and 290 females) with an average age of 64 (58, 69) years. According to the KL grading system, the patients were divided into two groups: the KL 1-3 KOA group (206 cases) and the KL 4 KOA group (194 cases). The demographic characteristics, blood laboratory results, and knee osteoarthritis grouping of the two groups (severe group vs. nonsevere group) are shown in Table 1. In the comparison between the severe group and the nonsevere group, the variables with significant differences ($P < 0.05$) included age, physical illnesses, pulse, systolic pressure, red blood cell count, haemoglobin, haematocrit, lymphocyte percentage, absolute value of lymphocytes, average haemoglobin content, mean corpuscular haemoglobin concentration (MCHC), coefficient of the variation of red blood cell distribution width, red blood cell distribution width (SD value), albumin, total bilirubin, alkaline phosphatase, potassium, sodium, α-hydroxybutyrate dehydrogenase, lactic dehydrogenase, blood urea nitrogen (BUN), β2 microglobulin, homocysteine determination, serum cystatin C, glomerular filtration rate, and erythrocyte sedimentation rate.

There were 172 KOA patients (43 males and 129 females) in the validation cohort, with an average age of 62.41 ± 6.36 years (Table S1). The patients can be divided into two groups by the same grading method: the KL 1-3 KOA group and the KL 4 KOA group. Because the blood laboratory results of different hospitals contain different items, the validation cohort lacks the red blood cell distribution width (SD), ratio of large platelets, β2 microglobulin, serum cystatin C, adenosine deaminase and estimated glomerular filtration rate. The comparison between the severe group and the nonsevere group in the validation group shows that there are seven variables with the same significant differences as those in the training group: age, pulse, systolic pressure, average haemoglobin content, mean corpuscular haemoglobin concentration (MCHC), coefficient of the variation of red blood cell distribution width, and homocysteine determination. The other four variables with significant differences were breathing rate, prealbumin, gamma glutamyltransferase, and fibrinogen degradation products.

3.2. Nomogram Variable Screening and Construction. In the LASSO regression analysis of the training cohort, 400



(a)



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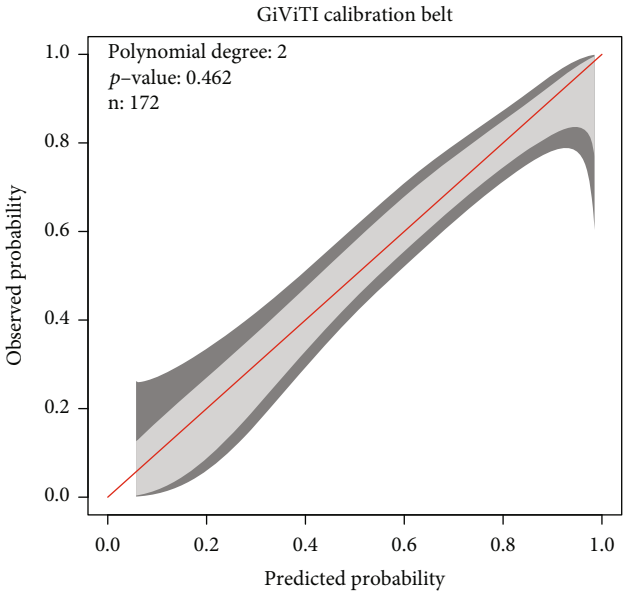

Confidence level	Under the bisector	Over the bisector
80%	NEVER	NEVER
95%	NEVER	NEVER

(c)

Figure 3: Continued.

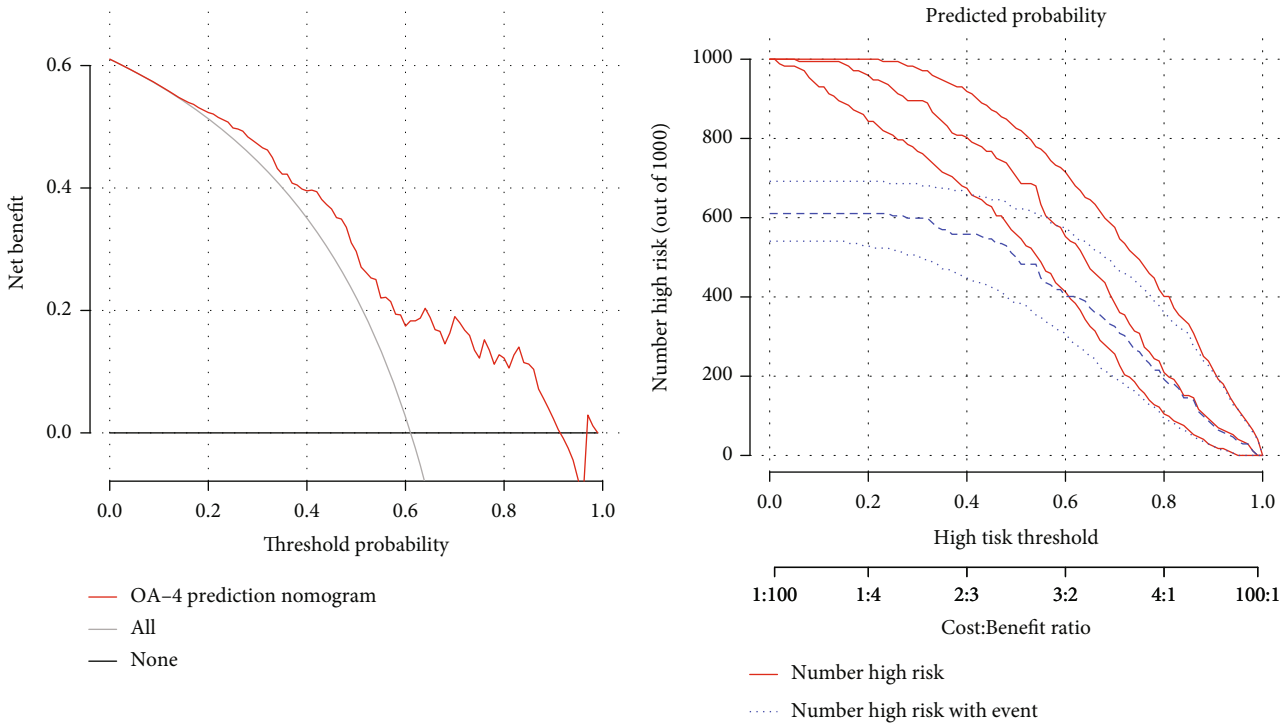

Figure 3: Evaluation of the KOA nomogram and its clinical use in patients with KOA in the validation cohort. (a) Nomogram prediction of osteoarthritis severity in patients with knee osteoarthritis. (b) ROC curve based on the predictive nomogram for osteoarthritis severity. (c) Calibration plots for predicting osteoarthritis severity. (d) Decision curve analysis for the osteoarthritis severity nomogram in patients with knee osteoarthritis. (e) Clinical impact plot for predicting osteoarthritis severity.

patients had 81 features, which were reduced to 14 potential nonzero coefficient predictors related to KOA. These 14 factors are as follows: age, pulse, diastolic pressure, haemoglobin, absolute value of lymphocytes, MCHC, alkaline phosphatase, total cholesterol, potassium, α-hydroxybutyrate dehydrogenase, lactate dehydrogenase, BUN, β2 microglobulin, and ABO blood type (Figures 1(a) and 1(b)). As determined by the multivariate logistic regression analysis of the above 14 factors, only the P values of age and MCHC were less than 0.05, and the P values of pulse, absolute value of lymphocytes, and BUN were less than 0.1 (Figure 1(c)). Finally, the above five factors were included in the nomogram model to predict the severity of KOA (Figure 1(d)). In this study, a dynamic nomogram was used to visually demonstrate the diagnostic performance of these five variables (age, MCHC, pulse, absolute value of lymphocytes, and BUN) for severe KOA (Figure S1).

3.3. Evaluation of the Nomogram. The C-index and AUC were 0.802, which indicates that the nomogram has a good degree of discrimination for the severity of KOA (Figure 2(a)). The GiViTi calibration curve ($P = 0.065$) in this study also consistently showed a good nomogram (Figure 2(b)). The changes in the NRI and IDI were used to compare the accuracy between the nomogram model and the two-variable model (the model established by age and MCHC). The NRI and IDI were 0.091 and 0.033, respectively (both $P < 0.05$). In addition, the AUC of the nomogram was higher than that of the two-variable model (0.802 vs. 0.783, $P < 0.05$). These indicators show that the nomogram is more accurate than the two-variable model.

3.4. Clinical Use of the Nomogram. This study predicts severe DCA of KOA, as shown in Figures 2(c) and 2(d). The DCA results show that the nomogram that was used to differentiate severe KOA in this study population is more beneficial than all of the patient intervention or nonintervention schemes because it has a threshold probability of 0.01-0.78 (Figure 2(c)). In addition, the clinical impact chart shows that the predicted number of high-risk patients is always greater than the actual number of noncompliant patients, which seems to be accompanied by an acceptable cost–benefit ratio (Figure 2(d)). These results indicate that the nomogram has high clinical application potential for determining the severity of KOA patients.

3.5. Validation of the Nomogram. The nomogram model in the training cohort included age, MCHC, pulse, absolute value of lymphocytes, and BUN (Figure 3(a)). Then, the same variables as those of the training cohort were used in the validation cohort to construct a diagnosis model for patients with severe KOA, and the nomogram model was evaluated. In the validation cohort, both the C-index and AUC were 0.755 (Figure 3(b)). In addition, the P value of the GiViTi calibration curve was 0.462 (Figure 3(c)). These three evaluation indexes all show that the nomogram model

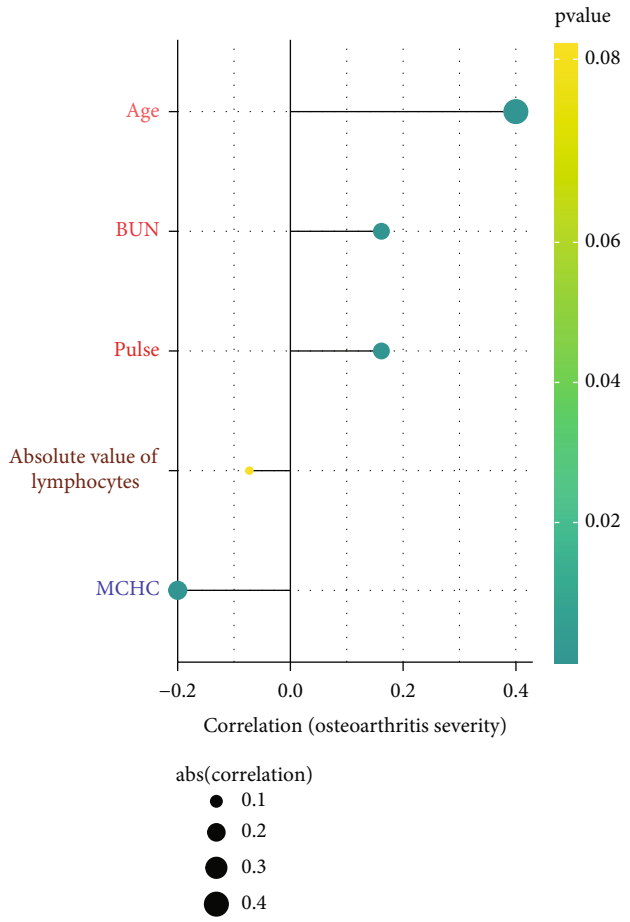

Figure 4: Correlation analysis of nomogram-related markers and osteoarthritis severity.

has certain value in the diagnosis of patients with severe KOA in the validation cohort. DCA was performed in the validation cohort to estimate the net benefit to patients (Figure 3(d)). DCA showed the obvious net benefits of the nomogram model for almost all threshold probabilities (Figure 3(e)), especially the threshold probabilities between 5 and 91% (Figure 3(d)).

3.6. Correlations between Nomogram-Related Markers and Osteoarthritis Severity. In both the training cohort and the validation cohort, age, MCHC, pulse, absolute value of lymphocytes, and BUN were well presented as the factors included in the establishment of the nomogram model. Spearman correlation analysis showed that except the absolute value of lymphocytes, other indicators were correlated with the severity of osteoarthritis (Figure 4). Age ($r = 0.4$), pulse ($r = 0.16$), and BUN ($r = 0.16$) were positively related to the osteoarthritis severity. MCHC ($r = -0.2$) is negatively proportional to the osteoarthritis severity.

4. Discussion

KOA is a chronic disease occurring in the knee joint caused by the interaction of many factors; it is characterized by articular cartilage degeneration and secondary bone hyperplasia. As the most common joint disease, it is estimated that 302 million people in the world are affected by KOA, and it has become one of the main causes of disability in the elderly [8, 28, 29]. Epidemiological survey data in China show that the prevalence rate of symptomatic KOA in China is 8.1% at present, and frequent knee pain affects the activity and quality of life of up to 25% of adults [30]. The high prevalence and disability rate of KOA have greatly affected the patients' quality of life and social and economic development. During the early stage of KOA, the articular cartilage still has a certain regenerative capacity, but during the late stage of KOA, the articular cartilage may permanently lose its regenerative capacity [31, 32]. According to the diagnosis and treatment of KOA, experts have divided KOA into early, middle stage, and late stages. In the early stage, drug treatment is recommended, but in the middle and late stages, invasive treatments such as repair and joint replacement are recommended [33]. Therefore, early identification of the severity of KOA plays an important role in the treatment and prognosis of KOA.

The nomogram model can visualize the results of logistic regression and can be directly used to predict the individual disease risk, which is easy to popularize and apply in the clinic. Studies at home and abroad have confirmed that nomogram models can be used to predict the prognosis of hepatocellular carcinomas, melanomas of the head and neck, gliomas, young patients with gastric cancer, and the risk of anastomotic leakage after rectal cancer surgery [34–38]. In the field of KOA, the prediction accuracy and clinical value of nomograms have also been confirmed, and nomograms can be used to predict the probability of replacement surgery in the late stage of KOA and the probability of complications after joint replacement [18, 39]. However, there is little literature on the establishment of a nomogram model of KOA severity that is related to the clinical application of X-ray films to evaluate KOA severity. Based on the abovementioned influencing factors of KOA severity, a nomogram model for predicting KOA severity was established for the first time, which realized visual and individualized prediction, helped to formulate strategies to prevent KOA, supplemented the shortcomings of imaging methods in evaluating KOA severity, and proposed a new method for indirect evaluation of KOA severity by nonimaging methods. In clinical work, the nomogram model of this study can be used in primary medical units without access to imaging equipment (for example, community health service stations), in patients who are unwilling to receive radiation, in patients who cannot receive radiation (for example, pregnant women), and in patients who have been bedridden for a long time and have difficulty with X-ray examinations.

A large number of studies have reported the relationship between age and KOA. Jurmain found that the incidence of osteoarthritis increased with age [39]. Calce et al. found that most of the changes in KOA patients can be explained by age [40]. Deng et al. suggested that ageing is the key driving force of osteoarthritis [41]. Zhang et al. reported that osteoarthritis is an age-related arthritis and the main cause of chronic disability in the elderly [42]. This study is consistent with the above conclusions: it was found

that age is an independent risk factor for patients with severe KOA. With increasing age, the severity of KOA increased ($r = 0.4$, $P < 0.001$).

There is no literature that directly supports the correlation between pulse and KOA severity. However, a large number of studies have proven that cardiovascular disease (CVD) is closely related to osteoarthritis, and there is a positive correlation [43–46]. Moreover, some studies have pointed out that vascular lesions around joints are one of the pathogeneses of osteoarthritis, and these vascular lesions have been proven to be similar to CVD in pathology and are considered to be a manifestation of systemic metabolic abnormalities [47], which further verifies the close relationship between CVD and osteoarthritis. These considerations make it easier for us to understand the results of this study: pulse is an independent risk factor for patients with severe KOA, and with the acceleration of the pulse, the severity of KOA increases ($r = 0.16$, $P < 0.001$). Output per stroke is an important indicator of cardiac function. The greater the output per stroke, the better the cardiac function. Under the same cardiac output, the faster the pulse is, the smaller the stroke output; the slower the pulse is, the larger the stroke output. However, CVD is positively correlated with osteoarthritis. It has been found that the faster the pulse and the smaller the output per pulse, the worse the heart function and the more severe the osteoarthritis, which could explain the results of our study.

BUN is a nitrogen-containing compound in the plasma and is filtered out from the glomerulus and excreted. When renal insufficiency is decompensated, BUN will increase. Therefore, BUN is used as an index to evaluate glomerular filtration function in clinical work. There is no literature to support that BUN is directly related to KOA. However, the literature has proven that BUN increases with age [48], and age is closely related to KOA [39–42]. These conclusions can fully explain the results of our study; the higher the BUN ($r = 0.16$, $P < 0.001$) is, the heavier the severity of KOA.

Many scholars have found that the absolute value of lymphocytes is inversely related to the severity of KOA [49–52]; that is, the smaller the absolute value of lymphocytes is, the heavier the severity of KOA. Additionally, the larger the absolute value of lymphocytes is, the lighter the severity of KOA. This is consistent with our research results.

Many studies have reported the importance of low MCHC in predicting the prognosis of diseases [53–55], including hepatectomy, chronic obstructive pulmonary disease, and the development of cardiovascular diseases in dialysis patients. However, no literature has proven the relationship between MCHC and KOA. MCHC is defined as the amount of haemoglobin per litre of blood/haematocrit per litre of blood. There is a positive correlation between MCHC and haemoglobin, and it has been reported in the literature that haemoglobin tends to decrease with age [56], so MCHC also tends to decrease with age. Age is closely related to KOA [36–39]. This finding fully explains the results of this study, which showed that with a decrease in MCHC ($r = -0.2$, $P < 0.001$), the severity of KOA increases.

The C-index of KOA severity predicted by the nomogram model in this study was 0.802. The internal verification shows that the KOA severity predicted by this model is in good agreement with the actual KOA severity. The calibration curve further verifies that the model prediction has excellent discrimination and accuracy. In addition to excellent prediction accuracy, this study also confirmed that the nomogram model can effectively predict KOA severity by ROC curve analysis. To avoid data overfitting in the process of building the nomogram model in the training cohort, this study used external data for verification. The AUC performance of the validation cohort was as good as that of the training cohort. There was no significant difference in AUC between the training cohort and the validation cohort ($P = 0.272$). This also further shows that the nomogram model has good discrimination for severe KOA from patients with nonsevere KOA in the validation cohort. By introducing a clinical decision curve and clinical influence curve to investigate the advantages and disadvantages of statistical inference results, the results further confirmed that this model has strong clinical practicability and high benefit in the training cohort and validation cohort.

The limitations of this study are as follows: (1) the sample size is small; (2) the nomogram for predicting KOA severity needs to be further verified by multicentre and large-scale case studies.

5. Conclusions

In this study, a nomogram model for predicting KOA severity was established for the first time by combining five influencing factors, including age, pulse, absolute value of lymphocytes, MCHC, and BUN. Individualized prediction of KOA severity can be obtained, and these can help to directly identify patients with severe KOA, help to formulate strategies for preventing KOA, and may open up new ideas for indirectly evaluating KOA severity by nonimaging means.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available because of restricted access to our hospital database but are available from the corresponding author upon reasonable request.

Ethical Approval

Ethical approval for the study was obtained.

Disclosure

The manuscript has been submitted as a preprint in Research Square (doi:10.21203/rs.3.rs-1680169/v1) [57].

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Qingzhu Zhang and Pengcheng Wang designed the study. Qingzhu Zhang was responsible for the preparation of the manuscript. Yinhui Yao and Jinzhu Wang contributed to the data collection. Yufeng Chen and Dong Ren played an important role in the analysis of outcomes. Yinhui Yao and Pengcheng Wang revised the manuscript. All authors read and approved the final manuscript.

Acknowledgments

The present work was supported by the Central Guidance for Local Science and Technology Development Fund Project in Hebei Province (21627708G).

Supplementary Materials

Table S1: demographics and clinical characteristics of 172 patients with knee osteoarthritis in the validation cohort. Figure S1: dynamic nomogram prediction of osteoarthritis severity in patients with knee osteoarthritis. *(Supplementary Materials)*

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 2751559, 10 pages
https://doi.org/10.1155/2022/2751559

Research Article

Accuracy of Magnetic Resonance Imaging in Diagnosing Placenta Accreta: A Systematic Review and Meta-Analysis

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Received 30 June 2022; Revised 26 July 2022; Accepted 1 August 2022; Published 26 August 2022

Academic Editor: Xi Lou

Background. The disease burden and incidence of placenta accreta are increasing worldwide. The morbidity and mortality associated with undiagnosed placenta accreta are both high, highlighting the important of early diagnosis and intervention. In recent years, increasing studies are exploring the diagnostic value of magnetic resonance imaging (MRI) for placenta accreta. Compared with traditional ultrasound, MRI has the advantages of high-resolution, multiangle imaging, and less influence by amniotic fluid and intestinal gas. However, the reported diagnostic accuracy among studies was inconsistent. Therefore, this study is aimed at exploring the diagnostic value of MRI for placenta accreta by systematic review and meta-analysis. *Methods*. Relevant literature were systematically searched in PubMed, Ovid, Embase, ScienceDirect database, CNKI, and Wanfang database by using medical subject headings and relevant diagnostic terminologies such as sensitivity, specificity, likelihood ratio, receiver-operating characteristic curve, and area under the curve. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the curve of the included literature were analyzed using stata 17.0 software. Publication bias of the included studies was assessed by Deek's funnel plot. Cochrane Q statistics and I^2 statistics were used to test the heterogeneity. *Results*. A total of 10 primary publications, comprising 4 retrospective studies and 6 prospective studies, were included in this meta-analysis. The gestational weeks of pregnant women ranged from 32 to 35 weeks, and the sample size ranged from 37 cases to 575 cases. Only 4 studies used the blind method in the process of clinical diagnosis by MRI. The combined sensitivity, specificity, and area of curve under summary receiver-operating characteristic for the diagnosis of placenta accreta by MRI were 0.88 (95% CI, 0.79-0.93), 0.79 (95% CI, 0.68-0.87), and 0.91 (95% CI, 0.88.-0.93), respectively. The combined positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and diagnostic score were 4.17 (95% CI, 2.62-6.66), 0.16 (95% CI, 0.09-0.29), 26.61 (95% CI, 10.22-69.28), and 3.28 (95% CI, 2.32-4.24), respectively. No publication bias was noted. *Conclusion*. Diagnosis of placenta accreta by MRI has good accuracy and predictive value that warrants clinical promotion.

1. Introduction

Placenta accreta spectrum (PAS) refers to the abnormal attachment of placental trophoblasts to the uterine myometrium that can be further divided into placenta accreta, placenta increta, and placenta perforata based on the depth of invasion of the myometrium [1, 2]. Risk factors for PAS mainly include advanced maternal age, cesarean section, scarred uterus, placenta previa diagnosed before delivery, uterine lesions, and assisted reproductive technology. The primary pathophysiological mechanism of placenta accreta may be related to a specific or a combination of factors, such as basal decidua loss, abnormal local oxygen tension, excessive trophoblast invasion, and abnormal vascular remodeling [3, 4]. With the increase in abortion and cesarean section rates, the incidence of placenta accreta has shown an increasing trend worldwide. A recent multicenter Chinese population-based study showed that the incidence of placenta accreta in China had increased from 0.03% in 1980 to 2.2% in 2022, which was higher than in the coastal areas than that in inland areas. Furthermore, the prevalence in developed regions was higher than that in underdeveloped

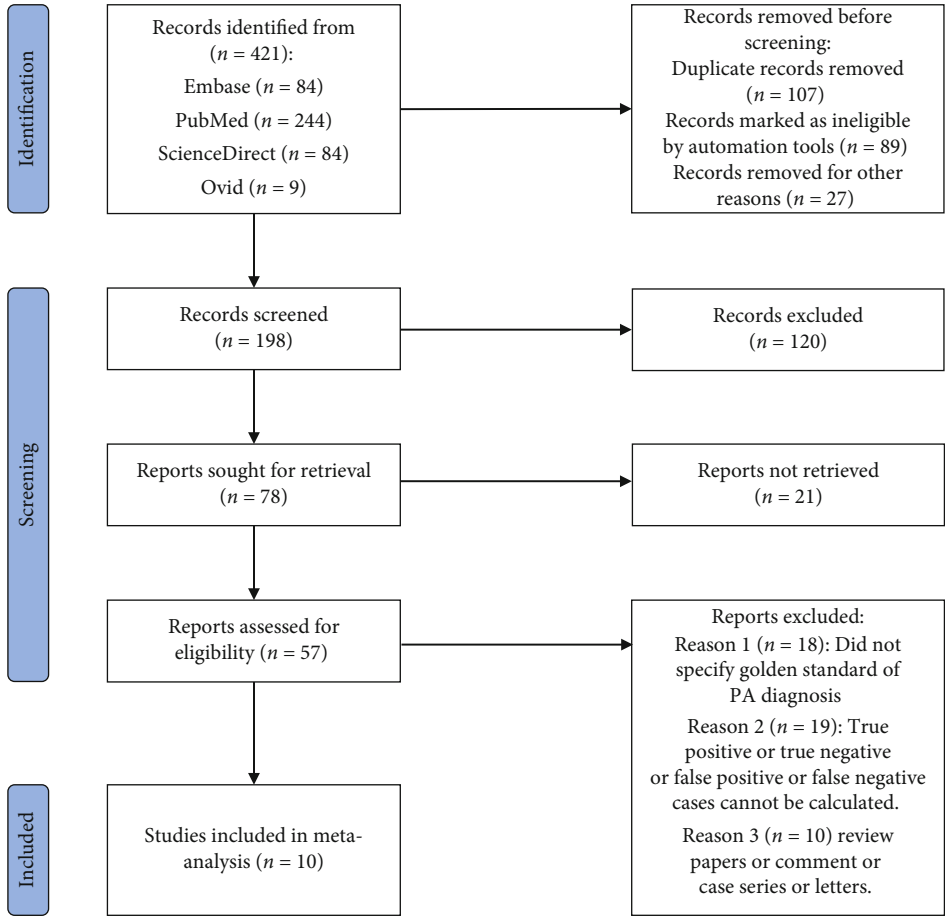


Figure 1: PRISMA flowchart of literature screening.

areas in central and western China [5]. Studies have shown that the perinatal mortality of placenta accreta is about 7% [6], while about 50-60% of placenta accreta is not diagnosed before delivery [7, 8]. Due to the increasing disease burden, early diagnosis of placenta accreta is essential for decreasing maternal mortality or morbidity.

Doppler ultrasound is currently the primary imaging technique for diagnosing placenta accreta thanks to its non-invasiveness, economic advantage, and wide availability. However, its diagnostic yield for placenta accreta is adversely influenced by amniotic fluid, intestinal gas, and placental position [8]. In recent years, magnetic resonance imaging (MRI) has been increasingly adopted in the diagnosis of prenatal placental implantation in the realization of its advantages of high-resolution, multiangle imaging, and limited influence by amniotic fluid and intestinal gas [6]. Previous Chinese and English literature have reported the diagnostic accuracy of MRI for placenta accreta with inconsistent sensitivity and specificity. Therefore, a meta-analysis can obtain a more reliable conclusion by systematically combining the indicators of diagnostic accuracy of included studies. Thus, the purpose of this study is to assess the clinical value of MRI for the diagnosis of placenta accreta by systematic review and meta-analysis of published diagnostic studies.

2. Methods

2.1. Retrieval Strategy. In this study, the following Medical Subject Headings (MeSH) were used in PubMed, Ovid, Embase, ScienceDirect databases, CNKI, and Wanfang databases, respectively, from inception to April 2022: ("placenta accreta" OR "Accreta, placenta" OR "placenta increta" OR "placenta percreta") AND ("MRI", "magnetic resonance imaging") AND ("diagnosis" OR "diagnostic accuracy" OR "sensitivity" OR "specificity"). The database was supplemented and improved by screening other relevant unpublished literature, meeting notes, and contacting experts in relevant clinical fields. The literature screening process is shown in Figure 1 per the PRISMA guideline.

2.2. Inclusion and Exclusion Criteria. Retrieved publications were subject to the inclusion and exclusion criteria established below. Inclusion criteria are (1) MRI was used to assist in the diagnosis of placenta accreta in pregnant women with a history of cesarean section or placenta previa; (2) the sample size should be at least 8 cases per group; (3) indicators of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) required for the combined effect value could be calculated directly or indirectly according to

Table 1: Characteristics of documents included in the analysis.

Included studies	Mean gestational weeks	Sample size	TP	FP	FN	TN	Literature type	Whether the blind method was used
Yan et al. (2022) [18]	33.3 ± 4.6	47	16	3	4	31	Prospective study	No
Riteau et al. (2014) [17]	34 ± 4.7	42	16	25	5	25	Retrospective study	Yes
Maher et al. (2014) [16]	32.4 ± 4.3	575	42	160	7	533	Prospective study	No
Lopes et al. (2019) [15]	35.4 ± 1.1	37	16	28	1	21	Retrospective study	Yes
Elhawary et al. (2013) [11]	33.1 ± 5.1	39	8	5	1	31	Prospective study	No
Ding et al. (2021) [14]	32.92 ± 4.1	89	17	8	2	72	Prospective study	Yes
Einerson et al. (2020) [13]	34.8 ± 4.1	68	44	10	23	24	Prospective study	Yes
Ayati et al. (2017) [12]	32.1 ± 3.98	82	24	12	8	58	Retrospective study	No
Zhang et al. (2021) [10]	34.51 ± 3.19	128	101	3	3	27	Prospective study	Yes
Xiao et al. (2027) [9]	33.29 ± 5.72	150	58	18	2	92	Retrospective study	No

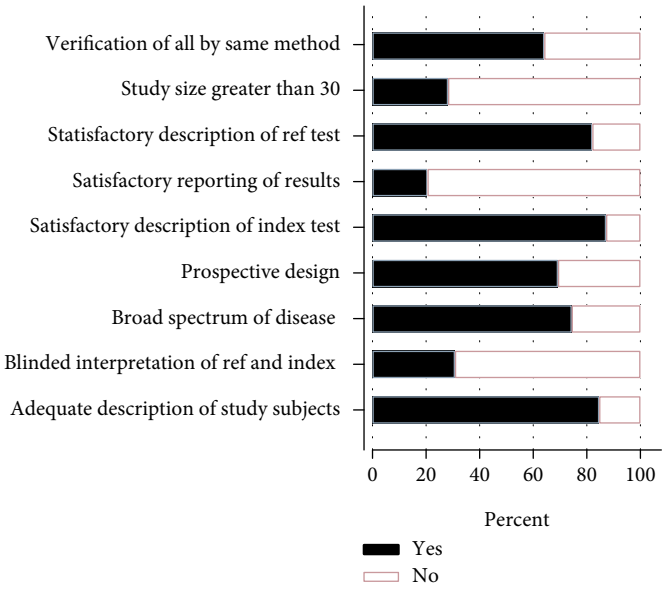


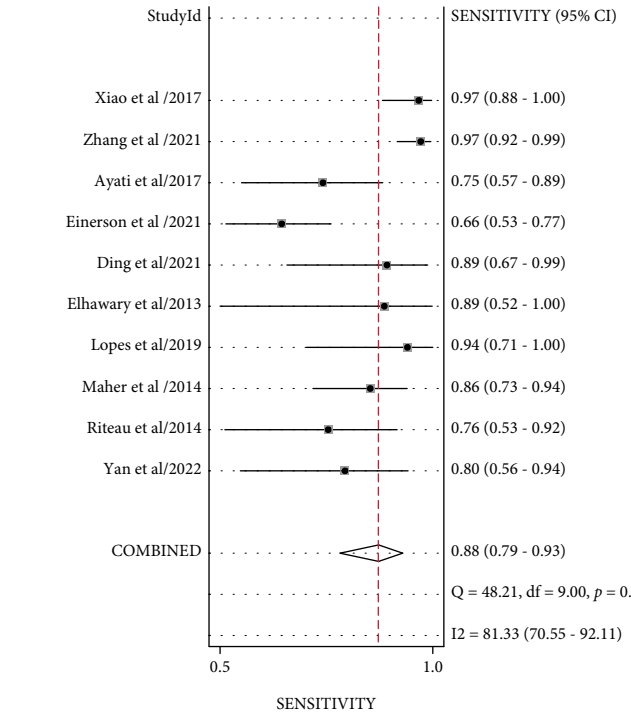
Figure 2: Sectional bar chart of literature quality evaluation summary by diagnostic experimental research quality evaluation scale tool.

the data of the original study; and (4) the diagnosis of placenta accreta was established by histopathological analysis.

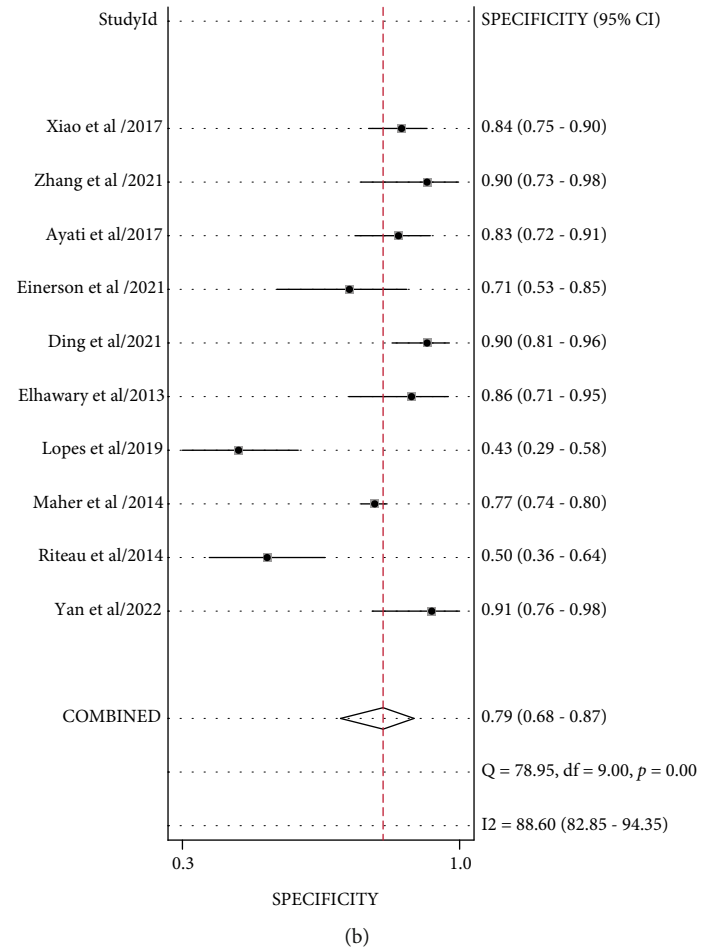
Exclusion criteria are (1) academic review, academic conference, review, and case report; (2) the data provided by the article was not enough to calculate the diagnostic accuracy; (3) withdrawn articles; (4) the research content was irrelevant to this study; and (5) publications with study population overlap.

2.3. Documentation and Evaluation. The following data were extracted from the included studies two independent researchers: author, publication time, study design (prospective or retrospective), demographic characteristics of the study population (gestational age), sample size, TP, FP, FN, TN, sensitivity, specificity, and the diagnostic gold standard. Discrepancies between the 2 investigators were settled by discussion or consulting with a third investigator. The methodological quality and risk bias of the included studies were assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS), which assessed a total of 14 items phrased as questions that evaluated the disease spectrum, the interpretability of the examination results, whether the blind method was used in the implementation of the trial, the use of the gold standard, the disease progress, the evaluation bias, the combined bias, and the rationality of the included cases.

2.4. Statistical Methods. In this study, STATA17.0 (MP) was used for statistical calculation. The relevant diagnostic accuracy indicators, including sensitivity, specificity, diagnostic odds ratio (DOR), negative likelihood ratio, and positive likelihood ratio, were pooled. The summary receiver-operating characteristic (SROC) curves were used to calculate the area under the curve (AUC) of the combined model. The heterogeneity among the included studies was quantified using the Cochrane Q statistics and I^2 statistics. When the I^2 statistic exceeded 50%, the random-effect model based on the Dersimonian-Laird method was used to merge the



(a)



(b)

Figure 3: Combined sensitivity and specificity forest plot. (a) Combined sensitivity forest map. (b) Combined specificity forest plot.

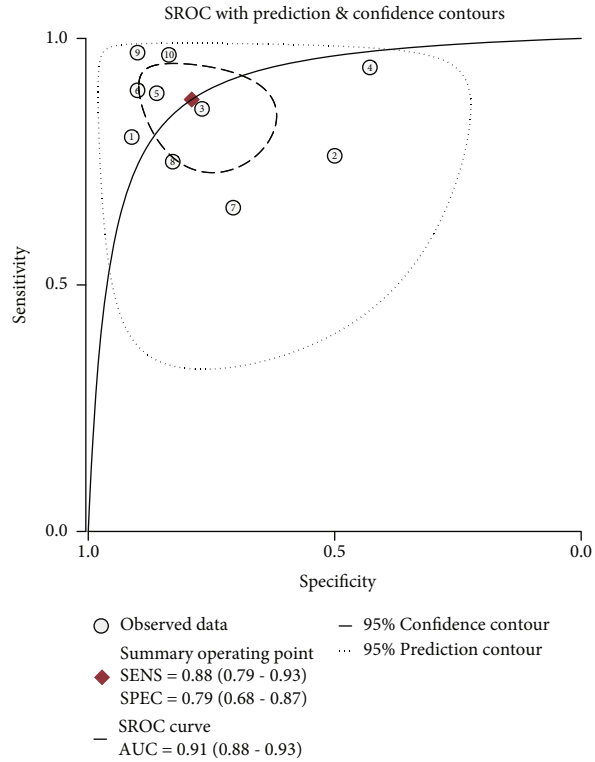


Figure 4: Summary receiver-operating characteristic and the area under the curve after combination.

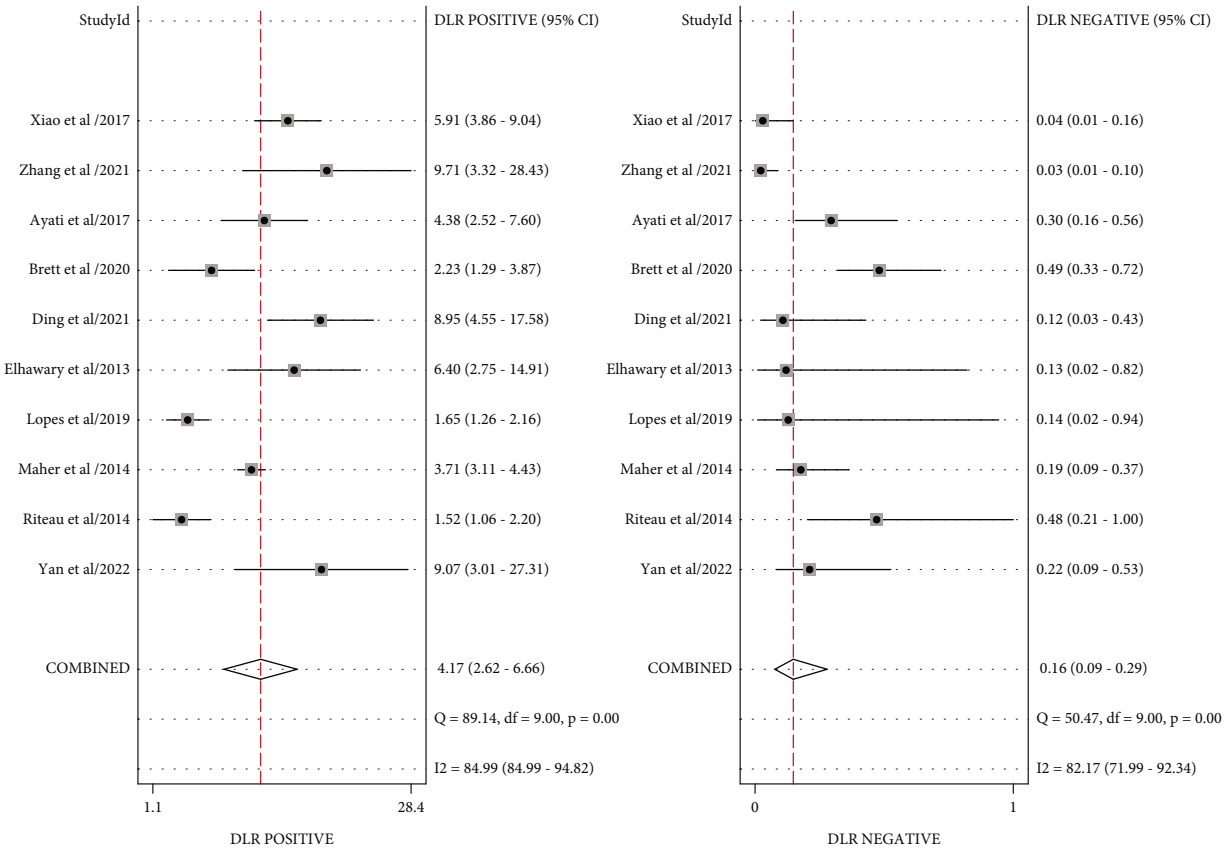


Figure 5: Forest plot for likelihood ratio after combination (LR+, LR-).

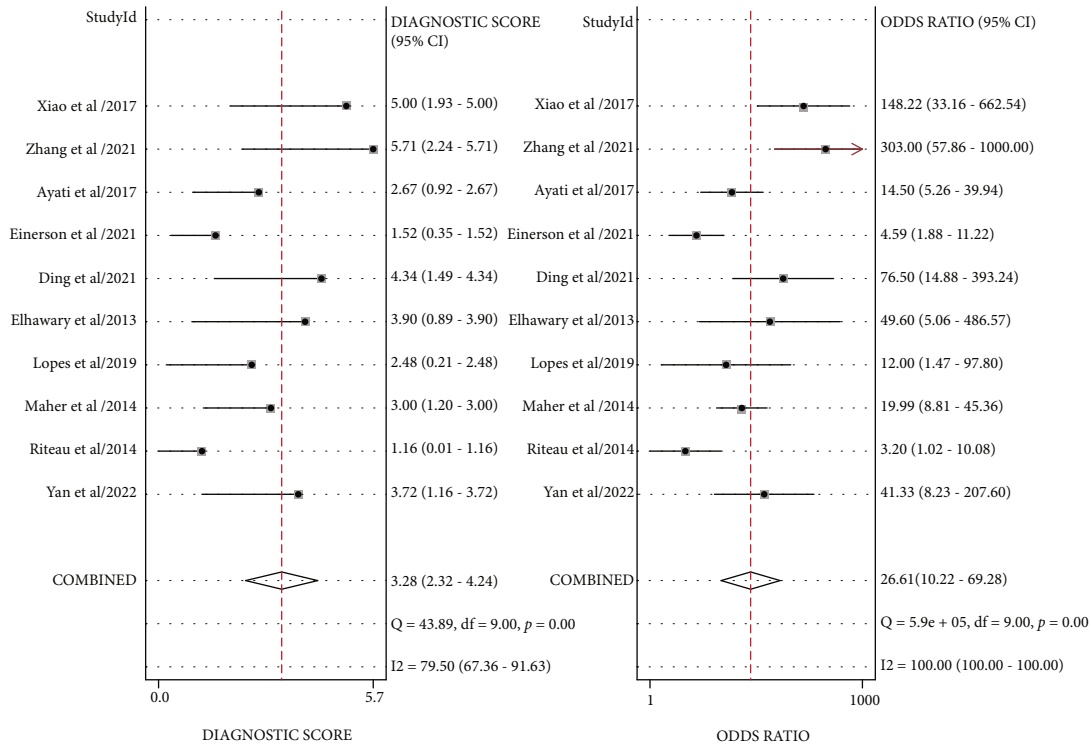


Figure 6: Forest plot for diagnostic odds ratio and diagnostic score after combination.

diagnostic accuracy indicators when the I^2 statistic >50%. Otherwise, the Mantel-Haenszel's fixed-effect model was used. Publication bias of the included studies was assessed by Deek's funnel plot. All hypothesis tests were statistically significant with two-sided $P < 0.05$.

3. Results

3.1. Search Results. A total of 421 relevant literature were generated through the systematic search. After screening according to the inclusion/exclusion criteria, a total of 10 publications [9–18] were included in this meta-analysis, including 4 retrospective studies and 6 prospective studies. The gestational weeks of pregnant women ranged from 32 to 35 weeks, and the sample size ranged from 37 cases to 575 cases. Among the 10 publications, only 4 studies used a blind method in the process of clinical diagnosis with MRI. The characteristics of the included studies are shown in Table 1.

3.2. Literature Quality Evaluation. The MIDAS command in STATA 17.0 MP was used to draw a segmented bar chart containing the evaluation criteria of each QUADAS [19]. As shown in Figure 2, the overall quality of the included literature was high. Most of the included literature described the gold standard used, the diagnostic criteria for placenta accreta, and the demographic characteristics and related risk factors for study population. However, most studies included a small sample size, and less than half of the studies used a blind method in diagnosing placenta accreta using MRI.

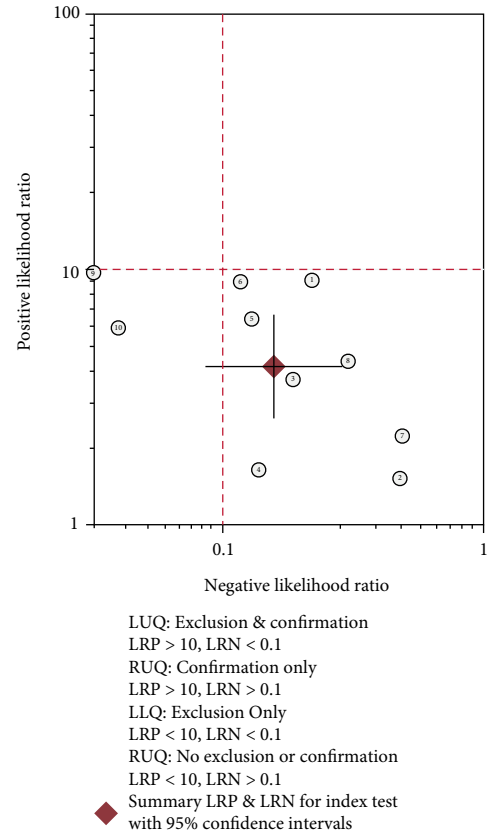


Figure 7: Distribution scatter diagram of the likelihood ratio (LR +/LR-) of each study and combined estimated value.

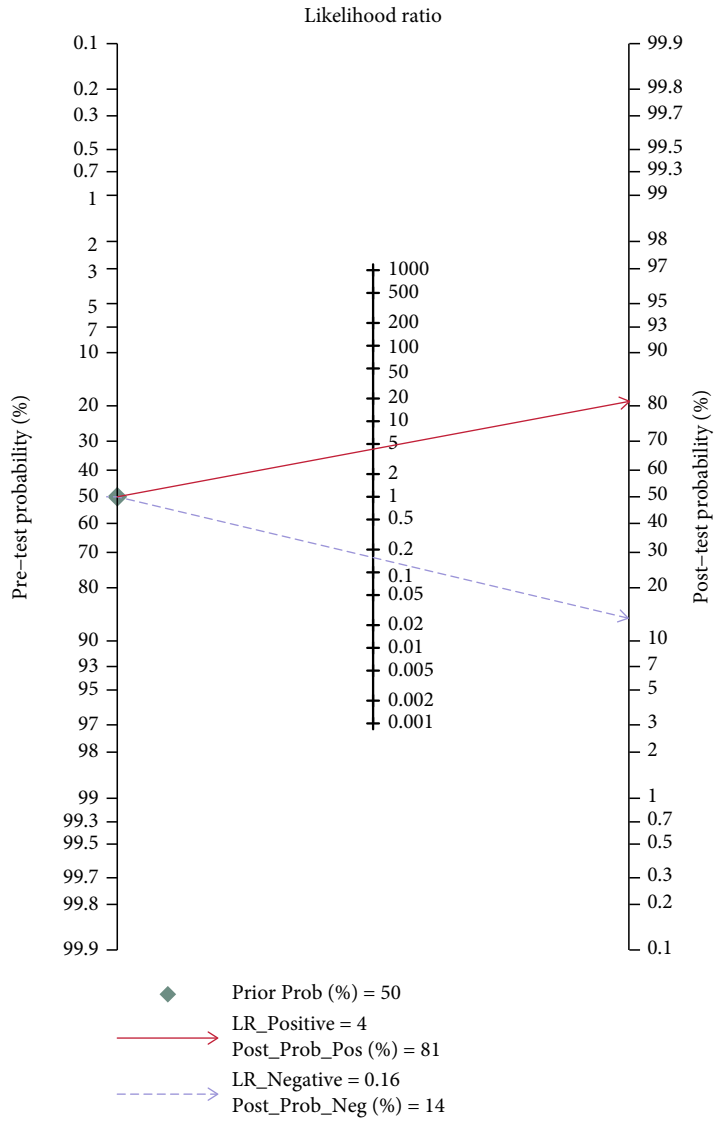


Figure 8: Fagan nomogram of the accuracy of MRI in the diagnosis of placenta accrete.

3.3. Meta-Analysis of the Accuracy of MRI in Diagnosing Placenta Accreta

3.3.1. Heterogeneity Analysis. The results indicated high heterogeneity ($Q = 8.131$, $I^2 = 75.95\%$), for which the random-effects model was used to combine the effect sizes. In addition, the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and I^2 of the diagnostic odds ratio were all >50%.

3.3.2. Combined Effect Analysis. The pooled sensitivity, specificity, and AUC were 0.88 (95% CI: 0.79-0.93), 0.79 (95% CI: 0.68-0.87), and 0.91 (95% CI, 0.88.-0.93), respectively. The combined diagnostic odds ratio, positive likelihood ratio, negative likelihood ratio, and diagnostic score were 26.61 (95% CI, 10.22-69.28), 4.17 (95% CI, 2.62-6.66), 0.16 (95% CI, 0.09-0.29), and 3.28 (95% CI, 2.32-4.24), respectively (Figures 3–6). The scatter plot of the likelihood ratios showed that the pooled estimates with 95% confidence interval were located in the lower right quadrant, suggesting that the combined accuracy of MRI for diagnosing placenta accreta was poor (Figure 7).

3.3.3. Fagan Nomogram Analysis. A 50% predicted probability was assessed to simulate a clinical situation, resulting in a posttest probability of 81% for a positive test result, while the negative likelihood ratio was 0.16, and the negative posttest probability was 14% (Figure 8).

3.4. Publication Bias. The Deek funnel plot (Figure 9) showed a slope coefficient of 0.611, indicating that there was no publication bias in the included studies.

4. Discussion

This study showed that MRI has good accuracy in diagnosing placenta accreta. Depending on the degree of myometrial invasion [20], placenta accreta is associated with life-threatening complications that include maternal bleeding,

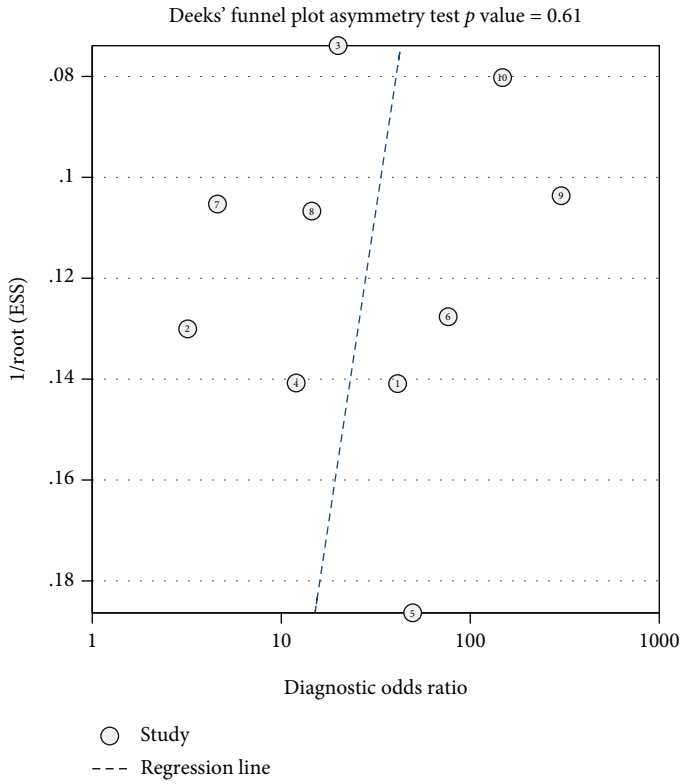


Figure 9: Deek funnel plot showing publication bias.

uterine perforation, or even death [21, 22]. Studies have shown that placenta accreta accounted for roughly 1/3 to 1/2 of postpartum emergency hysterectomy [20]. Common risk factors for placenta accreta include advanced maternal age (≥35 years), assisted reproductive technology [6, 23], placenta previa, history of uterine injury, Asherman's syndrome, abnormal uterine anatomy, or uterine pathological status (such as bicornate uterus, adenomyosis, and submucosal myoma) [21]. An apparent dose-response relationship between the frequency of cesarean section and the incidence of placenta accreta has also been noted, as exemplified by the fact that the risk of placenta accreta at the first cesarean section is only 3% [24], which increases to an astonishing 40-67% at 3rd to fifth cesarean section [25]. Epidemiological studies showed accompanying cesarean section rate increase in China [26], and the incidence of placenta accreta had also increased from 0.25/1000 in 1970 [27] to 0.79/1000 in 2003 [28] and 1/533 in 2015 [29]. Although ultrasound [30] is the preferred imaging method for the clinical diagnosis of suspected placental implantation, Aitken et al. have shown that MRI has obvious advantages over ultrasound in predicting the depth of placental implantation and invasion of the surrounding tissue [31]. Furthermore, Bakri et al. [32] and Thorp et al. [33] also suggested that even though ultrasound diagnosis had the advantages of economy and convenience that supports its utility as the mainstream diagnostic technique for placental implantation in the future, MRI has superior diagnostic performance for pathologies of the posterior placenta, thanks to its higher resolution and multiangle imaging of soft tissue that can clearly depict the adjacent anatomical position and vascular distribution during placenta implantation. In addition, MRI can provide more reference information for cesarean section that helps to reduce the risk of intraoperative bleeding. Thus, MRI can still be used as an auxiliary diagnostic method even when ultrasound has clearly diagnosed placenta accreta [34, 35]. However, the imaging signs of placenta accreta by MRI also partially coincide with those of normal pregnant women, such as thinning of the myometrium, uneven signals in the placenta, and blurring of the placenta myometrium junction. The respiratory movement of the fetus and pregnant women may also cause artifact interference to the image quality, which greatly increases the false negative or false positive results of MRI interpretation. Some researchers believe that MRI suffers from several safety and ethical problems, such as long scanning time, annoying scanning noise, and heavy abdominal coil. Therefore, ultrasound is still recommended as the first-line imaging modality for placenta implantation [36].

This study suffers from several limitations. First, most of the included studies did not report the risk factors and baseline characteristics of placenta accreta before the study. Most of the study population was not randomized, which might introduce bias to the present meta-analysis. Second, there was no unified imaging standard for the diagnosis of placenta accreta by MRI. The interpretations of MRI images may be subject to the reader's experience, which may explain the differences in the sensitivity and specificity of placenta accreta diagnosis by MRI reported. Third, this study excluded publications published in languages other than

English and Chinese, which may introduce bias on the true diagnostic value of MRI for placenta accreta. However, we believe that this bias should be relatively small since no publication bias was observed in this study. At last, the fact that less than 4 studies were available for each country rendered subgroup analysis at the regional level difficult. Regional differences was considered to be the most likely source of heterogeneity among studies.

5. Conclusion

This study showed that MRI had good diagnostic accuracy for diagnosing prenatal placenta accreta. However, due to insufficient evidence for the economic benefit between ultrasound and MRI and considerable differences in imaging diagnostic criteria, it is still recommended to take ultrasound as the first-line imaging modality for placenta accreta. Nonetheless, MRI as an auxiliary imaging modality can still supplement clinical useful information.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Huien Lin and Li Li contributed equally to this work.

Acknowledgments

The study was supported by Haikou Maternal and Child Health Hospital.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 3462392, 11 pages
https://doi.org/10.1155/2022/3462392

Research Article

The Association between Physical Exercise during Pregnancy and Maternal and Neonatal Health Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Received 21 June 2022; Revised 24 July 2022; Accepted 25 July 2022; Published 21 August 2022

Academic Editor: Xi Lou

Objective. To explore the effect of exercise during pregnancy on the maternal and neonatal health outcomes. *Methods*. Eligible papers were systematically retrieved from PubMed, Embase, OVID, and ScienceDirect. Two researchers independently extracted the primary endpoints from the included literature. Random-effect model or fixed-effect model were utilized to generate and compute relative risk and mean difference, as appropriate. Publication bias was quantified and assessed using the funnel plot with Egger's test. *Results*. This study included 13 literatures with a total of 3047 pregnant women with gestational weeks more than 10 weeks. The incidence of vaginal delivery was significantly higher in the intervention group than that in the control group (28.7% vs 23.3%, $P < 0.001$). The differences of duration of the first stage and second stage of labor between the interventional group and control group were both statistically insignificant (mean difference: 27.92, 95% CI: −70.60, 14.7, $P = 0.20$; mean difference: 0.63, 95% CI: −4.47, 5.74, $P = 0.81$). In addition, there were no significant differences with regard to gestational age at delivery (mean difference = −0.23, 95% CI: −1.29, 0.83, $P = 0.67$), Apgar score (mean difference = 0.06, 95% CI: −0.13, 0.26, $P = 0.53$), and birth weight (mean difference = −23.78, 95% CI: −60.66, 13.11, $P = 0.21$) between the 2 groups. Women in the intervention group were more likely to experience vaginal delivery than the control group (RR = 1.27, 95% CI: 1.04, 1.55, $P = 0.01$). *Conclusions*. Physical exercise during pregnancy could improve the incidence of natural labor.

1. Introduction

Regular aerobic exercise is essential for maintaining healthy. Exercise during pregnancy is also vital because women of childbearing age have a significantly higher risk of developing gestational diabetes that is highly related to weight gain and altered hormone metabolism during pregnancy. The American College of Obstetricians and Gynecologists recommended 30 minutes of moderate-intensity aerobic exercise every day for pregnant women without obstetric or other complications in 2002 [1]. In fact, many studies have shown that exercise during pregnancy can significantly reduce the risk of placenta previa [2], gestational diabetes [3], preterm delivery [4], and postpartum depression [5]. Exercise can effectively improve the tolerance of labor pain during delivery and postpartum physical function and prevent weight gain during pregnancy. On the contrary, a host of studies have also reported that exercise intervention during pregnancy also impacts the duration of labor, which is highly correlated with the health outcomes of pregnant women and newborns [6]. If the duration of the first stage of labor is prolonged,

Table 1: Basic characteristics of the literature included in the analysis.

Authors	Study type	Sample size		Duration of the first stage of labor		Duration of the second stage of labor		Gestational age at birth		Spontaneous labor		Apgar score		Birth weight		NOS
		Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	
Salvesen et al. (2014) [16]	RCT	31	31	373 ± 266	377 ± 373	44 ± 27	38 ± 24	NA	NA	NA	NA	NA	NA	NA	NA	7
da Silva et al. (2017) [17]	RCT	204	407	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3244 ± 424	3254 ± 457	6
Sanda et al. (2018) [12]	RCT	295	294	293.4 ± 201	257.1 ± 181	40.5 ± 25	41.5 ± 24.1	279 ± 12	279 ± 13	NA	NA	9.6 ± 0.7	9.4 ± 1.1	3410 ± 486	3449 ± 539	7
Zarezadeh et al. (2016) [18]	RCT	40	40	329.86 ± 220.68	451.3 ± 187.99	NA	NA	NA	NA	34	14	NA	NA	NA	NA	6
Toosi et al. (2016) [11]	RCT	60	60	252 ± 84	288 ± 54	48.9 ± 11.9	51.6 ± 10	274 ± 8	276 ± 6	41	29	9.3 ± 1.3	10 ± 1.6	3185 ± 453	3175 ± 392	8
Ghodsi et al. (2014) [19]	RCT	40	40	299.6 ± 126.87	147.8 ± 40	29.5 ± 13.99	32.5 ± 13.68	NA	NA	35	35	NA	NA	3059 ± 339	3255 ± 456	8
Price et al. (2012) [20]	RCT	31	31	555 ± 300	504 ± 204	47.4 ± 36	28.4 ± 12.5	NA	NA	27	19	9 ± 0.5	8.7 ± 0.5	3329 ± 519	3308 ± 103	8
Rodriguez et al. (2017) [21]	RCT	50	50	NA	NA	NA	NA	NA	NA	45	23	NA	NA	3361 ± 361	3417 ± 473	8
Ghandali et al. (2021) [14]	RCT	55	55	110 ± 70.94	164 ± 99.81	33.4 ± 24.51	50.36 ± 38.59	NA	NA	45	42	9.94 ± 0.24	9.88 ± 0.38	NA	NA	7
Garnaes et al. (2017) [13]	RCT	38	36	NA	NA	NA	NA	NA	NA	29	29	9.6 ± 0.5	9.4 ± 1.2	3719 ± 695	3912 ± 413	7
Murtezani et al. (2014) [22]	RCT	30	33	NA	NA	NA	NA	NA	NA	22	17	8.7 ± 0.8	8.2 ± 0.5	3250.8 ± 465.0	3237.9 ± 368.9	7
Barakat et al. (2018) [15]	RCT	255	253	462.83 ± 208.37	409.15 ± 185.74	36.21 ± 25.93	33.23 ± 22.53	278.5 ± 11	277.79 ± 8.57	139	115	9.8 ± 0.5	9.94 ± 0.85	3273 ± 415	3256 ± 466	8
Perales et al. (2016) [10]	RCT	83	83	399 ± 322.1	537.4 ± 409.3	40.6 ± 42.8	37.4 ± 44.7	277 + 8.8	277.9 ± 8.3	69	71	9.8 ± 0.5	9.9 ± 0.2	3183 ± 446	3232 ± 383	8

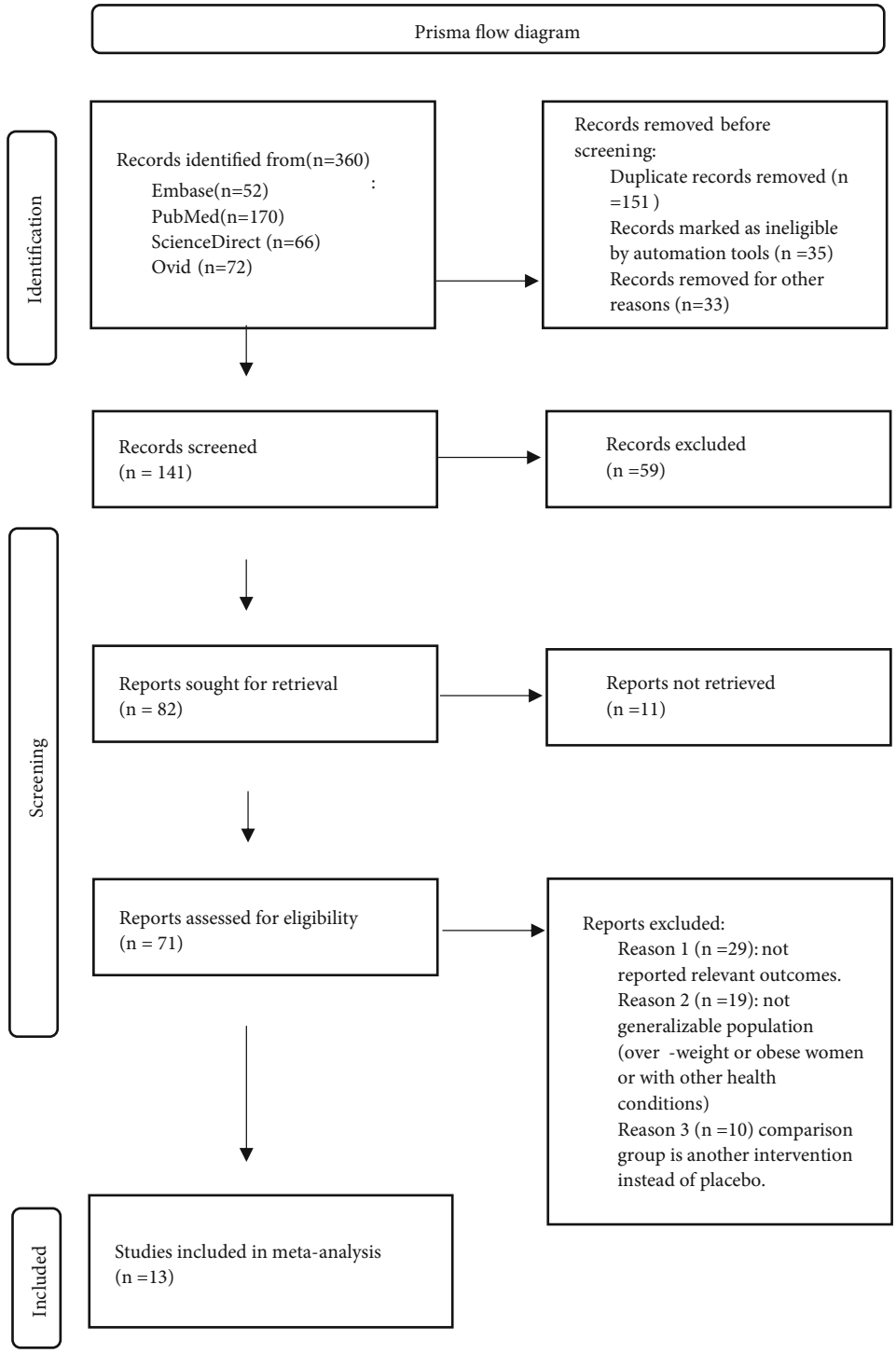

Figure 1: Prism flow chart. Process of meta-analysis for screening included literatures.

the fetal head may be squeezed by the birth canal, resulting in a decrease in Apgar score and even stillbirth [7]. The prolonged duration of the second stage of labor may increase the risk of obstetric canal laceration, cesarean section, and pelvic floor muscle injury. Therefore, it is of great clinical significance to determine health interventions that reduce the time of labor and improve the health outcomes of mothers and infants.

Although regular exercise can improve physical health, the effect of exercise during pregnancy on the maternal and neonatal outcome remains controversial [8, 9]. For example, Perales et al. found that the exercise during pregnancy did not increase the incidence of vaginal delivery [10], while other studies have come to the opposite conclusion [11–13]. Therefore, in view of the increasing number of randomized controlled trials (RCT) in recent years to

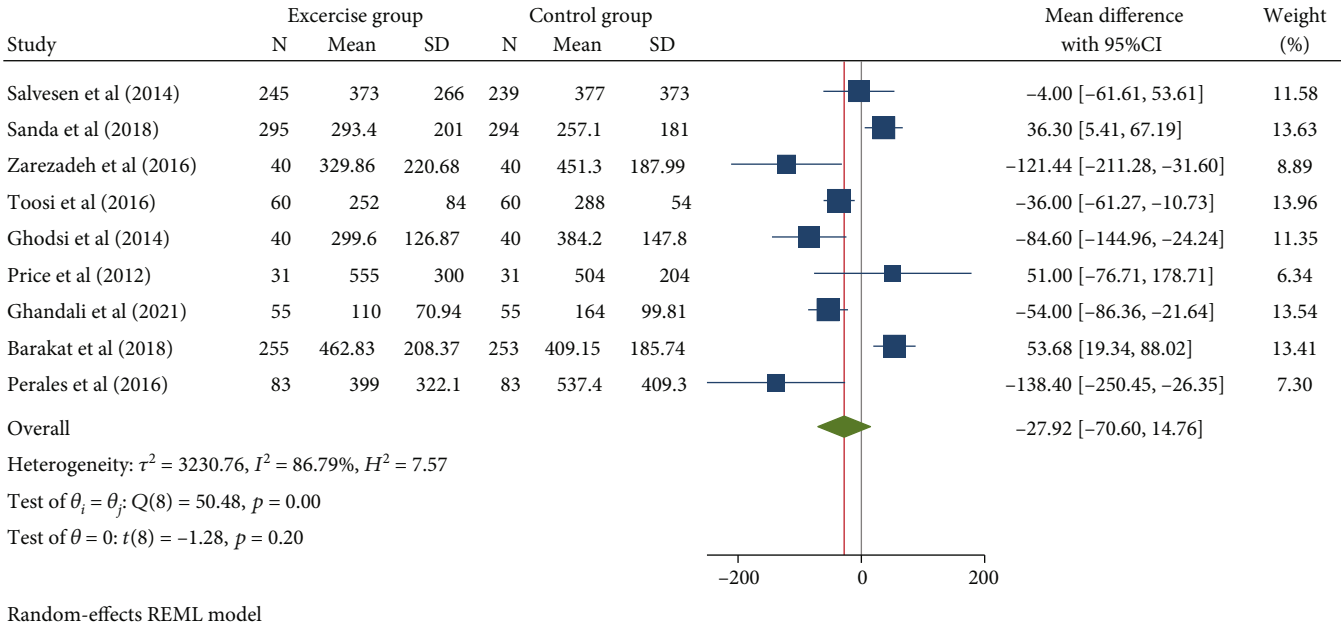

Figure 2: Forest map of the effect of exercise intervention during pregnancy on the duration of the first stage of labor.

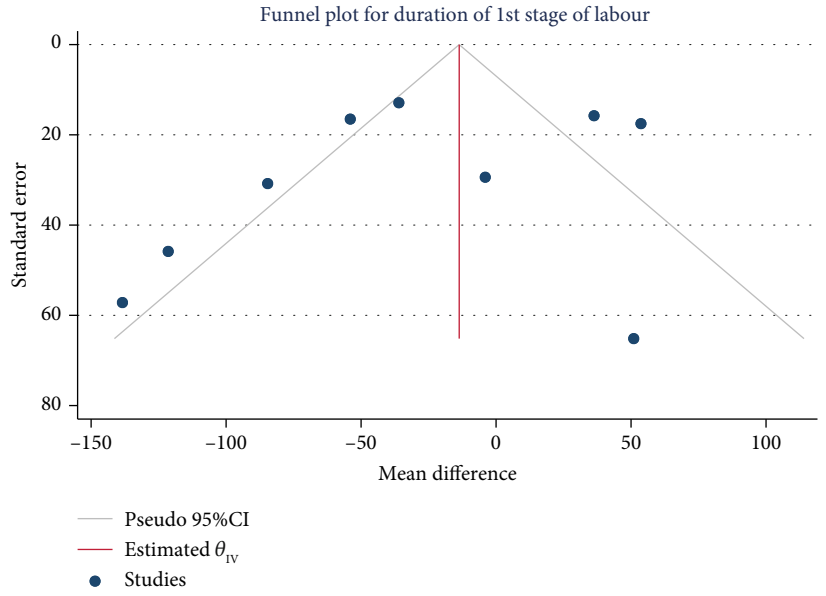

Figure 3: Funnel chart of the effect of exercise intervention during pregnancy on the duration of the first stage of labor.

explore the impact of exercise during pregnancy on maternal and neonatal health outcomes [12, 14, 15], we aimed to quantify the effect of exercise intervention during pregnancy on the health outcomes of newborns and pregnant women through systematic review and meta-analysis, thus providing clinical evidence for preventing adverse health outcomes in pregnant women and newborns.

2. Methods

2.1. Literature Search. The databases of PubMed, EMBASE, ScienceDirect, and OVID were used for literature retrieval from inception to May 15, 2022. The search keywords were ("exercise" OR "aerobic" OR "physical activity") AND ("Pregnancy"[Mesh Terms OR "Pregnant") AND ("maternal outcome" OR "neonate outcome" OR "Apgar" OR "delivery∗" OR "labor" OR "gestational age").

2.2. Literature Screening. Retrieved literatures were subject to the following inclusion and exclusion criteria. Inclusion criteria are as follows: (1) The study design was a RCT. (2) The study population was adult pregnant women with gestational weeks longer than 10 weeks. (3) The intervention method studied was regular exercise, including aerobic

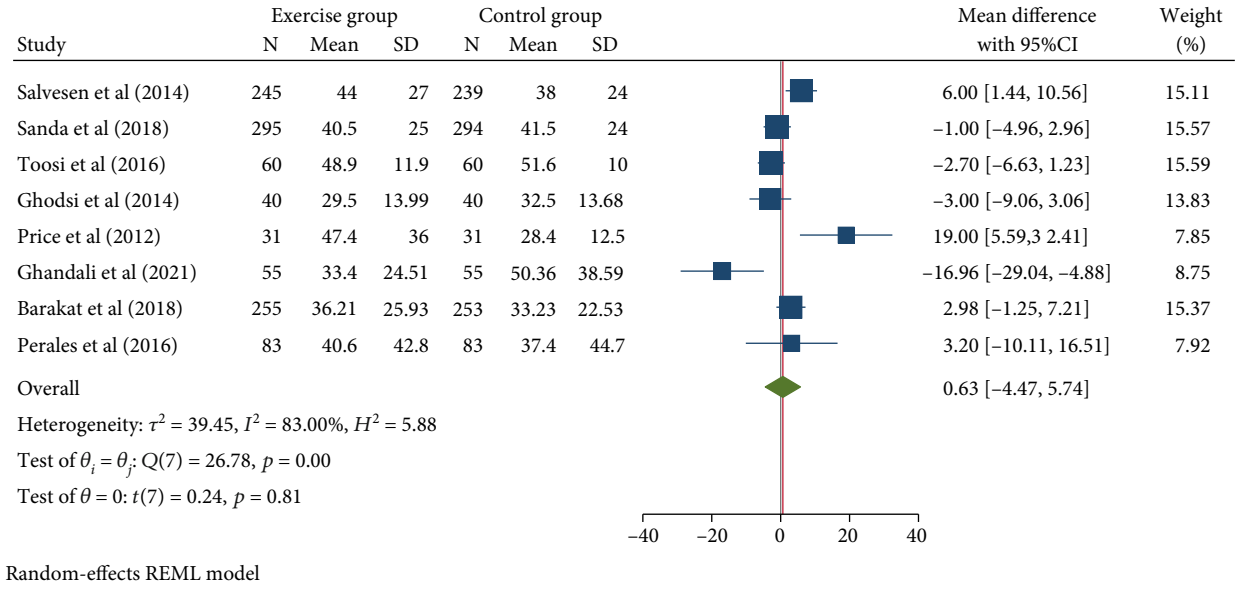

Figure 4: Forest map of the effect of exercise intervention during pregnancy on the duration of the second stage of labor.

Figure 5: Funnel chart of the effect of exercise intervention during pregnancy on the duration of the second stage of labor.

exercise, resistance exercise, yoga, and swimming. The control group received no exercises. (4) The primary endpoint of the study included at least one of the following six categories: duration of the first stage of labor, duration of the second stage of labor, mode of delivery, gestational age at birth, birth weight and newborn Apgar score.

Literature exclusion criteria are as follows: (1) Studies with no clear definition of intervention, short follow-up time, or the control group also received exercise. (2) Studies with population overlap. (3) The sample size of the interventional group or the control group was less than 20. (4) Non-original articles, such as comments, academic conferences, reviews, case reports. (5) Studies with Newcastle-Ottawa Scale (NOS) score less than 5. This study did not limit the characteristics of pregnant women, such as age, body mass index, prior history of diabetes, hypertension, or other chronic diseases, and whether they are primiparas.

2.3. Document Data Sorting and Evaluation. YL. W and LJ. W independently extracted the following data from the included literature: study type, number of patients, primary endpoint indicators such as the duration of the first stage of labor and the duration of the second stage of labor, mode of delivery, gestational age at birth, birth weight, and neonatal Apgar score. The continuous variable and binary variable were expressed as mean difference ± standard deviation and ratio of

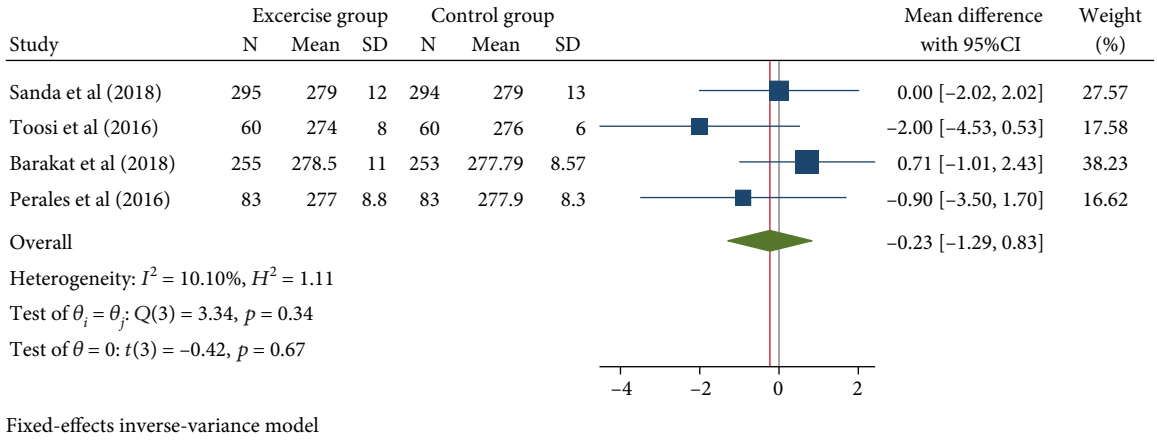

Figure 6: Forest map of the effect of exercise intervention during pregnancy on gestational age at birth.

the number of events in the intervention group and the control group, respectively, as shown in Table 1. The NOS was applied to evaluate the methodological quality of all the included literature. Those with a score below 5 were considered at high-risk for bias, whereas those with a score above 8 were considered at low-risk for bias. When discrepancies emerged between the 2 investigators emerged, an agreement could be reached through discussion with the third researcher.

2.4. Statistical Methods. Data analysis and merging in this study were done using STATA 17.0 software, and Endnote X9 was used for literature management. The Cochran's Q and I^2 statistics were used to assess the magnitude of heterogeneity between studies. For $I^2 > 50\%$, the random-effect model based on restricted maximum likelihood method was used; otherwise, the fixed-effect model based on the inverse variance model was used. In addition, the funnel plot was applied to measure publication bias in the meta-analysis. The geometric symmetry of the funnel plot was assessed using Egger's and Begg's tests. All hypothesis tests were considered statistically significant at $P < 0.05$, and all hypothesis tests were two-sided.

3. Results

3.1. Search Results and Literature Characteristics. A total of 360 relevant literatures were retrieved. According to the inclusion and exclusion criteria, 13 studies with 3047 pregnant women were finally included in the meta-analysis. Detailed process of literature retrieval and screening was presented in Figure 1. Among the 13 studies, 9 reported the duration of the first stage of labor, 8 reported the duration of the second stage of labor, 4 reported the indicators of gestational age at birth, 8 evaluated the Apgar score 5 minutes after birth, and 10 recorded the newborn birth weight and the mode of delivery. According to the Cochrane systematic evaluation system, 2 studies did not describe the grouping concealment and blind method of randomized grouping, which was considered to have a moderate risk of bias, and the rest of the literature had a minimal risk of bias. The NOS score ranged from 5 to 8, including 8 low-risk bias literature, 3 medium-risk bias literature and 2 high-risk bias literature.

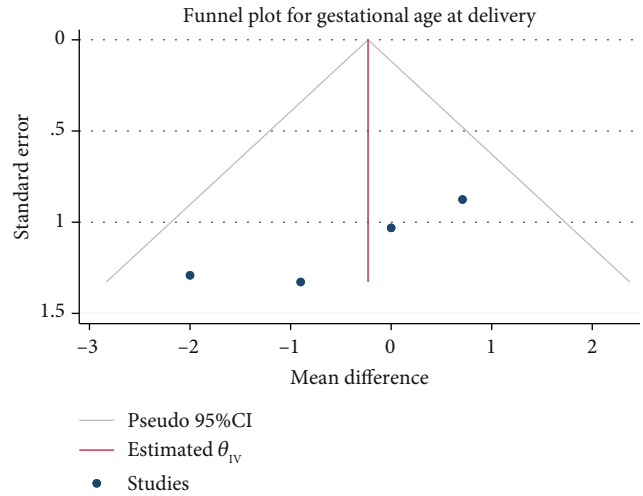

Figure 7: Funnel chart of the effect of exercise intervention during pregnancy on gestational age at birth.

3.2. Duration of the First Stage of Labor. A total of 2199 children in 9 studies were pooled for the duration of the first stage of labor. The random effect model was used to combine the mean difference, given the high degree of heterogeneity ($H^2 = 7.57$, $I^2 = 86.79\%$, $P = 0.20$). The results of the meta-analysis (Figure 2) showed that compared with the control group, the duration of the first stage of labor of pregnant women with exercise intervention during pregnancy was statistically insignificant (mean difference: −27.92, 95% CI: −70.60, 14.76, $P = 0.20$). The funnel chart (Figure 3) showed no obvious publication bias.

3.3. Duration of the Second Stage of Labor. A total of 8 studies with 2119 pregnant women were included in this study. The random effect model was used to combine the mean difference in the presence of high heterogeneity ($H^2 = 5.88$, $I^2 = 83.00\%$, and $P = 0.81$). The meta-analysis results (Figure 4) showed that the duration of the second stage of

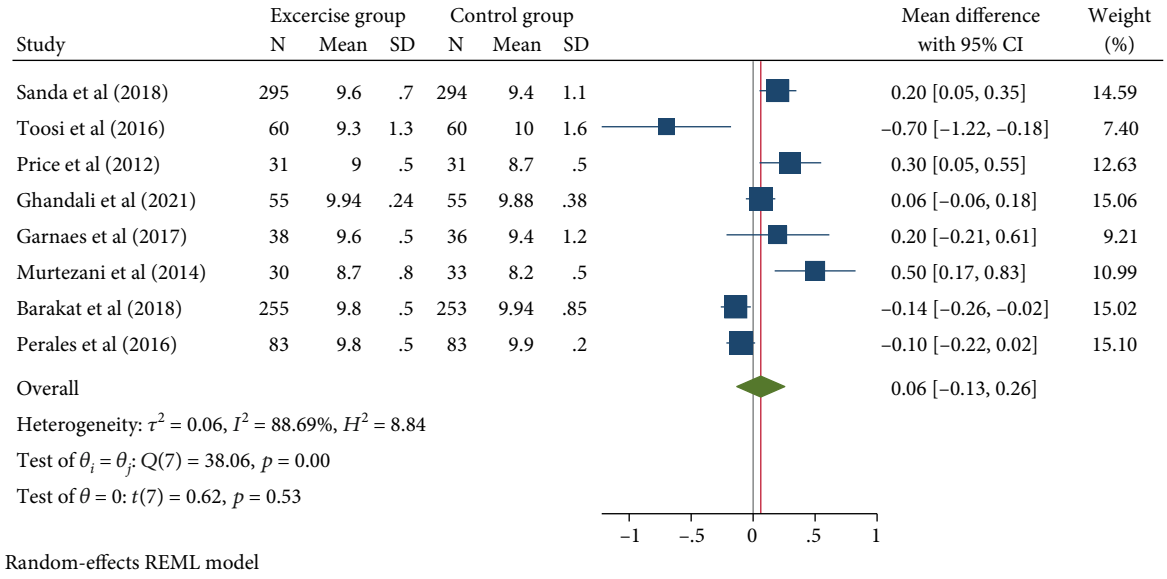

Figure 8: Forest map of the impact of exercise intervention during pregnancy on labour mode.

labor did not differ significantly between the interventional and control group (mean difference: 0.63, 95% CI: −4.47, 5.74, $P = 0.81$). No obvious publication bias was observed (Figure 5).

3.4. Gestational Age at Birth. A total of 1383 patients in 4 publications were included in this study. The fixed-effect model was applied to combine mean difference in the presence of low degree of heterogeneity ($H^2 = 1.11$, $I^2 = 10.10\%$, and $P = 0.67$). The meta-analysis (Figure 6) found no significant differences with regard to the gestational age at birth between the interventional group and the control group (mean difference = −0.23, 95% CI: −1.29, 0.83, $P = 0.67$). There was no obvious publication bias (Figure 7).

3.5. Mode of Delivery. Meta-analysis (Figure 8) using the random-effect model ($H^2 = 5.74$, $I^2 = 82.56$, $P = 0.01$) suggested that compared with the control group, pregnant women with exercise intervention were significantly more likely to have spontaneous labor (RR = 1.27, 95% CI: 1.04, 1.55, $P = 0.01$). No obvious publication bias was noted (Figure 9).

3.6. Apgar Score. A total of 2373 newborns in 10 studies were included in this study. The results of the meta-analysis (Figure 10) with the random-effect model ($H^2 = 8.84$, $I^2 =$ 88.69%, and $P = 0.53$) showed the newborn Apgar score between the interventional and control group was statistically insignificant (mean difference = 0.06, 95% CI: −0.13, 0.26, $P = 0.53$). The funnel chart (Figure 11) demonstrated no obvious publication bias.

3.7. Birth Weight. The heterogeneity test results of the 10 publications with 1363 participants were $H^2 = 1.00$, $I^2 =$ 0.00%, and $P = 0.21$. The fixed-effect model was then used. There was no significant differences with regard to the birth weight between the 2 groups (mean difference = −23.78, 95%

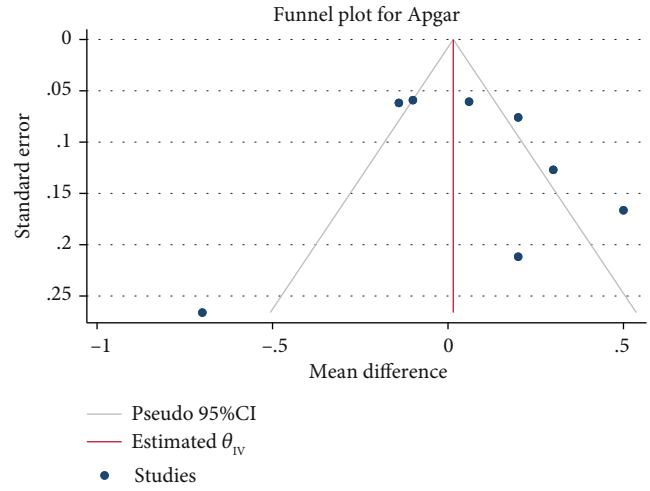

Figure 9: Funnel chart of the impact of exercise intervention during pregnancy on labour mode.

CI: −60.66, 13.11, and $P = 0.21$, Figure 12). There was no publication bias (Figure 13).

4. Discussion

This study showed that exercise intervention during pregnancy would increase the incidence of natural delivery and newborn Apgar score. The time of the first stage of labor and newborn birth weight in the exercise intervention group was shortened by about 28 minutes and 23.78 g, respectively, despite these differences were statistically insignificant. Hopkins and Cutfield [23] found that the most far-reaching impact of exercise during pregnancy on the health status of newborns may be derived from the reduction of birth weight. In addition, some studies have shown that moderate birth weight reduction is positively related to a decrease in the risk of childhood obesity [24–26]. Compatibly, the

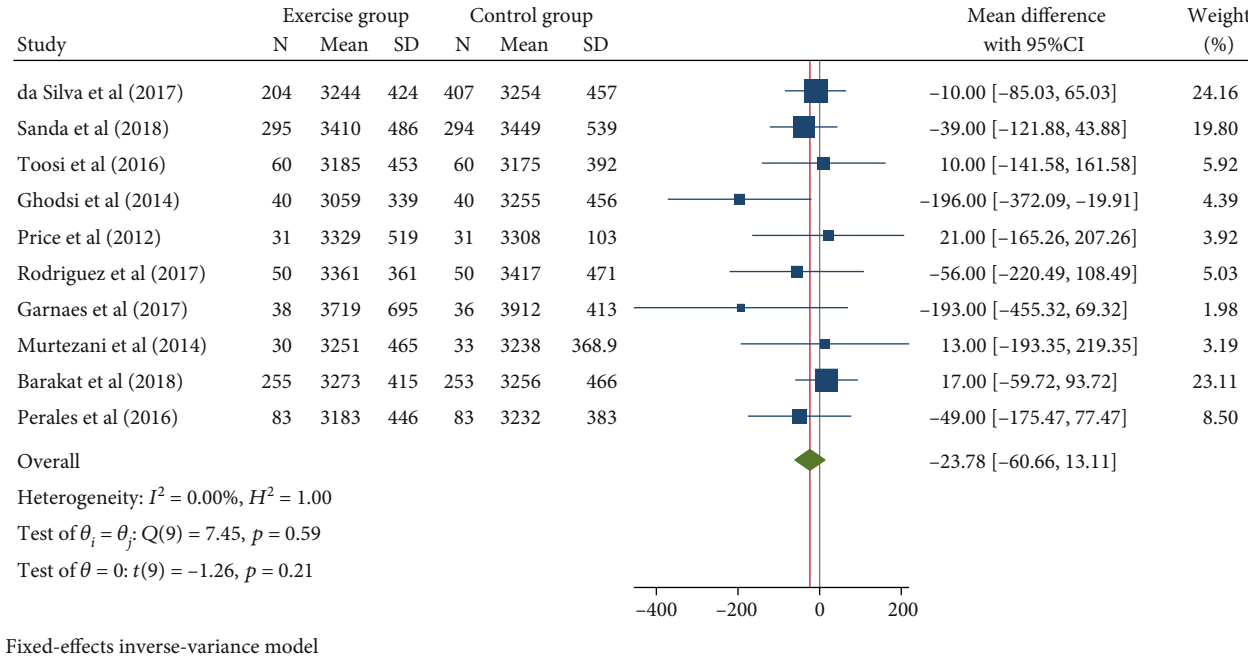

Figure 10: Forest map of the effect of exercise intervention during pregnancy on Apgar score.

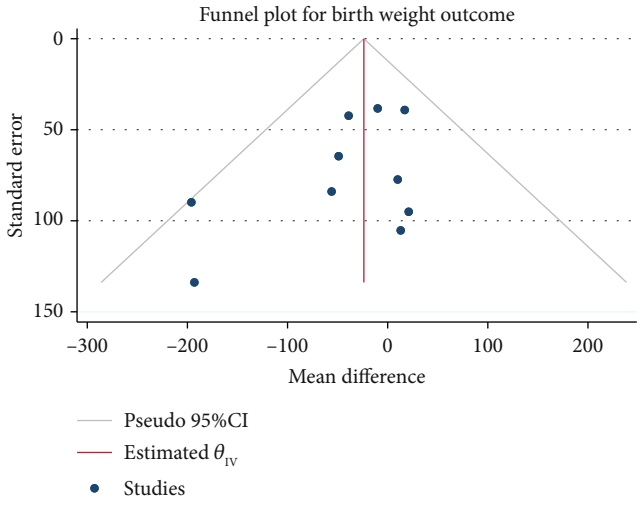

Figure 11: Funnel chart of the effect of exercise intervention during pregnancy on Apgar score.

newborns in the intervention group had lower birth weight and higher Apgar scores in the present study. Although prior studies suggested that low birth weight is also related to a series of health risks, the main reason against pregnant women from exercising properly during pregnancy is that exercise leads to the diversion of maternal oxygen and nutrients to skeletal muscle rather than to the fetus, which may affect the normal development of the fetus [27]. Nonetheless, the study by Sanabria-Martínez et al. [28] showed that the reduction of neonatal birth weight caused by exercise intervention during pregnancy was within the normal range and had no additional health hazard to the newborn. Some scholars believe that exercise during pregnancy may increase the risk of preterm birth, which is a leading cause of neonatal mortality [29], by increasing the level of norepinephrine. Norepinephrine has been shown to stimulate the uterine myometrium and induces preterm birth [30]. Increased risk of preterm birth has been demonstrated in a prior meta-analysis by Kramer and McDonald [31]. However, it is limited by small sample size that included three RCTs, which might lead to insufficient statistical power. Our study showed that exercise intervention during pregnancy did not affect the gestational weeks of newborns at birth, which was consistent with the conclusion of the 2012 meta-analysis [32] and the 2015 Cochrane meta-analysis [33].

According to the exercise guidelines of the American women's and children's Association [34], Poudevigne et al. recommended that reduced exercise intensity for pregnant women Resistance training can enhance pelvic floor muscles and improve pelvic stability, thus making pelvic floor muscles easier to relax during delivery and improving the position of the fetus in the birth canal. A host of factors affect the duration of delivery, such as the number of births and the time of the initiation of exercise intervention. The duration of the first stage of labor of the primipara was significantly longer than that of the multipara. The study by Zarezadeh et al. only included the primipara [18]. Therefore, it remains unclear at which stage of pregnancy does exercise intervention has the most significant impact on the health outcomes of the mother and fetus. In addition, some studies have suggested that pregnant women who have habits of regular exercise also have significantly higher exercise volume than women who have less exercise frequency in the early stages of pregnancy [35]. Therefore, studies would be more extrapolative by dividing study population into subgroups according to exercise habits, primipara/multipara, and the time of the exercise intervention.

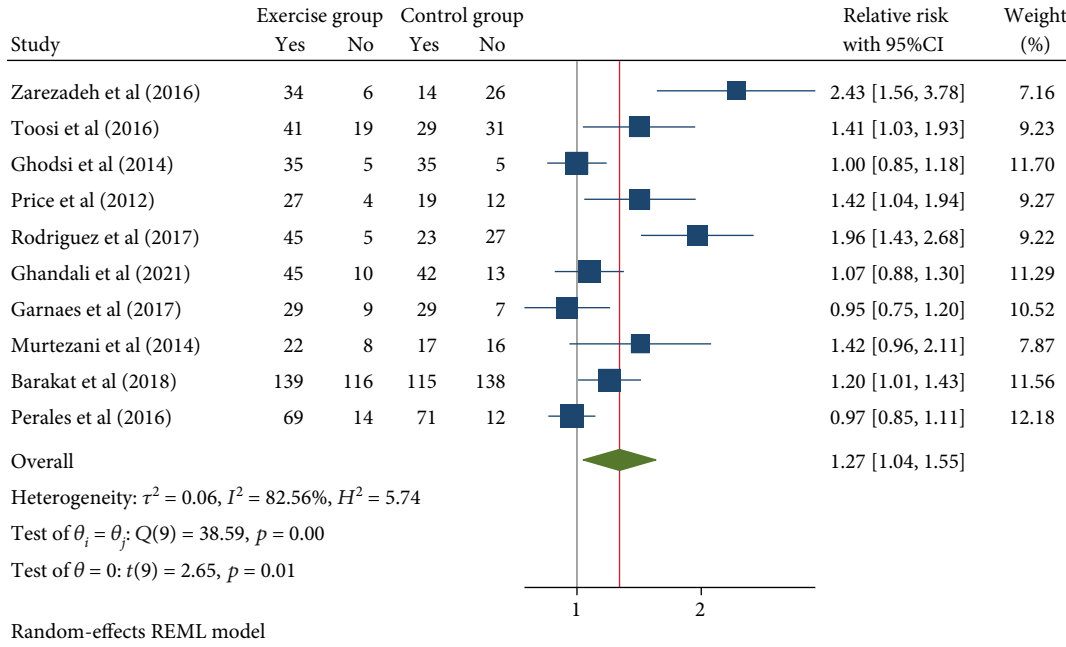

Figure 12: Forest map of the effect of exercise intervention during pregnancy on birth weight.

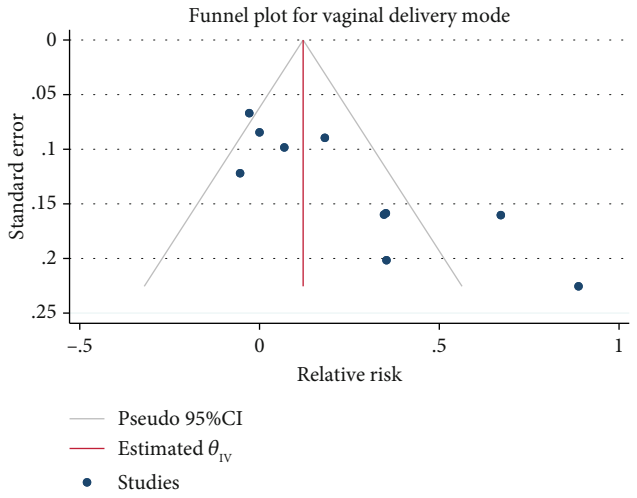

Figure 13: Funnel chart of the effect of exercise intervention during pregnancy on birth weight.

This study suffers from several limitations: (1) The sample size of some RCTs included in this study was small. Only three studies had a sample size of more than 100 cases [12, 15, 17]. (2) Some included studies did not clearly and completely clarify the specific methods of blinding and randomization. (3) Significant heterogeneity in the definition of exercise intervention, such as frequency, intensity, duration of exercise, and the gestational week for exercise intervention, were noted. (4) In some studies, the study population was limited to primiparas, while in others, the study population also included multiparas. Therefore, we cannot definitively exclude the effect of this possible confounding factor. (5) There were also differences in terms of whether the intervention was carried out under the researcher's supervision. Some studies used self-report results to evaluate the intervention, while exercise intervention in others was performed under the researcher's supervision. Therefore, the former might underestimate or overestimate the duration and intensity of exercise during pregnancy, thus introducing potential bias. (6) Differences in the distribution of other factors affecting the birth weight of newborns, such as exposure to environmental factors during pregnancy (noise, air pollutants, smoking, and mental health status of pregnant women during pregnancy) between the interventional and the control group were not reported in most studies.

In conclusion, our study results suggested that exercise intervention during pregnancy increased the incidence of natural delivery and was not associated with increased the health risks or adverse birth outcomes for perinatal pregnant women.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Yangling Wang and Liangjiao Wu contributed equally to this work.

Acknowledgments

The study was supported by The First Affiliated Hospital of Hainan Medical University.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 4627826, 8 pages
https://doi.org/10.1155/2022/4627826

Research Article

Comparison of Different Furosemide Regimens in the Treatment of Acute Heart Failure: A Meta-Analysis

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Received 15 June 2022; Revised 24 July 2022; Accepted 3 August 2022; Published 18 August 2022

Academic Editor: Xi Lou

Background. To compare the effects of different dosing schemes of furosemide on acute heart failure (AHF). *Methods*. Literature that compared the efficacy of continuous and intermittent administration of furosemide in AHF patients was retrieved from PubMed, Embase, the Cochrane Library, and ISI Web of Science from inception to May 2022. The primary endpoints included overall weight loss, 24-hour urine volume, length of hospital stay, 24-hour brain natriuretic peptide (BNP) level change, and all-cause mortality. The RevmMan5.4 software was used to analyze the extracted data. *Results*. A total of 10 studies with 775 patients, including 338 receiving continuous furosemide administration and 387 receiving intermittent furosemide administration, were included. The analysis results showed significant differences in weight loss (MD = 1.08, 95% CI (0.75~1.40), $P < 0.00001$) and 24-hour urine volume (MD =335.23, 95% CI (140.98~529.47), $P = 0.0007$) between the 2 groups. There was no significant difference in terms of length of hospital stay (MD = −0.71, 95% CI (-2.74~1.31), $P = 0.49$) and all-cause mortality (RR = 1.59, 95% CI (0.92~2.75), $P = 0.10$). *Conclusions*. Compared with intermittent administration, continuous infusion of furosemide had a significant effect on the 24-hour urine volume and total weight loss in patients with AHF.

1. Introduction

Acute heart failure (AHF) is a life-threatening clinical syndrome characterized by rapid deterioration of heart function caused by structural and/or functional cardiac abnormality that is associated with significant morbidity and mortality. The prevalence of heart failure varies with a specific region and population. In developed countries, the prevalence of AHF varies from 1.5% to 2.0% for the general population, and the incidence in people aged over 70 is even higher than 10% [1]. Studies have shown that AHF represents an enormous economic burden to both the families and society in terms of emergency admission, readmission, and prolongation of hospital stay [2].

Fluid retention is a typical consequence of heart failure caused by impaired cardiac contraction. In the current clinical practice, intravenous diuretics are fundamental for the treatment of AHF, with about 90% of hospitalized AHF patients receiving diuretics to reduce fluid retention and improve oxygenation [3, 4]. However, available data on the use of intravenous diuretics are predominantly limited to expert opinions and prospective studies that investigated that the optimal administration mode and dosage remain controversial. Studies have shown that large doses of diuretics were associated with adverse effects, such as activation of the angiotensin system and sympathetic nervous system, electrolyte disorder, and deterioration of renal function [5]. Associations between high-dose diuretics and adverse clinical outcomes, including renal failure, heart failure deterioration, and death, were noted [5]. In addition, the optimal mode of administration has always been controversial. Data suggested that continuous infusion has potential benefits such as decongestion compared with intermittent injection [6, 7]. Although some studies have evaluated the role of continuous infusion of diuretics for patients with heart failure [7–9], there have been some studies supporting that circulatory continuous infusion of diuretics can better

help patients with diuresis; these studies have not reached consistent conclusions due to differences in sample size, infusion duration, and dose, and there are still some controversies. Therefore, in this paper, we conducted a meta-analysis of multiple literatures. Therefore, we conducted this systematic review and meta-analysis to compare the differences in total weight loss, 24-hour urine volume, length of hospital stay, and mortality between continuous intravenous furosemide infusion and intermittent injection.

2. Materials and Methods

2.1. Literature Search. Databases such as PubMed, Embase, the Cochrane Library, and ISI Web of Science were searched from the inception to May 2022. Studies that compared the effects of different dosing schemes of furosemide for AHF were collected. The search terms were "Acute heart failure", "AMF", "diuretics", "Furosemide", "Loop diuretics", and "Continuous infusion". The joint search was conducted with Medical Subject Headings (MESH) and free words. References to the target literature were also examined.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria were as follows: (1) study type: randomized controlled trials (RCTs); (2) participants: hospitalized AHF patients, regardless of race, nationality, and gender; (3) intervention group: furosemide continuous infusion; (4) control group: intermittent injection of furosemide every 12 hours; and (5) outcomes: the primary endpoints were the overall weight loss, 24-hour urine volume, length of hospital stay, 24-hour brain natriuretic peptide (BNP) level changes, and all-cause mortality. Exclusion criteria were as follows: (1) non-RCT or animal studies, (2) studies with patient overlap, (3) literature with incomplete data or no indicators, and (4) subjects receiving diuretics other than furosemide.

2.3. Data Extraction and Quality Control. Potentially eligible RCTs were independently screened and cross-checked by Huang and Guo. Disagreements were resolved through discussion or consultation with Huang. Data extraction included the following: (1) general information: title, first author, publication time, and country; (2) patient demographics, clinical characteristics, laboratory test results, physical examination indicators, previous personal history, medical history, treatment history, and interventions of subjects; (3) risk of bias assessment indicators, including method of randomization, blinding of assignment and outcome assessment, completeness of outcome data, and selective reporting; and (4) outcomes of interest, including overall weight loss, 24-hour urine output, length of hospital stay, and 24-hour BNP.

RevMan 5.4 software was used to evaluate the quality of RCTs included. The risk of bias assessment table included the following items: random allocation method, allocation concealment scheme, blind method, blind method of result evaluation, the integrity of result data, selective report, and other biases.

2.4. Statistical Methods. RevMan 5.4 software was used for meta-analysis. Two-sided $P < 0.05$ indicated statistical significance. The mean difference (MD) and relative risk ratio (RR) with 95% confidence interval (CI) were used to analyze the continuous variables and binary variables, respectively. The I^2 was used to test the interstudy heterogeneity. In the presence of no obvious heterogeneity ($P > 0.05$ and $I^2 < 50\%$), the fixed effects model was applied. Otherwise, the random effects model was used to explore the source of heterogeneity with subgroup analysis. Egger's test was used to evaluate the publication bias.

3. Results

3.1. Literature Search Results. A total of 1628 English publications were obtained through database retrieval. After screening and eliminating duplicate literature, 823 were obtained. The title and abstract of the literature were read, and articles that did not meet the inclusion/exclusion criteria were excluded. The remaining 86 publications were downloaded for full-text reading. Finally, 10 studies were included. The study flow chart is shown in Figure 1.

3.2. Study Subject Demographics. The included 10 studies compared the continuous intravenous injection of furosemide with furosemide intermittent injection in hospitalized AHF patients [8–17]. Studies were performed in Asia, Europe, North America, and Africa, with 3 from the United States [10–12], 2 from Italy [8, 9], and 1 from China [13], Turkey [14], India [15], Israel [16], and Egypt [17], respectively. The largest sample, with a total of 308 cases, was reported from the United States [11] (Table 1). A total of 775 patients were included, with 388 in the intervention group and 387 in the control group.

3.3. Weight Loss. A total of 7 studies [8–14] with 655 AHF patients reported overall weight loss during hospitalization. The fixed effects model was used for analysis, given the absence of interstudy heterogeneity ($I^2 = 0\%$, $P = 0.90$, Figure 2). The results showed that compared with intermittent administration, continuous injection of furosemide was associated with significantly more pronounced overall weight (kg) loss in AHF patients during hospitalization (MD = 1.08, 95% CI (0.75~1.40), $P < 0.00001$) (Figure 2). Egger's test showed no publication bias among the literature ($P > 0.05$).

3.4. Length of Hospital Stay. Seven studies [9–15] included 657 AHF patients and reported the length of hospital stay. The result of the heterogeneity test was $P < 0.00001$ and $I^2 = 84\%$ (Figure 3). There was significant heterogeneity among the studies, which was analyzed by the random effects model. The results showed that compared with intermittent administration, there was no difference in hospital stay (days) between continuous administration and AHF patients (MD = −0.71, 95% CI (-2.74~1.31), $P = 0.49$) (Figure 3). Egger's test showed no publication bias among the literature ($P > 0.05$).

3.5. 24-Hour Urine Volume. 24-hour urine volume was reported in 216 AHF patients from 4 studies [8, 9, 12, 16]. In the absence of significant heterogeneity ($I^2 = 19\%$, $P = 0.30$, Figure 4), the fixed effects model was used. Compared with intermittent administration, continuous administration was associated with significantly increased 24-hour urine volume (mL) in AHF patients (MD =335.23, 95% CI

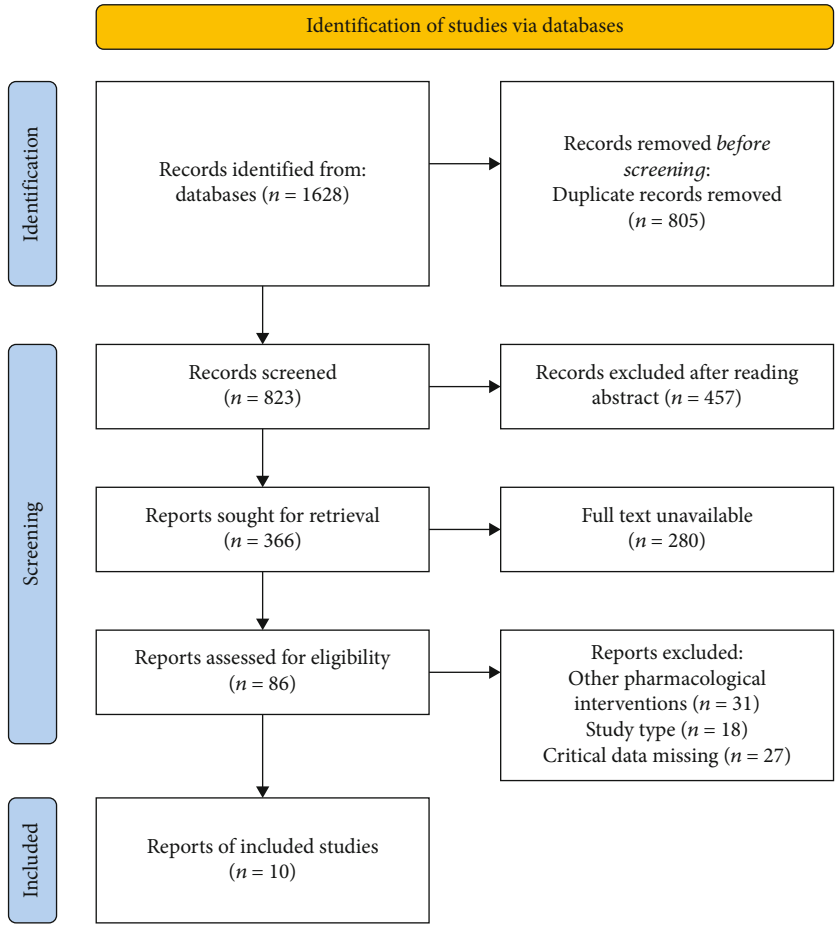

Figure 1: Document screening flow chart.

(140.98~529.47) (Figure 4). No publication bias was noted ($P > 0.05$).

3.6. 72-Hour Urine Volume. In total, 3 studies [10, 11, 13] with 230 AHF patients reported 72-hour urine volume. There was significant heterogeneity among the studies ($I^2 = 89\%$, $P = 0.0002$, Figure 5), which were analyzed by the random effects model. There was no significant difference in 72-hour urine volume (mL) between the continuous administration group and the intermittent injection group (MD =494.29, 95% CI (-671.43.05~1660.00), $P = 0.41$) (Figure 5). Egger's test showed no publication bias among the literature ($P > 0.05$).

3.7. Changes in BNP Level. Meta-analysis of 221 AHF patients from 3 studies [8, 9, 13] using the random effects model ($I^2 = 71\%$, $P = 0.03$, Figure 6) showed that continuous administration of furosemide was not associated with significantly decreased BNP levels (pg/mL) as compared with the furosemide intermittent injection (MD = 86.97, 95% CI (-117.31~291.24), $P = 0.40$) (Figure 6). Egger's test showed no publication bias among the literature ($P > 0.05$).

3.8. All-Cause Mortality. All-cause mortality was reported in 531 AHF patients from 5 studies [9, 11, 12, 15, 17] without obvious interstudy heterogeneity ($I^2 = 0\%$, $P = 0.59$, Figure 7). No significant differences in terms of all-cause mortality were observed between continuous administration and intermittent administration (RR = 1.59, 95% CI (0.92~2.75), $P = 0.10$) (Figure 7). Egger's test showed no publication bias among the literature ($P > 0.05$).

4. Discussion

AHF is a multietiological clinical syndrome characterized by sudden decrease in heart function. People over 70 years old have a higher incidence that can reach over 10%, causing substantial economic costs to the families and society [1, 2]. Currently, intravenous diuretics are still the primary treatment for AHF. Nonetheless, the optimal dosing regimen has not been determined.

In this meta-analysis, we found that compared with intermittent administration, continuous injection of furosemide could significantly reduce the weight of AHF patients. In addition, the 24-hour urine volume increased more significantly in hospitalized AHF patients receiving continuous furosemide administration. No significant differences were found in terms of the length of hospital stay, BNP level, and all-cause mortality between the two groups.

Table 1: Basic information of included literature and risk of bias assessment.

Study/year	Country	Sample size	Design	Dose of daily furosemide (mg)	Duration of interventions (hours)	Outcomes used in meta-analysis	Risk of basis
Makhoul/1997 [16]	Israel	20	Single-centre RCT	cIV: 329 ± 186.7 iIV: 324 ± 110.8 (divided in 3 doses)	24	Total urine output in 24 h	Low risk
Allen/2010 [10]	USA	41	Single-centre RCT	cIV: 162 ± 48 iIV: 162 ± 52 (divided in 2 doses)	48	Changes in weight loss Length of hospital stay Total urine output in 72 h	Uncertain risk
Thomson/2010 [12]	USA	56	Single-centre RCT	cIV: 197 ± 148 iIV: 172 ± 97	100	Changes in weight loss Length of hospital stay Total urine output in 24 h Mortality	Uncertain risk
Felker/2011 [11]	USA+Canada	308	Single-centre RCT	cIV: 162 ± 48 iIV: 162 ± 52 (divided in 2 doses)	72	Changes in weight loss Length of hospital stay Total urine output in 72 h Mortality	Uncertain risk
Shah/2014 [15]	India	60	Single-centre RCT	cIV: 100 iIV: 100 (divided in 2 doses)	48	Length of hospital stay Mortality	High risk
Yayla/2015 [14]	Turkey	29	Single-centre RCT	cIV: 160 iIV: 160 (divided in 2 doses)	48	Changes in weight loss Length of hospital stay	Uncertain risk
Palazzuoli/2014 [9]	Italy	82	Single-centre RCT	cIV: 170 ± 70 iIV: 160 ± 80	112	Changes in weight loss Length of hospital stay Total urine output in 24 h Changes in BNP Mortality	Uncertain risk
Palazzuoli/2015 [8]	Italy	58	Single-centre RCT	cIV: 165 ± 85 iIV: 165 ± 85 (divided in 2 doses)	120	Changes in weight loss Total urine output in 24 h Changes in BNP	Low risk
Ragab/2018 [17]	Egypt	40	Single-centre RCT	cIV: 120/240 iIV: 120/240 (divided in 3 doses)	24	Mortality	Uncertain risk
Zheng/2021 [13]	China	81	Single-centre RCT	cIV: 160/200 iIV: 160/200	72	Changes in weight loss Length of hospital stay Total urine output in 72 h Changes in BNP	Uncertain risk

Note: cIV: continuous intravenous; iIV: intermittent intravenous.

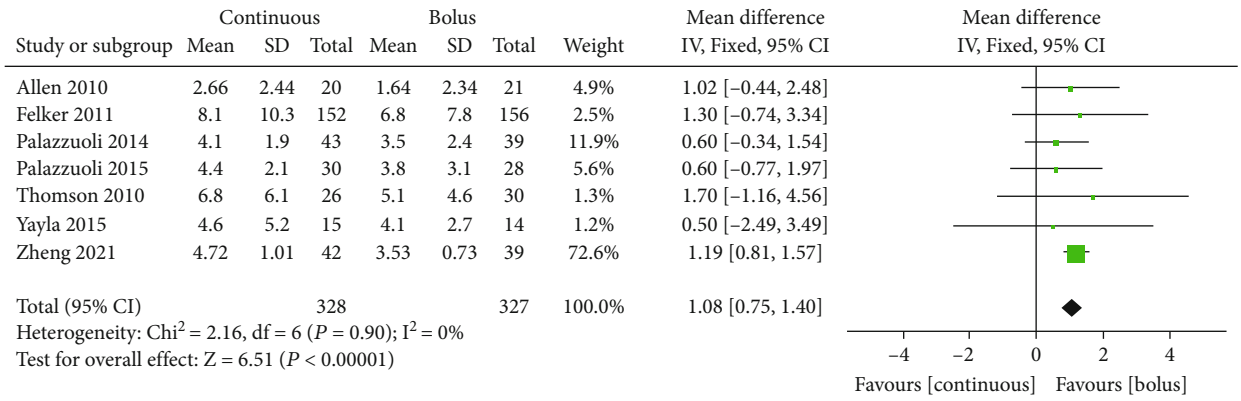

Figure 2: Forest chart of total weight loss between continuous intravenous injection and intermittent injection of furosemide.

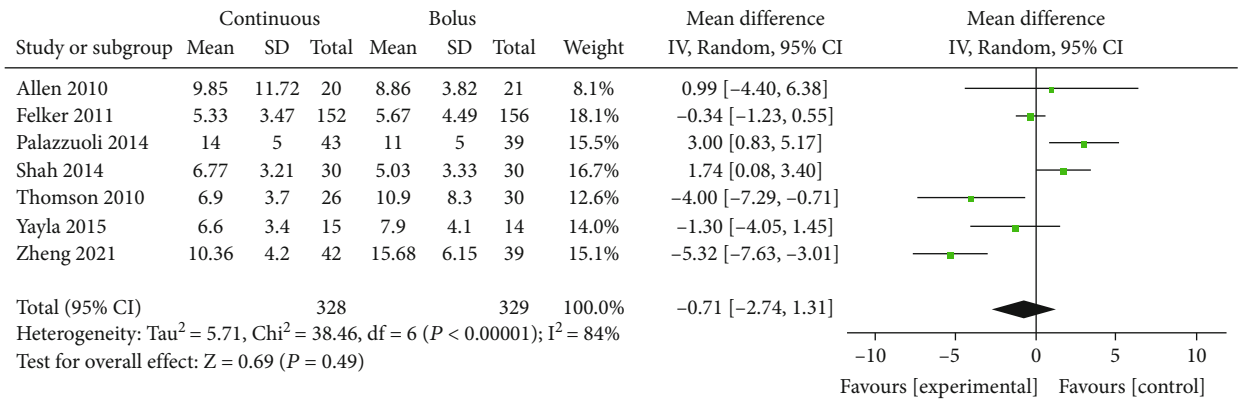

Figure 3: Comparison forest chart of hospitalization days between continuous intravenous injection and intermittent injection.

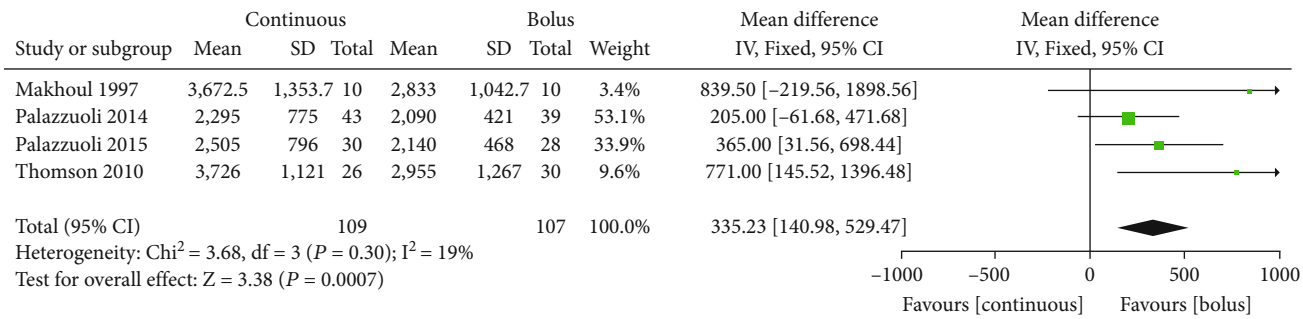

Figure 4: Comparison forest chart of 24-hour urine volume between continuous intravenous injection and intermittent injection.

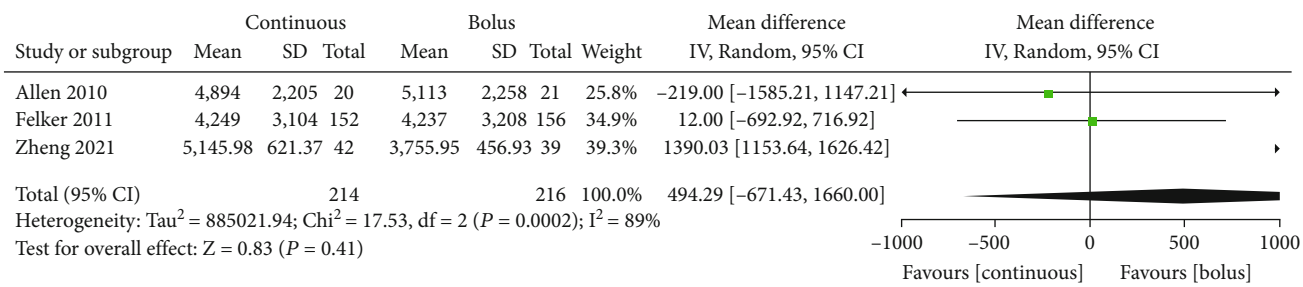

Figure 5: Comparison forest chart of 72-hour urine volume between continuous intravenous injection and intermittent injection.

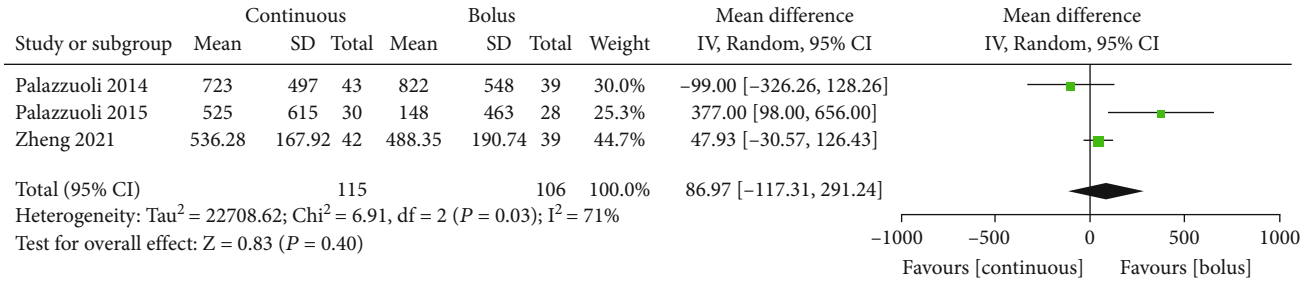

Figure 6: Forest chart of BNP changes in patients with continuous intravenous injection and intermittent injection.

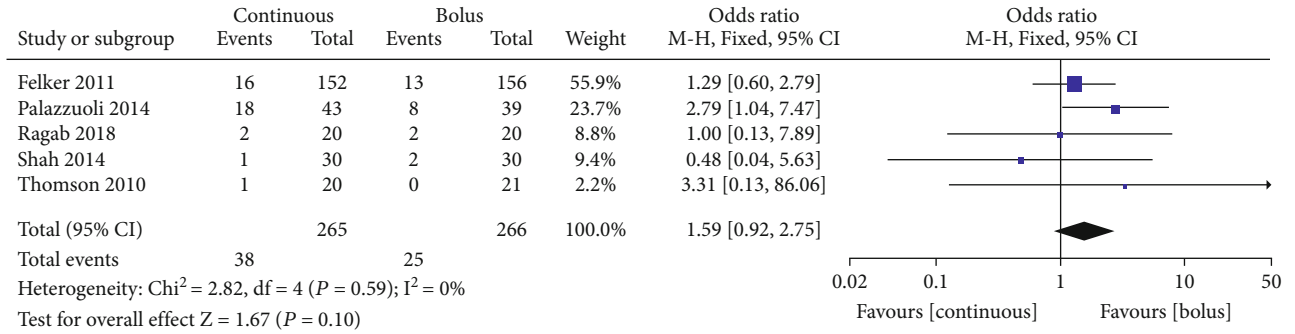

Figure 7: Forest chart of all-cause mortality in patients with continuous intravenous injection and intermittent intravenous injection.

Our study showed that continuous administration can increase patients' urine volume, which is consistent with the results of previous analyses by Amer et al. [18], Kuriyama et al. [19], and Ng et al. [20]. In addition, there was no obvious heterogeneity in the studies. Among all the observation indicators, the data on patients' weight change during hospitalization in each study was the most complete, which might be related to the convenience of weight measurement. Therefore, continuous injection of furosemide can reduce patients' weight better than intermittent injection of furosemide.

In treating AHF, increasing the urine output is an important treatment goal. Our study showed that continuous administration can significantly increase the 24-hour urine volume but not the 72-hour urine volume. However, it should be noted that only three studies with significant interstudy heterogeneity have reported 72-hour urine volume. Our study finding is consistent with the results of Amer [18] and Ng et al. [20], which also noted that continuous furosemide administration can reduce patients' weight during hospitalization. Theoretically [21], continuous administration maintains a stable furosemide concentration and exerts a continuous diuretic effect by targeting the renal tubules. In comparison, with intermittent administration, the effective level could be maintained for a limited time after drug injection, and most diuretics will be excreted within 2 h. Intermittent injection of a large dose of furosemide leads to rapid decline of blood volume, thus increasing the incidence of adverse reactions such as hypokalemia and hypotension [22].

BNP is predominantly synthesized and secreted by the left ventricular cardiomyocytes. Since BNP secretion is positively correlated with the severity of AHF, it is often used as an important biomarker and prognosticator of heart failure [23]. Therefore, we investigated the changes in BNP levels in AHF patients after continuous or intermittent furosemide administration. We found no significant difference between the two groups regarding BNP changes, which is consistent with the findings that the two administration methods showed no differences in length of hospital stay and the prognosis of AHF. Additional studies with larger sample are needed to compare the 2 dosing regimens in terms of BNP level changes, hospital stay, and all-cause mortality.

Although continuous furosemide administration can promote the elimination of excessive body fluids and reduce body weight more efficiently, it did not improve the prognosis of AHF. Theoretically [24], continuous infusion of furosemide should be more conducive to weight loss and urine output and accelerate the reduction of cardiac congestive symptoms. AHF is a multifactorial disorder that cannot be prognosticated solely by eliminating body fluid volume. The use of furosemide can promote the elimination of body fluids and promote the excretion and loss of sodium, chlorine, potassium, calcium, magnesium, and phosphorus. Large dose of furosemide may cause water electrolyte disequilibrium, positional hypotension, shock, and related adverse reactions such as thirst, fatigue, muscle soreness, and arrhythmia [25], all of which may affect the prognosis of AHF. However, most studies did not include the changes in electrolytes as an observation indicator. Kuriyama et al. [19] found no significant difference between continuous and intermittent furosemide administration in terms of electrolyte changes in AHF patients through analysis of a few studies. Therefore, we believe that the change in electrolytes should also be studied as an important index of furosemide efficacy in AHF treatment.

The main advantages of this analysis lie in its precise definition, comprehensive retrieval strategy, and large sample size. Our limitation is that some results were heterogeneous, and some studies were not blind. The heterogeneity of the results was predominantly related to small sample size and different observation indicators among studies. In addition, the inclusion criteria also vary among studies. In the continuous injection group, furosemide was continuously injected by the intravenous pump. For intermittent administration, furosemide was taken orally whereas in others, it was injected intravenously. Due to the limited number of studies, we could only divide them into two groups based on whether it was continuous or intermittent administration. In addition, the specific dose of furosemide used in the treatment of AHF varies among studies, which might also be an important source of heterogeneity. Therefore, the benefits of continuous injection of furosemide need further experimental research and exploration. In conclusion, compared with intermittent injection, continuous intravenous injection of furosemide could promote excretion of excessive body fluid more effectively in AHF patients. However, there were no significant differences between the two groups with regard to length of hospital stay and mortality. The dosing regimen of furosemide in the treatment of AHF needs to be further explored.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Youpan Huang and Feijie Guo contributed equally to this work.

Acknowledgments

The project was supported by People's Hospital of Wanning Hainan.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 1191205, 10 pages
https://doi.org/10.1155/2022/1191205

Research Article

Association between Glucocorticoids and Mortality in Patients with Severe Pneumonia: A Systematic Review and Meta-Analysis Based on Randomized Controlled Trials

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Received 4 June 2022; Revised 20 July 2022; Accepted 22 July 2022; Published 8 August 2022

Academic Editor: Xi Lou

Objective. To explore the associations between glucocorticoid use and the clinical outcome of patients with severe pneumonia. *Methods*. Medical databases including PubMed, EMBASE, and ScienceDirect were searched for relevant literature. Two independent researchers extracted the primary endpoint from the included literature. The Cochrane Q test and I^2 statistics were used to evaluate the interstudy heterogeneity. The combined risk estimates were calculated by random effect model, and the source of heterogeneity was evaluated by subgroup analysis. Funnel plot and Egger's test were used to assess publication bias. $P < 0.05$ denoted statistical significance. *Results*. A total of 12 literature, including 8171 patients with 1083 deaths, were included in this study for meta-analysis. The use of glucocorticoids significantly increased the mortality (RR = 1.44, 95% CI: 1.13, 1.84, $P < 0.001$), the risk of requiring mechanical ventilation (RR = 1.62, 95% CI: 1.30, 2.02, $P < 0.001$), and the incidence of nosocomial infection (RR = 1.36, 95% CI: 1.01, 1.82, $P = 0.04$) in patients with severe pneumonia as compared with the control group. In addition, the use of glucocorticoids did not seem to be associated with length of treatment in the intensive care unit (mean difference = 1.47, 95% CI: -1.04, 3.96, $P = 0.25$) and the length of hospital stay (mean difference = 0.55, 95% CI: -3.90, 4.99, $P = 0.81$). *Conclusion*. The use of glucocorticoids may increase the mortality, the incidence of hospital-acquired pneumonia, and the need for mechanical ventilation in patients with severe pneumonia.

1. Introduction

Pneumonia is an infection of the lung that inflames the alveoli with resultant inflammatory secretions that prevent adequate oxygenation [1, 2]. During the infectious phase of pneumonia, excessive release of circulating inflammatory factors such as interleukin- (IL-) 10, IL-8, and IL-6 can lead to respiratory dysfunction [3]. An earlier study found that elevated levels of inflammatory factors increased patient mortality, especially in those with severe pneumonia that were associated with increased incidence of sepsis, lung injury, and acute respiratory distress syndrome (ARDS) [4]. Therefore, active and effective anti-inflammatory treatment is of great significance for severe pneumonia. Although severe pneumonia only accounts for about 10% of all pneumonia cases, it causes disproportionately high mortality [5]. Despite the continuous progress in antibiotic treatment and life support in recent years, the mortality associated with severe pneumonia has not decreased [5, 6].

Currently, glucocorticoid is the most effective anti-inflammatory medication. The therapeutic effect of glucocorticoids may be related to their ability to reduce the production of cytokines that mediate the inflammatory factor storm associated with severe pneumonia [7]. In addition, with the concept of critical illness-related corticosteroid insufficiency (CIRCI), glucocorticoid replacement therapy is gradually accepted in the field of critical medicine for conditions like sepsis and ARDS. Salluh et al. found that most patients with severe pneumonia suffered from adrenal crisis [8]. Some studies have also found that the low adrenaline

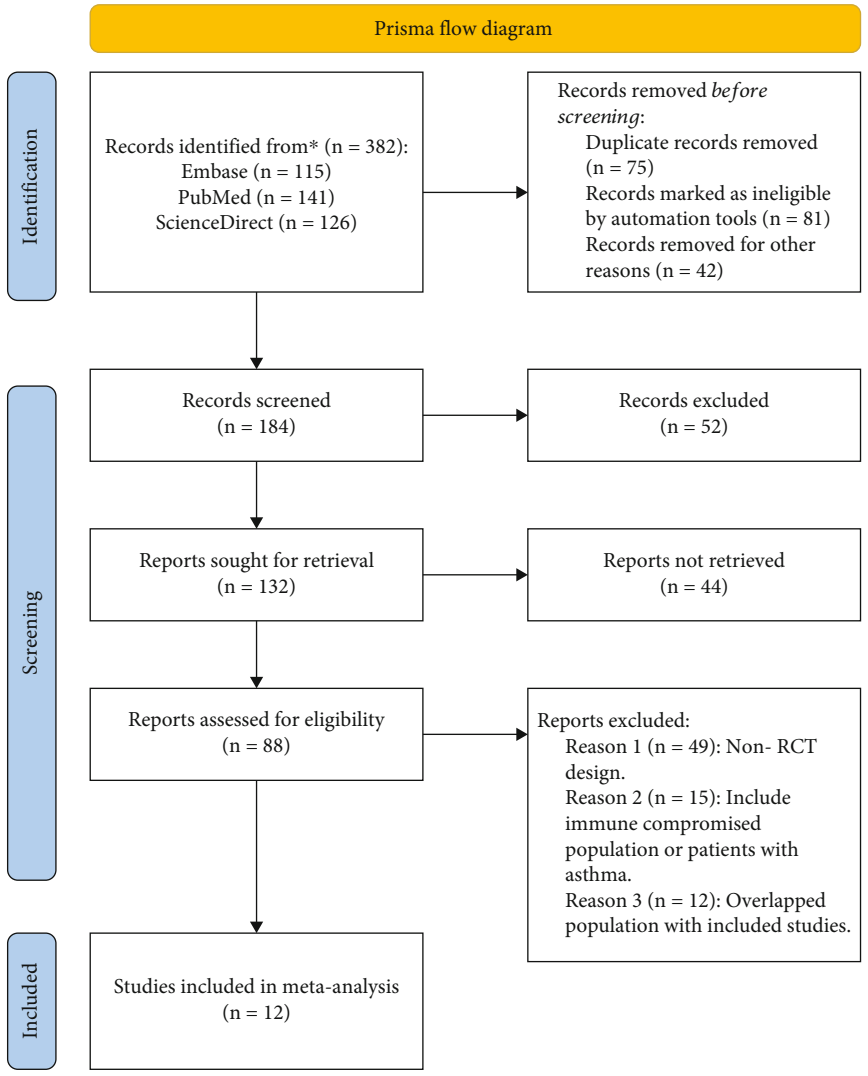

Figure 1: PRISMA flowchart. The process of screening meta-analysis into the literature.

level in the early stage of severe pneumonia was significantly correlated with unfavorable prognosis in severe pneumonia [9]. So far, many clinicians have used glucocorticoids in the treatment of patients with severe pneumonia, despite the optimal dose and administration frequency remain unclear.

Recent studies have shown that glucocorticoids may not improve the clinical outcome and may even increase mortality for severe pneumonia [10]. By contrast, many randomized controlled trials (RCT) have found that the use of glucocorticoids reduced the use of mechanical ventilation and the occurrence of ARDS in patients with severe pneumonia, shortened length of hospital stay, and reduced the 30-day mortality by 9% [11–13]. Therefore, there is still significant uncertainty regarding whether glucocorticoids can improve the prognosis of patients with severe pneumonia. Systematic meta-analysis can produce more reliable clinical evidence by combining the risk estimates of independent studies. Therefore, this study meta-analyzes the results from various RCTs to explore the role of glucocorticoids in improving the clinical outcome of severe pneumonia.

2. Methods

2.1. Bibliography Retrieval. This study used MeSH search words in PubMed, EMBASE, ScienceDirect, and other databases for literature retrieval. The search keywords are ("Pneumonia" [MeSH Terms] OR "acute respiratory distress syndrome" OR "acute respiratory failure") AND ("Steroid, corticosteroid" [MeSH Terms] OR "glucocorticoid") AND ("mortality" OR "hospital stay" OR "mechanical ventilation" OR "hospital acquired pneumonia" OR "ICU length of Stay").

2.2. Literature Screening. Inclusion criteria: (1) the type of study design was RCT; (2) the study population was patients with confirmed severe pneumonia ($PaO_2/FiO_2 < 300$ mmHg); (3) the treatment method studied was glucocorticoid (not limited to a particular drug type, dosage, and duration). The control group was treated with placebo; (4) the primary endpoint included at least one of the following six categories: mortality, the incidence of mechanical ventilation, the incidence of secondary infection in the hospital, the length of

Table 1: Characteristics of 12 included literatures.

Author	Study design	Location	Setting	Intervention/ placebo	Corticosteroids used	Mortality outcome (12)	Length of hospital stay (d) (7)	Length of ICU stay (d) (7)	ARDS incidence	Nosocomial infection (6)	Mechanical ventilation required (d) (mean ± SD) (10, 4)
Tongyoo et al. [14]	RCT	Thailand	In hospital	98/99	50 mg hydrocortisone intravenously every 6 h daily/ normal saline on the same time schedule	22/27 RR 0.82 (0.5-1.34)	NA	NA	22/27	17/19	16 ± 9.7/18.3 ± 10/ 33/21
Ceccato et al. [24]	Post hoc analysis of RCT	Spain	ICU	56/50	Methylprednisolone	2/1 HR 0.72 (0.11-5.44)	15.9 ± 17.3/16.4 ± 21.4	8.6 ± 11.4/7.9 ± 9.7	NA	NA	6/5
Nafae et al. [16]	Open-label RCT	Egypt	ICU	60/20	Hydrocortisone	4/6	9.27 ± 2.4/16.5 ± 2.24	3.1 ± 4.9/6.3 ± 8.2	NA	NA	8/5 1.2 ± 3.75/4.3 ± 7.83
Torres et al. [13]	Double-blinded RCT	Spain	In hospital	55/57	Methylprednisolone	6/9	11 (7.5-14)/ 10.5 (8-15) 11 ± 17.5/10.5 ± 18.9	5 (3-8)/6 (4-8) 5 ± 13.5/6 ± 10.8	NA	NA	5/10
Wittermans et al. [21]	Double-blinded RCT	Netherlands	In hospital	203/198	Dexamethasone	4/7	4.5 (4-5)/5.0 (4.6–5.4) 4.5 ± 5.1/5.0 ± 4.1	NA	NA	NA	NA
Fernández-Serrano et al. [15]	Double-blinded RCT	Spain	In hospital	28/28	Methylprednisolone	0/1	10 (9-13)/12 (9-18) 10 ± 7.64/12 ± 17.2	6.5 (5.5-9)/10.5 (6.25-24.5) 6.5 ± 6.68/10.5 ± 33.8	1/2	NA	1/5
Moreno et al. [17]	Propensity score matching study of RCT	Spain	ICU	604/1242	Methylprednisolone, prednisolone, or dexamethasone	166/234	NA	10 (5–19)/8 (5–18) 10 ± 23.1/8 ± 24.1	NA	139/248	506/921
Li et al. [18]	RCT	China	In hospital	1055/1086	Hydrocortisone, methylprednisolone, or dexamethasone	261/76	NA	NA	NA	227/154	367/49
Lee et al. [19]	RCT	Singapore	In hospital	612/2037	Hydrocortisone, methylprednisolone, or dexamethasone	70/33 HR 1.7 (1.1-2.6)	NA	NA	NA	NA	NA
Kim et al. [20]	Open-label RCT	Korea	ICU	107/138	Methylprednisolone or dexamethasone	62/37	30.8 ± 36.9/18.9 ± 20.0	13.5 ± 13.2/8.8 ± 9.2	66/70	61/30	91/71 13.3 ± 13.2/9.6 ± 10.0
Cao et al. [22]	Open-label RCT	China	In hospital	65/65	Hydrocortisone, methylprednisolone, or dexamethasone	27/10	NA	NA	NA	17/18	38/27
Brun-Buisson et al. [23]	Open-label RCT	France	ICU	83/125	Hydrocortisone, methylprednisolone, or hydrocortisone	28/21	23.2 (12.2-28.8)/18.1 (12.1-29.8)	22 (13–39)/17 (11–30)	NA	38/44	76/56 10.2 (9.8-16.8)/14.4 (13.2-23.3)

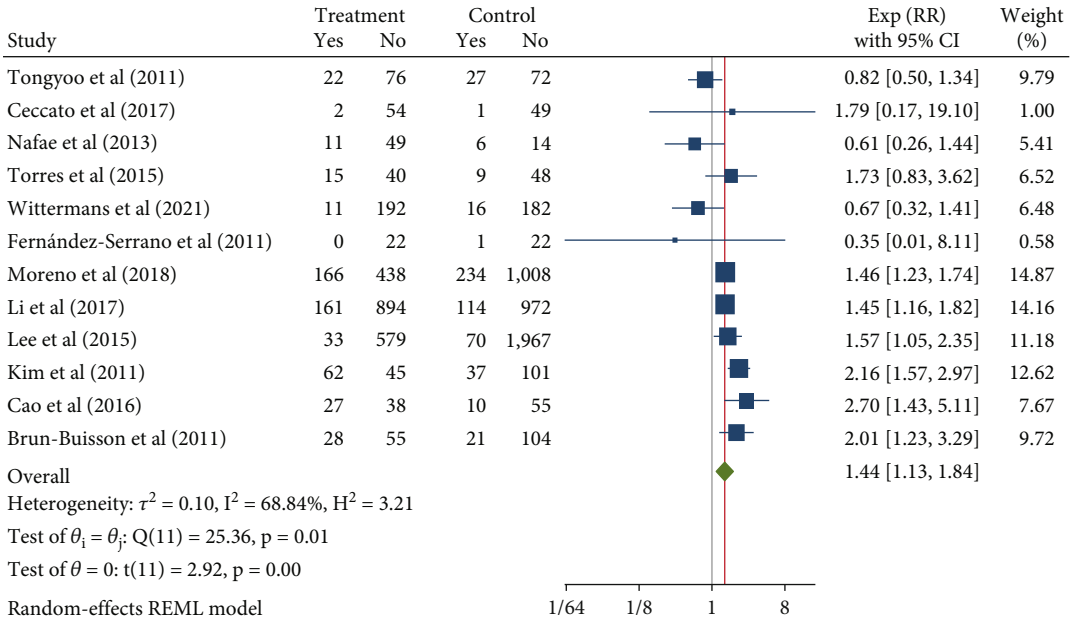

Figure 2: Forest diagram of the effect of glucocorticoids on mortality of severe pneumonia.

hospital stay, length of treatment in intensive care unit, and length of treatment with mechanical ventilation.

Exclusion criteria: (1) the study population was limited to a special population, such as people with immune function defects or a special patient group; (2) reports with study population overlap; (3) the sample size of the interventional group or the control group was less than 20; (4) nonoriginal articles, such as discussions, academic conferences, reviews, and case reports; (5) studies with Newcastle-Ottawa Scale (NOS) score less than 5. This study did not limit the pathogens causing severe pneumonia and the age of patients.

2.3. Document Data Sorting and Evaluation. The two researchers screened and extracted the following data from the included literature independently: study type (open trial or double-blind trial), country or region of the study population, number of people in the control group and the interventional group, type of glucocorticoid use, mortality, the incidence of mechanical ventilation, the incidence of secondary nosocomial infection, length of hospital stay, length of intensive care unit treatment, and length of mechanical ventilation. This study used the Cochrane risk of bias tool for systematic reviews and meta-analyses of RCTs by two investigators independently to assess risk of bias for each included study based on seven aspects: (1) method of generating random numbers (selection bias), (2) group concealment (selection bias), (3) blinding of investigators and subjects (implementation bias), (4) blinding (detection bias) to the primary endpoint measure, (5) integrity of research results and data, (6) selective reporting, and (7) other biases. The evaluation criteria are as follows: (1) if the evaluation criteria are met, the risk of bias is low; (2) a risk of bias was considered possible if one or more of the criteria were only partially met or were less accurate; (3) a high risk of bias was considered to exist if one or more of the criteria were not met or not reported.

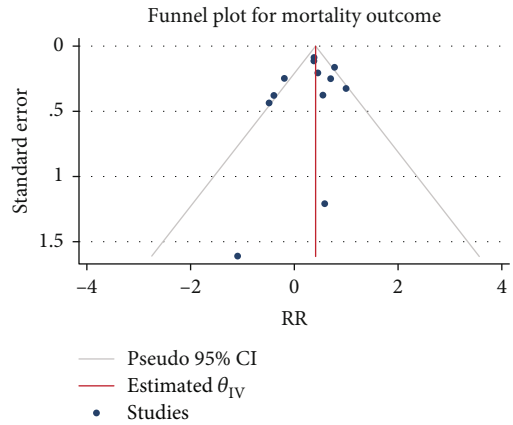

Figure 3: Funnel diagram of the effect of glucocorticoids on mortality of severe pneumonia.

2.4. Statistical Method. STATA 17.0 (SE) was used in this study for the statistical analysis. The observed primary clinical endpoint was expressed by relative risk (RR) or mean ± standard deviation for categorical variables and continuous variables, respectively. Interstudy heterogeneity was assessed using the Cochrane Q test and the I^2 statistic. For $I^2 \geq 50\%$, the random effect model of the restricted maximum likelihood probability method is used to combine the mean difference and the RR. Otherwise, the fixed effect model of the reverse variance method is used. Meta-analyses with 5 or more included studies were evaluated for publication bias by funnel plot description and the Egger and Begg tests. All statistical results in this study were considered statistically significant at $P \leq 0.05$, and the hypothesis tests were two-sided.

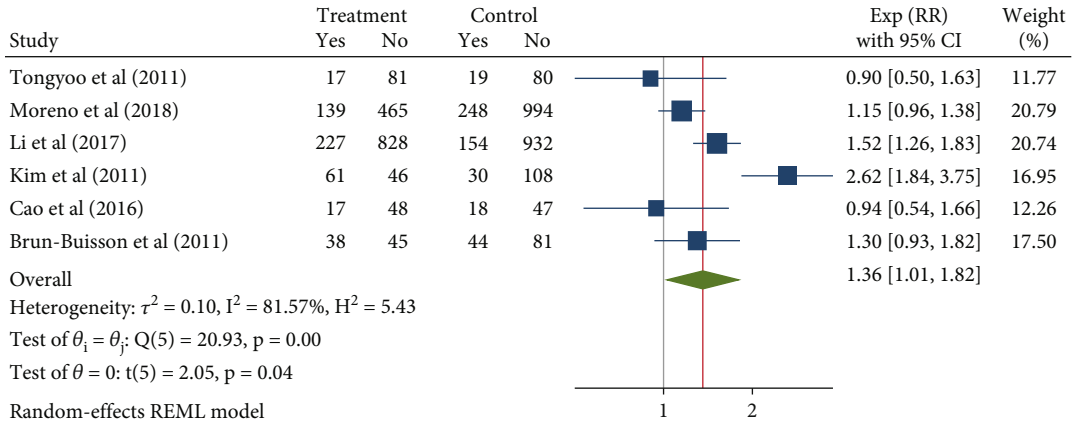

Figure 4: Forest chart of the effect of glucocorticoids on the incidence of hospital-acquired pneumonia in severe pneumonia.

3. Results

3.1. Search Results and Literature Characteristics. A total of 382 relevant literature were generated. Regarding the established literature inclusion criteria, a total of 12 studies [13–24] were finally included in the meta-analysis. The detailed literature retrieval and screening process is shown in the flowchart (Figure 1). The characteristics of the 12 included papers are shown in Table 1. A total of 8171 patients were included in these 12 studies, with 12 reported mortality-related indicators, 7 reported length of stay indicators and ICU length of stay, 6 evaluated secondary nosocomial infection caused by glucocorticoid use, and 10 reported the number of patients using mechanical ventilation and the time of mechanical ventilation in the interventional and control groups. Six studies used two or more types of glucocorticoids, including methylprednisolone, dexamethasone, prednisolone, and hydrocortisone. It was found that 3 literature did not describe the grouping concealment and blind method of randomized grouping that was considered to have a moderate risk of bias; the rest of the included studies were of mild risk of bias. The NOS score ranged from 5 to 8, including 9 high-quality documents, 3 medium-quality documents, and 0 low-quality documents.

3.2. Glucocorticoid-Related Mortality. A total of 8171 patients in 12 studies were pooled for assessing glucocorticoid-related mortality. The random-effect model was applied to combine the RR given the heterogeneity test indicated moderate heterogeneity ($H^2 = 3.21$, $I^2 = 68.84\%$, $P = 0.01$). The meta-analysis results (Figure 2) showed that compared with the control group, the use of glucocorticoids significantly increased the risk of death in patients with severe pneumonia (RR = 1.44, 95% CI: 1.13, 1.84, $P < 0.001$). The funnel chart (Figure 3) showed absence of obvious publication bias.

3.3. Incidence of Glucocorticoid-Related Nosocomial Infections. Six studies with a total of 4767 patients were included. The heterogeneity test results were $H^2 = 5.43$, $I^2 = 81.57\%$, and $P < 0.001$, so the random-effect model was used to combine the RR. Compared with the control group, the use of glucocorticoids significantly increased the risk of nosocomial infection in patients with severe pneumonia (RR = 1.36, 95% CI: 1.01, 1.82, $P = 0.04$, Figure 4). The funnel chart (Figure 5) indicated no obvious publication bias.

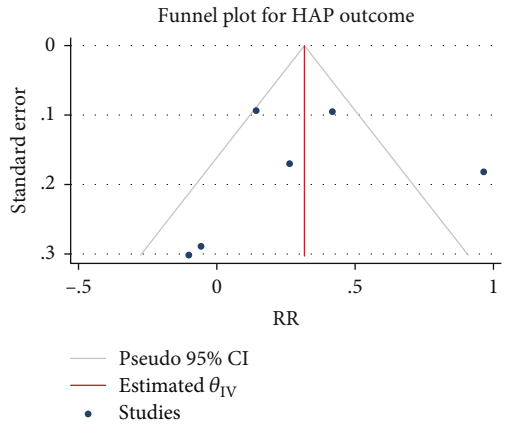

Figure 5: Funnel chart of the effect of glucocorticoids on the incidence of hospital-acquired pneumonia in severe pneumonia.

3.4. Incidence of Glucocorticoid-Related Mechanical Ventilation. The RR were pooled from 6 studies with a total of 4767 patients using the random-effect model given the high interstudy heterogeneity ($H^2 = 8.32$, $I^2 = 87.98\%$, $P < 0.001$). The meta-analysis results (Figure 6) showed that compared with the control group, the use of glucocorticoids significantly increased the risk of mechanical ventilation in patients with severe pneumonia (RR = 1.62, 95% CI: 1.30, 2.02, $P < 0.001$). Obvious publication bias was noted (Figure 7).

3.5. Length of Hospital Stay. A total of 1000 patients in 7 studies were included in this study. After confirming high interstudy heterogeneity ($H^2 = 20.91$, $I^2 = 95.22$, $P < 0.001$), the random-effect model was used to combine the mean difference. The meta-analysis results (Figure 8) showed that compared with the control group, the use of glucocorticoids did not seem to significantly increase the length of hospitalization

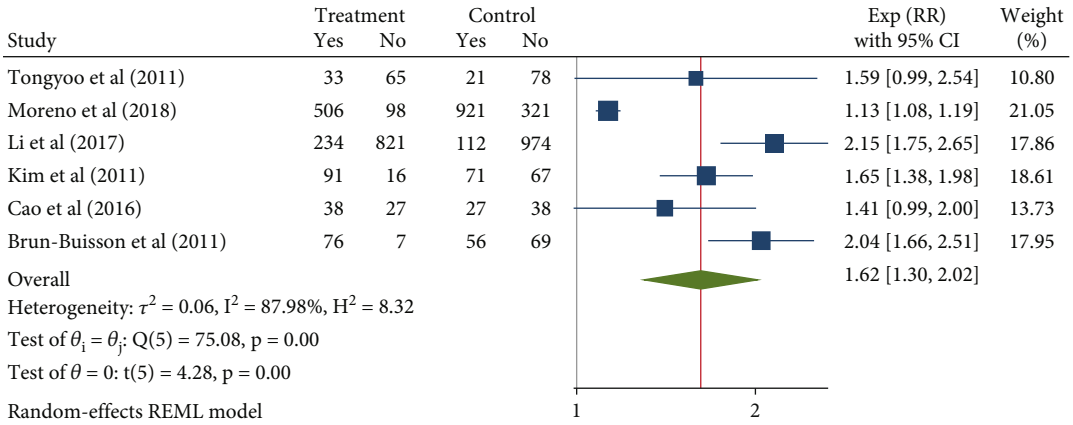

Figure 6: Forest diagram of the effect of glucocorticoids on the incidence of mechanical ventilation in severe pneumonia.

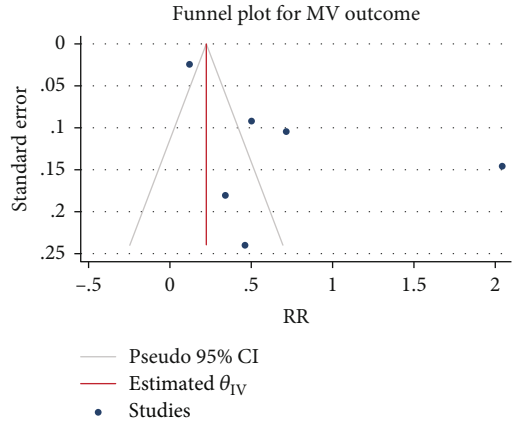

Figure 7: Funnel diagram of the effect of glucocorticoids on the incidence of mechanical ventilation in severe pneumonia.

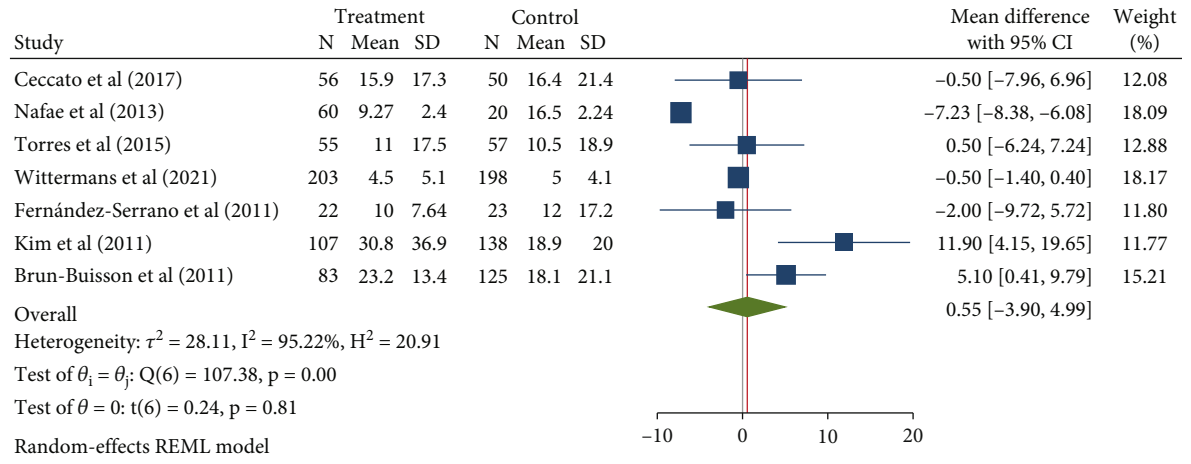

Figure 8: Forest diagram of the effect of glucocorticoid on the length of hospitalization of patients with severe pneumonia.

(mean difference = 0.55, 95% CI: -3.90, 4.99, $P = 0.81$). The funnel chart (Figure 9) showed obvious publication bias.

3.6. Length of ICU Stay. The results of the meta-analysis that combined a total of 2653 patients in 7 studies using the random-effect model ($H^2 = 3.15$, $I^2 = 68.24\%$, $P = 0.01$) showed the use of glucocorticoids significantly increased the number of patients with severe pneumonia treated in the intensive care unit for about 1.47 days (mean difference = 1.47, 95% CI: -1.02, 3.96), and the difference was not statistically significant, $P = 0.25$, as shown in Figure 10. There was no obvious publication bias (Figure 11).

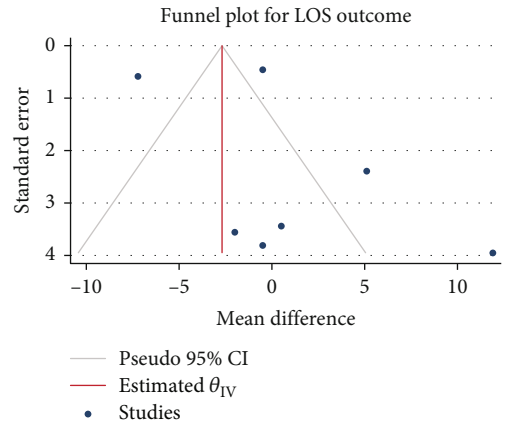

Figure 9: Funnel diagram of the effect of glucocorticoid on the length of hospitalization of patients with severe pneumonia.

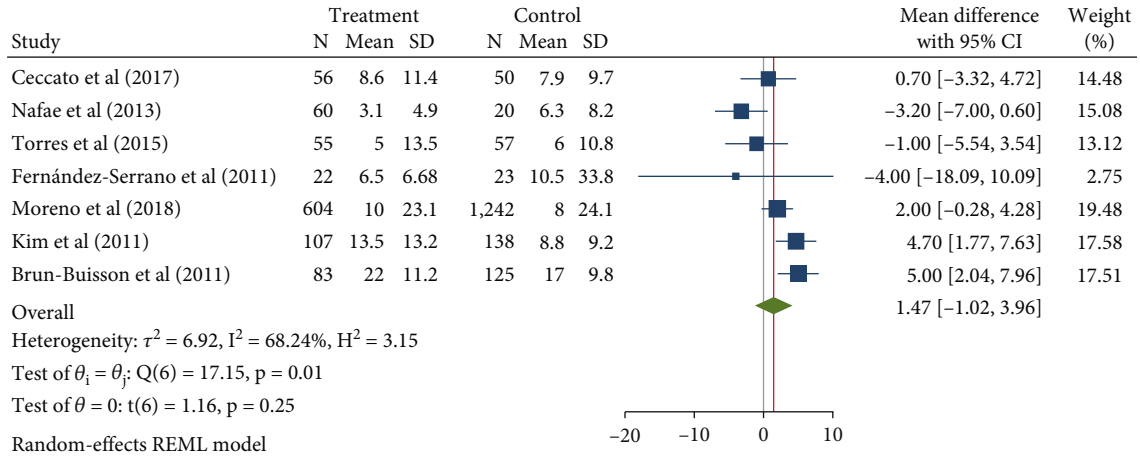

Figure 10: Forest diagram of the effect of glucocorticoids on the length of time patients with severe pneumonia need to be treated in the intensive care unit.

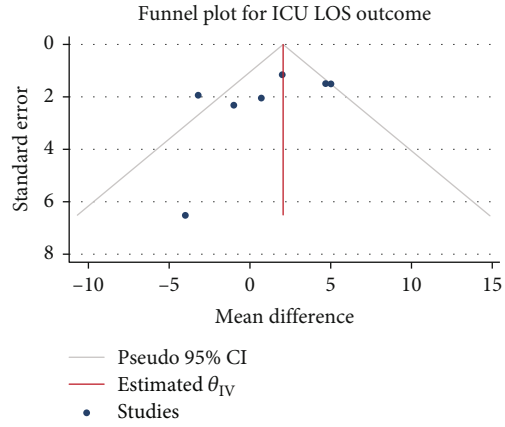

Figure 11: Funnel diagram of the effect of glucocorticoids on the length of time patients with severe pneumonia need to be treated in the intensive care unit.

3.7. Duration of Mechanical Ventilation. A total of 730 patients from four studies were included in this study. The heterogeneity test results were $H^2 = 3.91$, $I^2 = 74.45\%$, and $P = 0.01$, indicating moderate heterogeneity. The random-effect model was used to combine the mean difference. The meta-analysis results (Figure 12) showed glucocorticoids did not significantly reduce the need for mechanical ventilation maintenance treatment in patients with severe

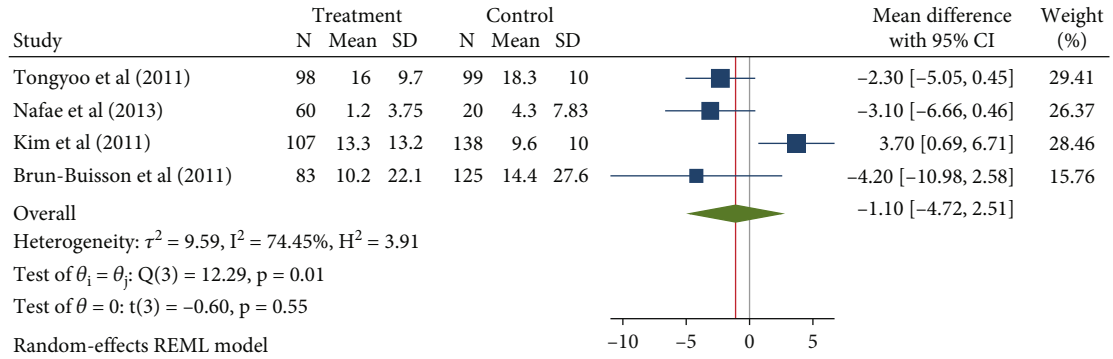

Figure 12: Forest diagram of the effect of glucocorticoids on the duration of mechanical ventilation in patients with severe pneumonia.

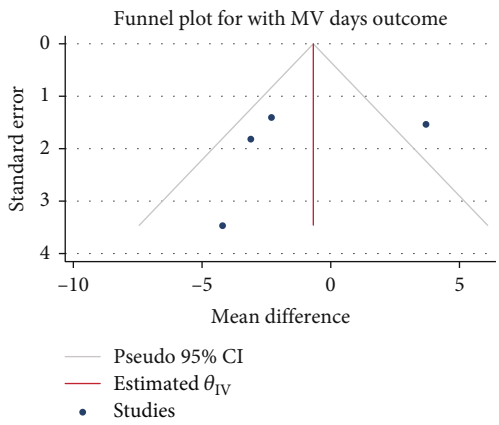

Figure 13: Funnel diagram of the effect of glucocorticoids on the duration of mechanical ventilation in patients with severe pneumonia.

pneumonia (mean difference = −1.10, 95% CI: -4.72, 2.51, $P = 0.55$). The funnel chart (Figure 13) showed no obvious publication bias, as shown in Figure 13.

4. Discussion

A total of 8171 patients with severe pneumonia were included in this study, including 1083 deaths. The all-cause mortality caused by severe pneumonia was 13.3%, which was comparable to that reported in the previous literature. In this study, 2301 patients needed mechanical ventilation. In addition, there were 1012 patients with secondary nosocomial infection. The main results of this study are as follows. (1) The use of glucocorticoids could increase the all-cause mortality of patients with severe pneumonia. (2) Glucocorticoid use increased the risk of requiring mechanical ventilation. (3) The incidence of nosocomial infection was higher in the glucocorticoid group than in the control group.

Usually, clinicians prefer to use glucocorticoids for adjuvant treatment in the early stage of severe pneumonia. The current clinical evidence supports the application of glucocorticoids in severe pneumonia for the following three reasons. First, glucocorticoids are potent inhibitors for the stimulation of the inflammatory cascade induced by pathogenic infection. Some studies proposed that the occurrence of the majority of severe pneumonia was usually related to excessive and uncontrolled inflammatory response. However, the exact anti-inflammatory mechanisms of glucocorticoids has not been fully clarified (3). However, it has been demonstrated that glucocorticoids play an essential role in activating genes that can encode anti-inflammatory factors and inhibit the expression of proinflammatory cytokines [25, 26]. In a case report of mechanical ventilation complicated with *Pseudomonas aeruginosa* infection, antibiotics combined with glucocorticoids has been shown to effectively reduce the inflammatory response, reduce the burden of bacterial proliferation in lung tissue, and improve the histopathological changes of the lung caused by inflammation [27]. In addition, critical illness-related corticosteroid insufficiency, which has been associated with excessive inflammation, was noted in 0-48% of patients with severe pneumonia. Moreover, some studies have found that the level of glucocorticoids could reasonably predict the severity of pneumonia [28].

On the other hand, it has also been known that glucocorticoids may exert a negative effect in patients with severe pneumonia with its associated immunosuppressive effect. Many pathogenic bacteria in hospital-acquired pneumonia are drug-resistant bacteria, such as *Clostridium difficile*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. A prior study that assessed the clearance of virus in vivo by real-time polymerase chain reaction reported slower virus clearance in the high-dose glucocorticoid group as compared with other groups [29]. Another study corroborated that slower virus clearance was associated with higher mortality in patients with ARDS [30].

This meta-analysis incorporated RCTs that were of high-quality and the research subjects covered a wide range of patient population, rendering the research conclusions potentially generalizable. In the meantime, this study also suffered from several limitations. (1) The sample size of a small part of the literature included in this study is relatively small, compromising statistical power and accuracy. (2) There are certain differences in terms of the definition of severe pneumonia among studies. Due to the differences with regard to patient characteristics, physician subjective judgment, and the various scoring scales used, it is difficult to reach a unified standard for the diagnostic criteria. These

different characteristics may have a certain impact on the outcome of severe pneumonia treated with glucocorticoid. Therefore, the clinical diagnosis of severe pneumonia should be as comprehensive as possible, including demographic characteristics, clinical characteristics, imaging findings, laboratory examinations, and etiological tests. (3) The best scheme (including dose and administration frequency) for glucocorticoids in patients with severe pneumonia has not been fully clarified in the clinical guidelines. Previous studies have found that the type and dosage of glucocorticoids and glucocorticoid titering will have a certain impact on the clinical outcome. Due to the significant differences in the administration schemes between studies, it is impossible to uniformly determine the type and frequency of glucocorticoids. Therefore, glucocorticosteroid type and dosage differences may account for the medium to a high degree of heterogeneity in some subgroup analyses in this study.

In conclusion, we noted that glucocorticoid use was associated with increased all-cause mortality, elevated incidence of hospital-acquired pneumonia, and the need for mechanical ventilation.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Qiufeng Tang and Qiongyan Chen contributed equally to this work.

Acknowledgments

The project was supported by the Hainan Province Clinical Medical Center.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 8497084, 9 pages
https://doi.org/10.1155/2022/8497084

Research Article

Efficacy of Traditional Chinese Medicine Combined with Chemotherapy in the Treatment of Gastric Cancer: A Meta-analysis

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Received 24 May 2022; Accepted 19 July 2022; Published 4 August 2022

Academic Editor: Xi Lou

Objective. Meta-analysis was conducted to explore the effects of CM combined with chemotherapy on the effective rate and survival rate of gastric cancer patients. *Methods.* Literature retrieval was performed in PubMed, MEDLINE, Embase, CENTRAL, and CNKI databases. The subject of the literature was to compare the efficacy of CM combined with chemotherapy and chemotherapy alone in patients with gastric cancer. According to the Cochrane manual, the risk of bias was assessed for inclusion in randomized controlled trials. The chi-square test was used for the heterogeneity test. Subgroup analysis and sensitivity analysis were used to explore the causes of heterogeneity. Funnel chart and Egger's test were used to assess publication bias. *Results.* This study included 761 patients with gastric cancer from 10 literatures. The effective rate of chemotherapy in the CM combined group was higher than that in the chemotherapy alone group (odds ratio (OR) = 1.96, 95% confidence interval (CI) (1.39, 2.78), $Z = 3.81$, $P = 0.0001$), and there was no heterogeneity among studies ($\text{chi}^2 = 5.68$, $P = 0.68$, $I^2 = 0\%$). There was no significant publication bias among all studies ($P > 0.05$). The one-year survival rate in the CM combined group was higher than that in the chemotherapy alone group (OR = 3.25, 95% CI (1.90, 5.54), $Z = 4.32$, $P < 0.0001$). There was no heterogeneity among studies ($\text{chi}^2 = 1.04$, $P = 0.79$, $I^2 = 0\%$) and no significant publication bias among studies ($P > 0.05$). The 3-year survival rate of gastric cancer patients in the traditional Chinese medicine combination group was higher than that in the chemotherapy alone group (OR = 1.71, 95% CI (1.06, 2.78), $Z = 2.18$, $P = 0.03$). There was no heterogeneity among studies ($\text{chi}^2 = 2.18$, $P = 0.54$, $I^2 = 0\%$), and there was no significant publication bias ($P > 0.05$). The incidence of nausea and vomiting after chemotherapy in gastric cancer patients in the Chinese medicine combination group was lower than that in the chemotherapy alone group (OR = 0.47, 95% CI (0.34, 0.64), $Z = 4.80$, $P < 0.00001$). There was no heterogeneity among studies ($\text{chi}^2 = 8.57$, $P = 0.48$, $I^2 = 0\%$), and there was no significant publication bias ($P > 0.05$). *Conclusion.* CM combined with chemotherapy can improve the effective rate and survival rate of gastric cancer and reduce the incidence of nausea and vomiting after chemotherapy. We recommend a large sample size, multicenter combined randomized controlled trial for validation.

1. Introduction

Gastric cancer is the most common malignant tumour of the digestive system and one of the leading causes of cancer-related death worldwide [1–3]. China is a high incidence area of gastric cancer, and its incidence rate and mortality rate rank at the forefront of malignant tumours [4–6]. Surgery and chemoradiotherapy are the main methods for treating gastric cancer. Still, these methods also burden patients, including stress responses, adverse reactions, and declining quality of life [7–9]. Chemotherapy may lead to nausea and vomiting, leucopenia, thrombocytopenia, mucosal inflammation, weight loss, and other adverse reactions in patients with gastric cancer [10–13]. In the comprehensive

treatment of tumours, traditional Chinese medicine, with its unique advantages, plays an indispensable role in increasing curative effect by strengthening physique, improving body tolerance, improving quality of life, and reducing adverse reactions. Previous randomized controlled trials have confirmed that traditional Chinese medicine combined with chemotherapy can enhance patients' quality of life with gastric cancer. However, the sample size of these studies was small, and there was a high risk of bias. Thus, they could not provide reliable conclusions.

Previous meta-analysis and systematic reviews were limited to the effects of traditional Chinese medicine combined with chemotherapy on adverse reactions, quality of life, and hematopoietic system of patients with gastric cancer [14, 15]. Traditional Chinese medicine combined with chemotherapy can benefit patients in the above aspects. However, whether traditional Chinese medicine can improve the efficacy and survival rate of chemotherapy in patients with gastric cancer has been controversial. Some studies have pointed out that traditional Chinese medicine combined with chemotherapy can improve the 1-year, 3-year, and 5-year survival rates of patients [16]. However, some studies have pointed out that the effects of traditional Chinese medicine combined chemotherapy and chemotherapy alone on the 1-year survival rate and 2-year survival rate of patients are similar. Still, there are differences in the 3-year survival rate [17]. Some studies have pointed out that traditional Chinese medicine cannot affect the effective rate of chemotherapy for gastric cancer [18], while some studies hold the opposite view [19, 20]. Therefore, we conducted a meta-analysis to explore the effect of traditional Chinese medicine combined with chemotherapy on the efficacy and survival rate of chemotherapy, as well as the effects of adverse reactions in patients with gastric cancer.

2. Materials and Methods

2.1. Literature Download. Literature search was conducted in PubMed, MEDLINE, Embase, CENTRAL, and CNKI databases. The search terms were (Chinese medicine OR Chinese drugs) AND (gastric cancer OR stomach cancer) AND (chemotherapy). There were no restrictions on document language and publication time.

2.2. Literature Screening. Inclusion criteria are as follows: (1) the subjects were chemotherapy patients with gastric cancer. (2) The experimental group and control group were set up in the study. (3) The experimental group was treated with traditional Chinese medicine combined with chemotherapy, and the control group was treated with chemotherapy alone. (4) The outcome of observation included at least one of the effective rate, survival rate, or incidence of nausea and vomiting after chemotherapy. (5) The type of study was randomized controlled study.

Literature exclusion criteria are as follows: (1) repeated reports and case reports, (2) the subjects were patients with other tumours and could not distinguish patients with gastric cancer, (3) there was no control group in the study, (4) the balance of baseline data between the experimental group and the control group was poor or baseline data were not compared, and (5) the required data cannot be obtained, and the author of the literature cannot be contacted to supplement.

2.3. Data Extraction. Zhang and Zhao independently extracted the data information in included literature, such as author, title, publication time, research type, number of the experimental group, number of the control group, treatment efficiency, survival rate, and incidence of nausea and vomiting after chemotherapy. The missing data in the literature could be obtained by contacting the literature author. After data extraction, two researchers performed cross-checking. In case of disagreement, Liu and Jing discuss and solve it together.

2.4. Literature Quality Evaluation. This paper evaluated the literature quality by Zhang and Jing. Randomized controlled trials were assessed for risk of bias according to the "Risk of bias assessment tool for randomized trials" in the Cochrane Handbook. The evaluation contents included the bias in the process of randomization, the bias from the established intervention measures, the bias of missing outcome data, the bias of outcome measurement, and the bias of selective reporting results.

2.5. Heterogeneity Test. The chi-square test was used for the heterogeneity test. When I^2 corrected by degrees of freedom was more than 50% or $p < 0.1$, it was considered that there was heterogeneity among published literatures, and a random effect model was used. Subgroup analysis and sensitivity analysis were used to explore the causes of heterogeneity. If the source of heterogeneity cannot be found, we could only describe the literature results without merging. When the I^2 corrected by degrees of freedom was less than 50% and $P \geq 0.1$, it is considered that there is no heterogeneity among the published literatures, and the fixed effect model was used.

2.6. Publication Bias Assessment. Funnel chart and Egger's test were used to evaluate the publication bias. $P > 0.05$ suggested no significant publication bias, and $P < 0.05$ indicated that there was a certain publication bias.

2.7. Statistical Method. This study used Cochrane software RevMan5.3 statistical analysis of the data. The effect quantity was statistically described by the odds ratio (OR) and 95% confidence interval (CI). Bilateral $P < 0.05$ indicates statistically significant.

3. Results

3.1. Characteristics of Included Literature. A total of 843 literatures were retrieved in the above database. According to the screening criteria, 833 literatures were excluded. 10 literatures with 761 gastric cancer patients were included in the study, including 435 patients with traditional Chinese medicine combined chemotherapy and 326 patients with chemotherapy alone. The flow chart of literature screening is shown in Figure 1. The basic information of the literature and the risk assessment of bias are shown in Tables 1 and 2.

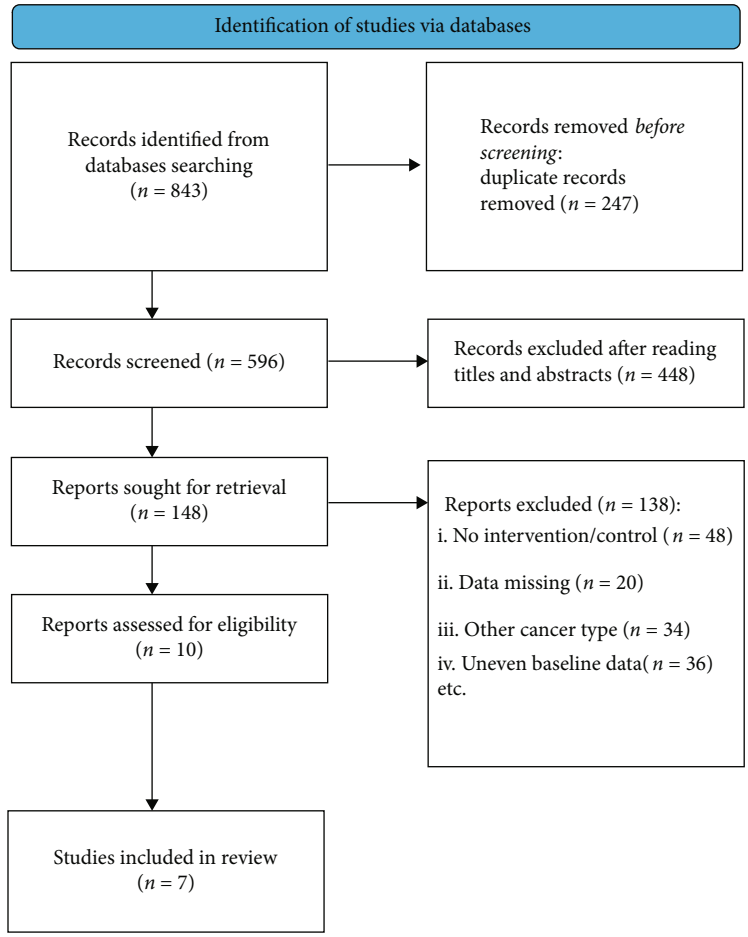

Figure 1: Flowchart of literature screening.

3.2. Comparison of Therapeutic Effectiveness between the Traditional Chinese Medicine Combined Group and Chemotherapy Alone Group. A total of 9 studies compared the effect of traditional Chinese medicine combined with chemotherapy and chemotherapy alone on the treatment efficiency of patients with gastric cancer included in our meta-analysis. The heterogeneity test showed that there was no heterogeneity among the nine studies ($chi^2 = 5.68$, $P = 0.68$, $I^2 = 0\%$). The fixed-effect model was used for consolidation. The effective rate of chemotherapy in the combination group of traditional Chinese medicine was higher than that in the chemotherapy alone group (OR = 1.96, 95% CI (1.39, 2.78), $Z = 3.81$, $P = 0.0001$), as shown in Figure 2. Funnel chart and Egger's test showed that the scatter points were approximately symmetrically distributed within the confidence interval and there was no significant publication bias ($P > 0.05$), as shown in Figure 3.

3.3. Comparison of 1-Year Survival Rate between the Traditional Chinese Medicine Combined Group and Chemotherapy Alone Group. A total of 4 studies compared the effects of traditional Chinese medicine combined with chemotherapy and chemotherapy alone on the 1-year survival rate of patients with gastric cancer included in our meta-analysis. The heterogeneity test showed that there was no heterogeneity among the four studies ($chi^2 = 1.04$, $P = 0.79$, $I^2 = 0\%$). The fixed-effect model was used for consolidation. The 1-year survival rate of gastric cancer patients in the traditional Chinese medicine combined group was higher than that in the chemotherapy alone group (OR = 3.25, 95% CI (1.90, 5.54), $Z = 4.32$, $P < 0.0001$), as shown in Figure 4. Funnel plots and Egger's test showed that the scatter points were approximately symmetrically distributed within the confidence interval, and there was no significant publication bias ($P > 0.05$), as shown in Figure 5.

3.4. Comparison of 3-Year Survival Rate between the Traditional Chinese Medicine Combination Group and Chemotherapy Alone Group. A total of 4 studies comparing the effect of traditional Chinese medicine combined with chemotherapy and chemotherapy alone on the 3-year survival rate of gastric cancer patients were included in our meta-analysis. The heterogeneity test showed that there was no heterogeneity among the 4 studies ($chi^2 = 2.18$, $P = 0.54$, $I^2 = 0\%$). A fixed-effect model was used for pooling. The 3-year survival rate of gastric cancer patients in the traditional Chinese medicine combination group was higher than that in the chemotherapy alone group (OR = 1.71, 95% CI (1.06, 2.78), $Z = 2.18$, $P = 0.03$), as shown in Figure 6. Funnel plots and Egger's test showed that the scatter points were

Table 1: The characteristics included literature.

Author	Year	No. of patients		CM regimen
		CM+chemotherapy	Chemotherapy	
Zhu et al. [21]	2006	40	40	Fuzheng anticancer granule, per os, 60 g, twice a day
Qi et al. [19]	2019	24	24	Xiaoaiping injection, intravenous drip, once daily
Zhou et al. [22]	1999	62	37	Shenqi Fuzheng injection 250 ml, intravenous drip, once daily
Liu et al. [20]	2009	28	19	Yiqi Bushen oral liquid, per os, twice a day
Wang et al. [18]	2007	34	32	Fuzheng Hewei decoction, per os, twice a day
Xin et al. [23]	1998	99	45	Shenqi Fuzheng injection 250 ml, intravenous drip, once daily
Liu et al. [24]	2002	35	16	Guben Yiliu III, per os, twice a day
Zhao et al. [25]	2007	30	30	Shenqi Fuzheng injection 250 ml, intravenous drip, once daily
Zhou et al. [16]	1996	35	35	Fuzheng Huoxue anticancer prescription, 100-200 mg, per os, 3 times a day
Jiang et al. [17]	2011	48	48	Self-prescribed prescription, per os, once a day

CM indicates for Chinese medicine.

Table 2: Risk of bias assessment of included studies.

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data	Selective reporting	Other bias
Zhu et al. [21]	High risk	High risk	Low risk	Uncertain	Low risk	Low risk	Low risk
Qi et al. [19]	Low risk	High risk	High risk	High risk	Low risk	High risk	Low risk
Zhou et al. [22]	Low risk	Uncertain	Low risk	High risk	Low risk	Uncertain	Uncertain
Liu et al. [20]	High risk	High risk	Uncertain	Low risk	Low risk	Low risk	Uncertain
Wang et al. [18]	High risk	Low risk	Low risk	High risk	Low risk	Uncertain	Low risk
Xin et al. [23]	High risk	Uncertain	High risk	Low risk	High risk	Low risk	Low risk
Liu et al. [24]	High risk	High risk	Uncertain	Low risk	Low risk	Low risk	Uncertain
Zhao et al. [25]	High risk	Uncertain	Low risk	High risk	Low risk	High risk	Uncertain
Zhou et al. [16]	Low risk	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk
Jiang et al. [17]	Low risk	Uncertain	Low risk	High risk	Low risk	High risk	Low risk

approximately symmetrically distributed within the confidence interval, and there was no significant publication bias ($P > 0.05$), as shown in Figure 7.

3.5. Comparison of the Incidence of Nausea and Vomiting between the Traditional Chinese Medicine Combination Group and Chemotherapy Alone Group. A total of 10 studies comparing the effects of traditional Chinese medicine combined with chemotherapy and chemotherapy alone on the incidence of nausea and vomiting after chemotherapy in gastric cancer patients were included in our meta-analysis. The heterogeneity test showed that there was no heterogeneity among the 10 studies ($\text{chi}^2 = 8.57$, $P = 0.48$, $I^2 = 0\%$). A fixed-effect model was used for pooling. The incidence of nausea and vomiting after chemotherapy in gastric cancer patients in the Chinese medicine combination group was lower than that in the chemotherapy alone group (OR = 0.47, 95% CI (0.34, 0.64), $Z = 4.80$, $P < 0.00001$), as shown in Figure 8. Funnel plots and Egger's test showed that the scatter points were approximately symmetrically distributed within the confidence interval, and there was no significant publication bias ($P > 0.05$), as shown in Figure 9.

4. Discussion

We compared traditional Chinese medicine with combined chemotherapy and chemotherapy alone by meta-analysis. The combined treatment could improve the chemotherapy efficiency and survival rate of patients with gastric cancer and reduce the incidence of nausea and vomiting. Zhu et al. [21] showed that the Fuzhengkang granule could improve the effective rate of superselective arterial chemotherapy. The incidence of adverse reactions in gastric cancer patients treated with chemotherapy combined with traditional Chinese medicine was lower than that of gastric cancer patients treated with chemotherapy alone. The half-year survival rate and 1-year survival rate of patients treated with traditional Chinese medicine combined with chemotherapy were higher, and the median survival time was longer. They suggest that traditional Chinese medicine can upregulate the expression of interleukin-2 and tumour necrosis factors-α and interferon-γ and downregulate the expression of the soluble interleukin-2 receptor in patients undergoing chemotherapy. It may explain why traditional Chinese medicine benefits patients with gastric cancer after

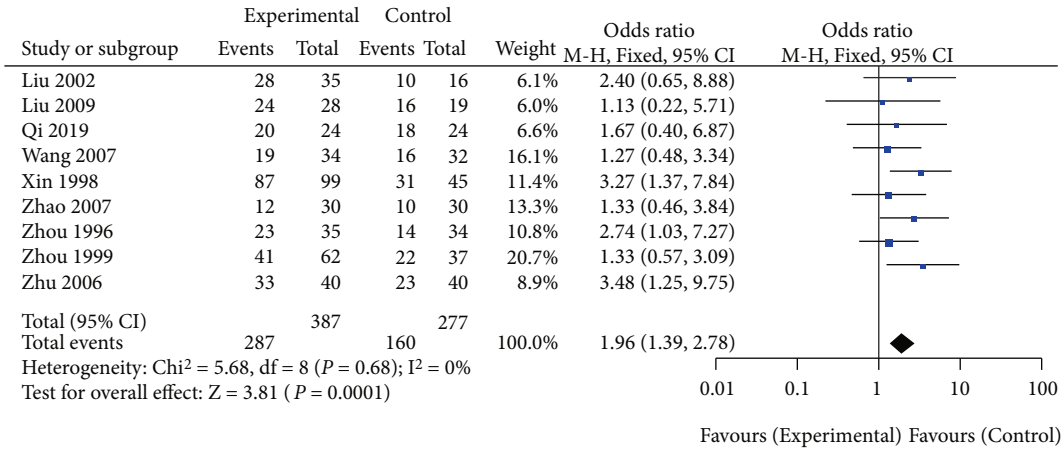

Figure 2: Forest diagram: comparison of effective rates between the Chinese medicine combination group and chemotherapy alone group.

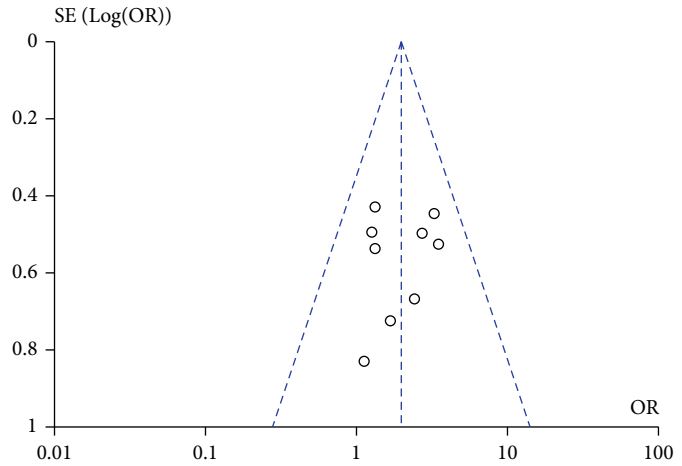

Figure 3: Funnel plot: comparison of effective rates between the traditional Chinese medicine combination group and chemotherapy only group.

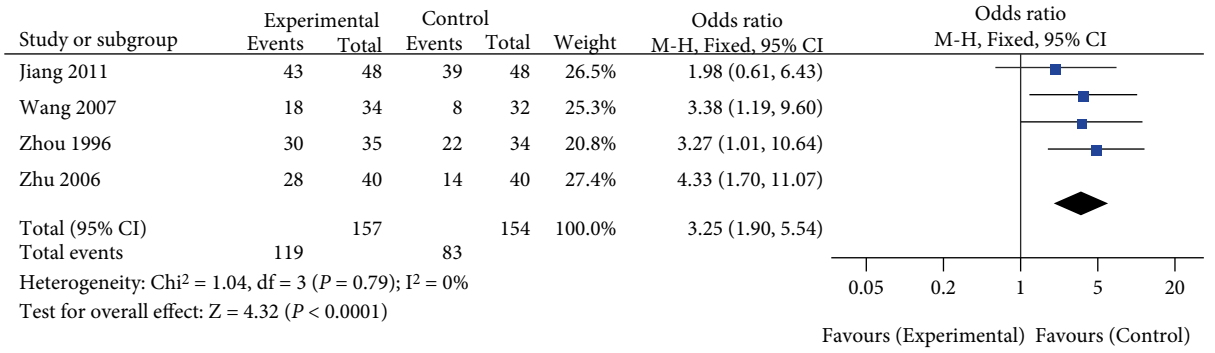

Figure 4: Forest plot: comparison of 1-year survival rate between the Chinese medicine combination group and chemotherapy alone group.

chemotherapy. Qi et al. [19] demonstrated that traditional Chinese medicine could improve the effective rate of chemotherapy and reduce the incidence of adverse reactions in patients with lung cancer and gastric cancer. However, there was no significant difference in platelet, leukemia, and red blood cell count between the traditional Chinese medicine combined chemotherapy group and the chemotherapy alone group. Zhou et al. [22] showed that patients with gastric cancer treated with traditional Chinese medicine combined with chemotherapy had a higher remission rate, a greater stability rate, and a higher improvement rate of life quality compared with patients treated with chemotherapy alone. Traditional

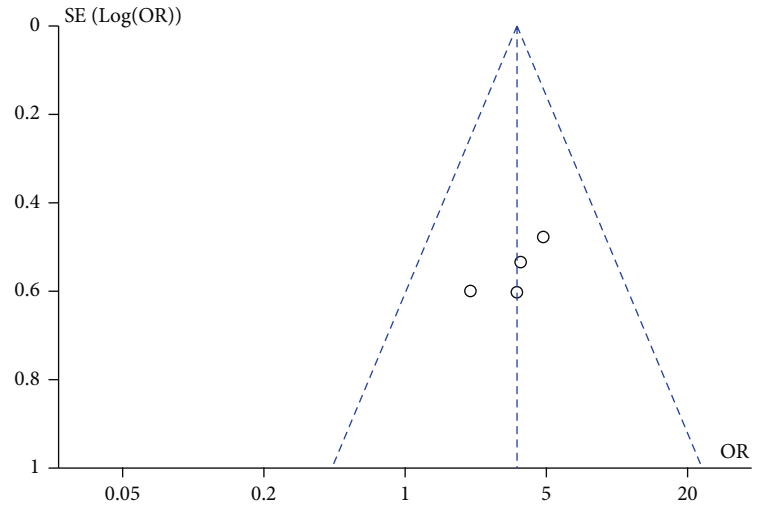

Figure 5: Funnel plot: comparison of 1-year survival rate between the Chinese medicine combination group and chemotherapy alone group.

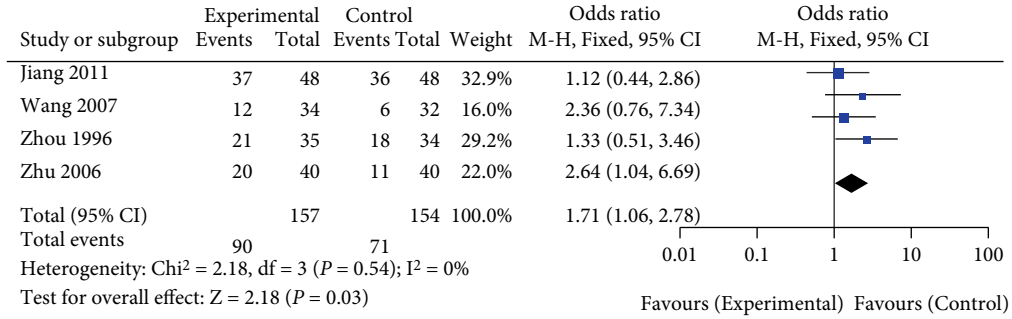

Figure 6: Forest plot: comparison of 3-year survival rate between the Chinese medicine combination group and chemotherapy alone group.

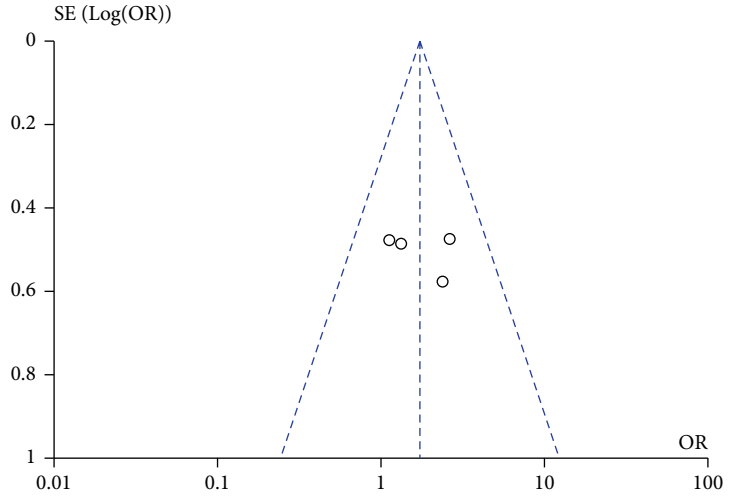

Figure 7: Funnel plot: comparison of 3-year survival rate between the Chinese medicine combination group and chemotherapy alone group.

Chinese medicine has a protective effect on the blood system. The incidence of leukopenia was lower in patients using traditional Chinese medicine. The study also pointed out that traditional Chinese medicine can improve the activity of natural killer cells, macrophages, and lymphocytes. Liu et al. [20] suggest that traditional Chinese medicine combined with chemotherapy can reduce the incidence of metastasis and recurrence in patients with gastric cancer within one year after the operation. Traditional Chinese medicine can improve the peripheral hemogram and immune

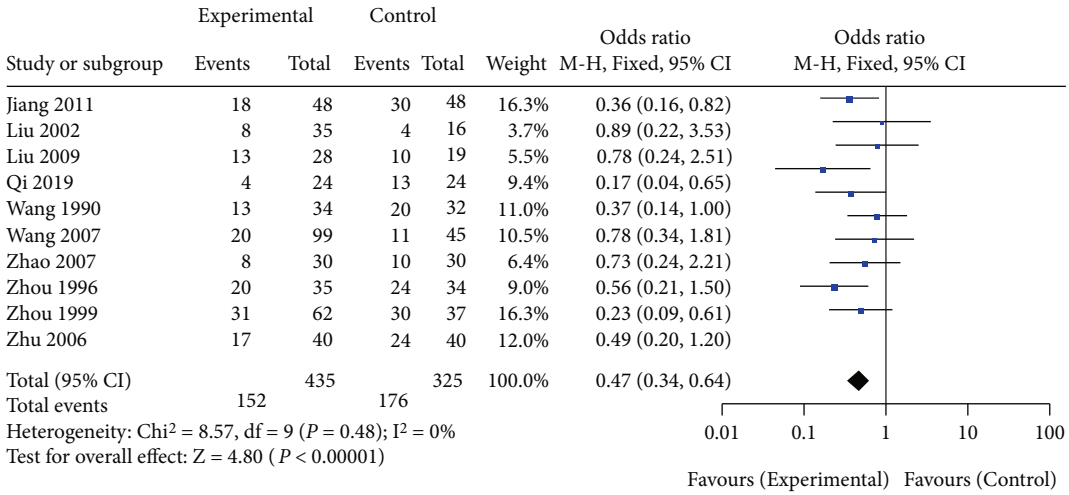

Figure 8: Forest diagram: comparison of the incidence of nausea and vomiting in the Chinese medicine combination group and the chemotherapy alone group.

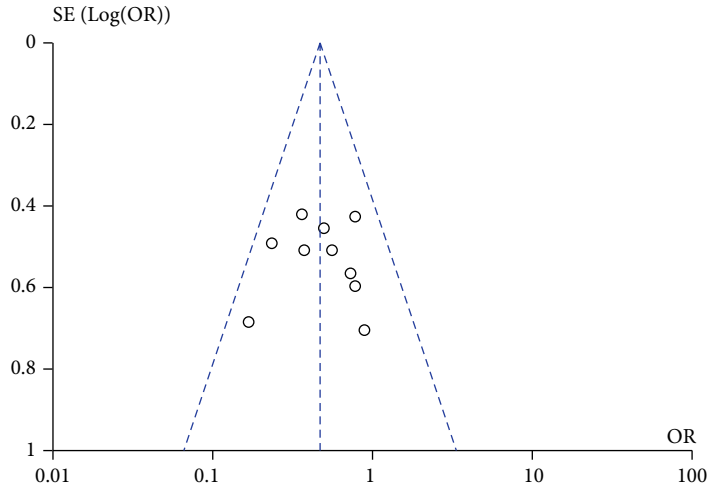

Figure 9: Funnel plot: comparison of the incidence of nausea and vomiting in the combination group and chemotherapy alone group.

function of patients with gastric cancer. Wang et al. [18] showed no significant difference between the traditional Chinese medicine combined chemotherapy group and chemotherapy alone group in terms of chemotherapy efficiency, clinical benefit rate, and half-year survival rate. However, the Chinese medicine combined with the chemotherapy group had a higher 1-year survival rate. Traditional Chinese medicine can reduce the incidence of adverse reactions, including leucopenia, nausea and vomiting, mucosal reaction, and fatigue. Xin et al. [23] showed that traditional Chinese medicine combined with chemotherapy could improve the remission rate and stability rate of patients with gastric cancer. Compared with chemotherapy alone, chemotherapy combined with traditional Chinese medicine can improve the clinical symptoms and quality of life of patients with gastric cancer. Traditional Chinese medicine combined with chemotherapy reduced the incidence of leucopenia. Their research also pointed out that traditional Chinese medicine can improve the immune function of patients with gastric cancer and activate immune cells through immune regulatory factors. Liu et al. [24] showed that traditional Chinese medicine could improve the short-term efficacy, immune function, and coagulation function of patients with gastric cancer undergoing chemotherapy. Traditional Chinese medicine can reduce the incidence of lymphocytopenia. Zhao et al. [25] illustrated that the effective short-term rate of traditional Chinese medicine combined chemotherapy group was higher than that of the chemotherapy alone group. Traditional Chinese medicine can improve the Karnofsky scores and stabilize the weight of patients. They also pointed out that traditional Chinese medicine can reduce peripheral nerve injury and gastrointestinal reactions. Zhou et al. [16] showed that traditional Chinese medicine could enhance the immune function of patients with gastric cancer by activating lymphocytes. In terms of 1-year survival rate, 3-year survival rate, and 5-year survival rate, traditional Chinese medicine combined with chemotherapy has more advantages. Jiang et al. [17] believed that there was no significant difference between the traditional Chinese medicine combined chemotherapy group and the chemotherapy

alone group in terms of 1-year survival rate and recurrence rate, 2-year survival rate, and recurrence rate. However, the 3-year survival rate of patients in the traditional Chinese medicine combined chemotherapy group was higher than that in the chemotherapy alone group. In comparison, the recurrence rate was lower than that in the chemotherapy alone group. The Karnofsky score for traditional Chinese medicine combined with the chemotherapy group was significantly higher than that of the chemotherapy alone group.

Among the literatures we included in the analysis, the research results of traditional Chinese medicine in reducing the incidence of chemotherapy-related nausea and vomiting were consistent. In addition, a previous meta-analysis [26] also confirmed that traditional Chinese medicine combined with chemotherapy could reduce the incidence of adverse events such as nausea and vomiting in patients with gastric cancer and play a positive role in improving the quality of life score of patients with gastric cancer. The weight of gastric cancer patients treated with traditional Chinese medicine combined with chemotherapy was more stable. In patients with low-grade gastric cancer, traditional Chinese medicine combined with chemotherapy could reduce the incidence of leukopenia and oral mucositis.

A previous network meta-analysis explored the optimal regimen of traditional Chinese medicine injection combined with XELOX regimen in the treatment of gastric cancer. Javanica oil emulsion and compound Kushen injection can improve chemotherapy efficacy. However, this study is only for one chemotherapy regimen, and this conclusion cannot be generalized [27].

There are some limitations to this study. The first is that the sample size included in the analysis is small, and there may be sample selection bias. Second, there were differences in TCM and chemotherapy regimens between studies, which may have affected the results. Finally, the literature included in the analysis was at high risk of bias, reducing the confidence of the conclusions.

In conclusion, traditional Chinese medicine combined with chemotherapy can improve the treatment efficiency and survival rate of patients with gastric cancer and reduce the incidence of nausea and vomiting after chemotherapy. We suggest a large sample size, multicenter randomized controlled trial for validation.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Wenxin Zhang and Yijuan Zhao contributed equally to this work.

Acknowledgments

The project was supported by the General Project of Natural Science Foundation of Hainan Province (No. 821MS0776).

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 3393191, 11 pages
https://doi.org/10.1155/2022/3393191

Research Article

Physical Therapy for at Least 6 Months Improves Motor Symptoms in Parkinson's Patients: A Meta-Analysis

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Received 27 June 2022; Accepted 20 July 2022; Published 31 July 2022

Academic Editor: Xi Lou

Objective. Long-term physical therapy helps to improve the motor symptoms of patients with Parkinson's disease, but the effectiveness is not clear. The purpose of this study was to evaluate the effect of long-term physical therapy on improving motor symptoms or daily activities in Parkinson's patients with drug use or discontinuation, as well as its impact on drug treatment dose. A subgroup analysis was conducted on different treatment methods to determine the most effective treatment method. *Methods*. The researchers independently searched databases, including PubMed, Medline, Embase, Ovid, Cochrane Library, and ISI Web of science. The search deadline was June 2022. A randomized controlled trial was conducted on Parkinson's disease patients with HY stages 1-3 who received continuous physical therapy for 6 months or more. Systematic evaluation and meta-analysis were carried out by using common clinical evaluation indicators, namely, MDS-UPDRS exercise score, daily activity (ADL) score, or LED dose. The quality of the literature was assessed using the modified Jadad scale of Cochrane's bias risk tool. *Results*. A total of 523 Parkinson's disease patients with HY stages of 1-3 were included in the study. The results showed that long-term physical therapy could improve patients' motor symptoms with combined antiparkinsonian drugs ($Z = 2.61$ and $P = 0.009$) and had a significant positive effect on the motor symptoms of patients with discontinued antiparkinsonian drugs ($Z = 2.73$ and $P = 0.006$). Meanwhile, it could reduce the LED dose of patients with Parkinson's disease. The difference was statistically significant ($Z = 2.58$ and $P = 0.010$). *Conclusion*. The results of this study indicated that physical therapy for at least 6 months or longer for patients with mild to moderate Parkinson's HY could effectively improve the motor symptoms of Parkinson's patients, whether or not combined with antiparkinson drugs. Meanwhile, long-term physical therapy reduced the LED dose of patients treated with drugs compared with patients in the control group who received short-term physical therapy, other types of intervention group, or no treatment.

1. Introduction

Parkinson's disease is a common and complex neurodegenerative disease. About 1.6 people in every 1000 people worldwide suffer from Parkinson's disease. The high prevalence greatly impacts patients and their families [1]. The main symptoms of Parkinson's disease (PD) are dyskinesia and motor symptoms, including bradykinesia, static tremor, rigidity, and postural and gait disorders. With the progress of the disease, these symptoms become more prominent and impact daily activities (ADL) [2, 3]. Traditionally, the treatment of Parkinson's disease is drug treatment. Still, the patient's physical function, daily activity participation, and activity ability decline with the progress of the disease, which leads to a continuous decrease in the patient's quality of life [4]. In addition, the drug effect becomes more and more limited as increasing drug dosage and progressing disease. Meanwhile, drug side effects can increase the risk of exercise complications [5]. At present, physical therapy combined with drugs has been widely used in the clinical management of Parkinson's disease [6].

Physical therapy is an intervention method that enhances muscle strength, aerobic exercise ability, balance ability, pos-

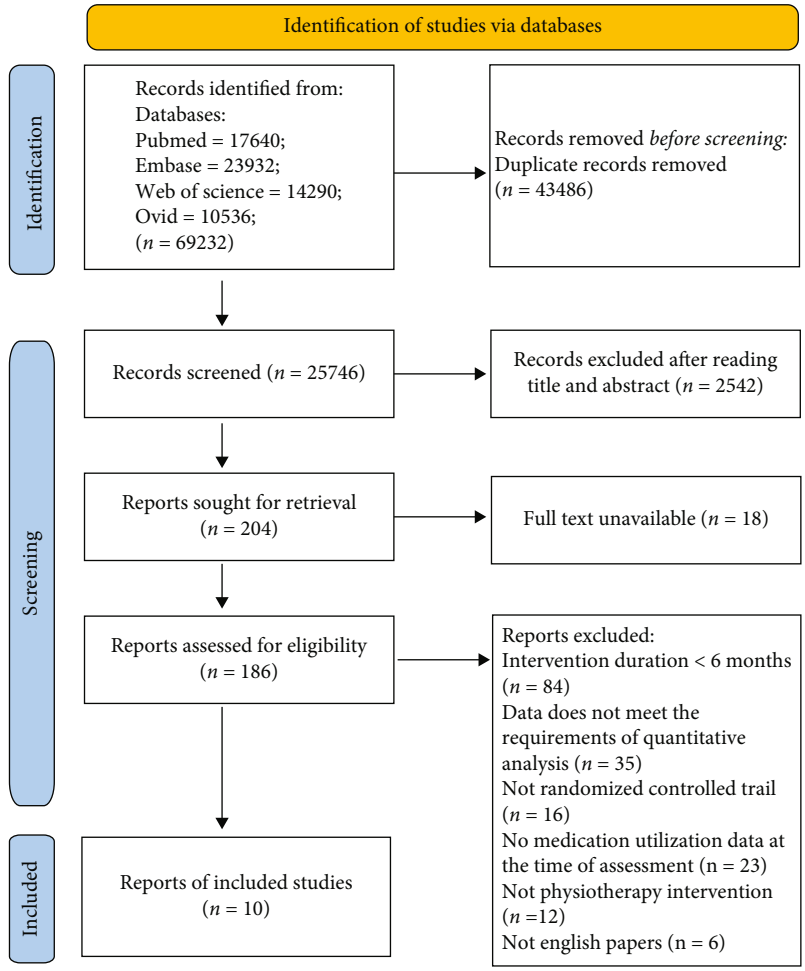


Figure 1: Document screening and exclusion process.

ture and gait, and body flexibility through reminders, exercise awareness strategies, and physical exercise [7]. Previous studies have shown that physical therapy has a short-term improvement effect on motor symptoms and daily activities of patients with Parkinson's disease [8–10]. However, a few evaluate the impact of long-term physical therapy on motor symptoms, daily activities, or a combined dose of drugs in patients with Parkinson's disease. Most physiotherapy widely used in the clinic is only short-term, which may be related to the lack of high-quality systematic evaluation and meta-analysis of long-term physiotherapy. Suppose long-term physical therapy is conducive to delaying motor symptoms and ADL damage, thus reducing the dosage of antiparkinson drugs. In that case, it may benefit a large number of patients. Currently, several randomized controlled trial (RCT) studies have carried out long-term physical therapy for at least 6 months or more to reveal its impact on motor symptoms, ADL, and drug dosage of PD patients [11–13]. Furthermore, previous studies on long-term physical therapy have primarily used various physical therapy measures, including compound aerobic exercise, strength exercise, multimodal exercise, or multidisciplinary treatment programs based on physical therapy [14]. However, it is not clear which type of long-term physical therapy can benefit patients the most.

In this study, data were extracted and analyzed from the long-term physical therapy randomized controlled trials that have existed for more than 6 months. This study evaluated the effect of long-term physical therapy on motor symptoms or daily activities of patients with drug use or discontinuation and its impact on drug treatment dose. We also conducted subgroup analysis on different treatment methods to determine the most effective treatment method.

2. Materials and Methods

2.1. Literature Search Strategy and Inclusion and Exclusion Criteria. Following the principle of Cochrane, 4 independent researchers conducted a comprehensive literature retrieval. Researchers independently searched the following databases: PubMed, Medline, Embase Ovid, Cochrane Library, and ISI Web of science. The search deadline was June 2022. The search keywords were "Parkinson disease" or "Parkinsonian" and "rehabilitation" or "physical therapy" or "physiotherapy" or "exercise" or "training." The range was human-related studies. Disagreements were resolved through negotiation and discussion.

The inclusion criteria were as follows: (1) parallel randomized controlled trials; (2) the document language was English;

Table 1: Characteristics and quality scores of included literature.

Study	Subjects, *n*		HY stage	Intervention		Outcome measures	Medication state in evaluation time	M-Jadad scale
	Experimental group	Control group		Experimental group	Control group			
Au 2022 [11]	15	15	1-3	Multidisciplinary rehabilitation 6 months	Multidisciplinary rehabilitation 6 weeks	MDS- UPDRS motor, ADL LED, etc.	On	5
Yang 2022 [13]	30	30	1-3	Multidisciplinary rehabilitation 18 months	Multidisciplinary rehabilitation 4 months	MDS-UPDRS motor, ADL LED, etc.	On	5
Mak 2021 [12]	33	31	1-3	Aerobic exercise 6 months	Usual care 6 months	MDS-UPDRS motor, ADL LED, etc.	On	5
Tollar 2019 [20]	19	20	1-2	Multidisciplinary rehabilitation 2 years	No exercise 2 years	MDS-UPDRS ADL, LED, etc.	On	4
Kolk 2019 [21]	65	65	1-2	Aerobic exercise 6 months	Stretching and relaxation 6 months	MDS-UPDRS motor, ADL LED, etc.	On/off	6
Ferreira 2018 [22]	18	17	1-3	Resistance exercise 6 months	No intervention 6 months	MDS-UPDRS motor, ADL, etc.	On	5
Kolk 2018 [23]	22	15	1-2	Aerobic exercise 6 months	No intervention 6 months	MDS-UPDRS motor, ADL, etc.	Off	5
Frazzitta 2015 [24]	20	20	1-2	Multidisciplinary rehabilitation 2 years	Usual care 2 years	MDS-UPDRS motor, ADL LED, etc.	Off	5
Cocros 2013 [25]	20	18	1-3	Resistance exercise 1 year	Fitness count exercise 1 years	MDS-UPDRS motor, LED, etc	On/off	6
Frazzitta 2012 [24]	25	25	3	Multidisciplinary rehabilitation 1 year	Usual care 1 year	MDS-UPDRS motor, ADL, LED, etc	On	4

N: patients number; HY: Hoehn and Yahr stage; MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; ADL: activities of daily living scale; LED: levodopa equivalent dose; on: on medication state; off: off medication state. M-Jadad scale: modified Jadad scale.

(3) the patients included in the study were mild to moderate Parkinson's disease patients with HY (Hoehn and Yahr stage); (4) patients received physical therapy at least once a week for 6 months or more; (5) two groups of comparative intervention experiments, namely, the long-term physical therapy experimental group and the control group, where the control group could be a short-term treatment intervention group, other types of intervention group, or no treatment group; (6) data that could be extracted before and after treatment to evaluate in this study, where data included movement disorder society UPDRS (MDS-UPDRS) motor score, daily activity (ADL) score, or levodopa equivalent dose (LED); and (7) the modified Jadad scale (RCT) score ≥4.

The exclusion criteria were as follows: (1) Non-Parkinson's disease patients with tremor paralysis symptoms; (2) atypical and widely used physical therapy interventions included but were not limited to dance, Tai Chi, qigong, yoga, music, boxing, and various nerve stimulation; (3) unable to judge whether the patient is in the state of drug use; and (4) the literature types were review, case-control study, case report, and other non-randomized controlled studies.

2.2. Document Data Extraction. In this study, 3 researchers extracted the basic information and data of the literature that met the inclusion criteria, and a third researcher checked the data. The extracted data and characteristics included literature characteristics (author, year of publication), patient characteristics (quantity, HY disease degree classification), physical therapy, result evaluation, and drug use during the experiment were collected. According to the previously published literature review [15], the common clinical evaluation indicators, namely, MDS-UPDRS motor score, daily activity (ADL) score, or LED dose, were used. Currently, the motor and ADL scores (MDS-UPDRS) are one of the world's standard measurement standards for exercise and the daily life of PD patients [16]. The types and doses of drugs used by different patients were different. Furthermore, the levodopa equivalent dose (LED) was adopted in this paper to facilitate the statistical conversion of the dosage of patients [17].

2.3. Statistical Analysis. The Review Manager software (version 5.4 of the Nordic Cochrane Centre, Copenhagen, Denmark) was used for statistical analysis and forest map, thus

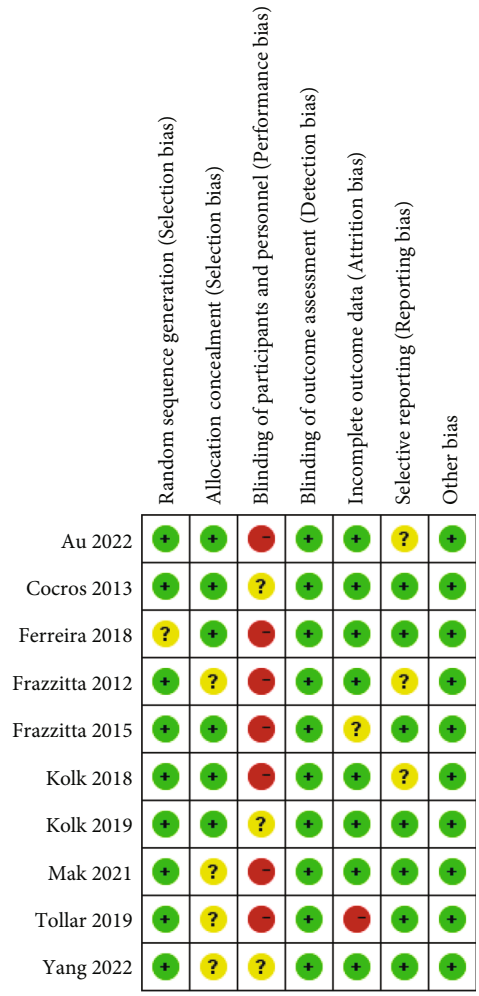


Figure 2: Summary of study bias risk.

evaluating the total effect comparison between the long-term physical therapy group and the control group. Due to the large differences between clinical and research methods between experiments, the standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for continuous variables using the random effect model. The studies with clinical homogeneity were divided into subgroups to analyze the specific effects of different types of physical therapy. The Chi-square test was used for the heterogeneity test. When $P < 0.05$, the difference was considered statistically significant.

2.4. Document Quality Evaluation. The modified Jadad scale of Cochrane's bias risk tool was used to assess the quality, bias, and risk of eligible studies [18]. The modified Jadad scale used in the literature evaluation was a widely used scale in clinical and research [19]. The improved M-Jadad scale was divided into random sequence generation (2 points), randomized hiding (2 points), blind method (2 points), and withdrawal (1 point), with a total of 7 points. 1-3 points were recognized as low-quality research, and 4-7 points were recognized for high-quality research. In addition, Cochrane's bias risk tool was used to evaluate the randomized controlled trials and make a risk bias map. Bias analysis included random sequence generation, random scheme concealment, participant blinding, result evaluation blinding, data integrity, selective reporting, and other biases. Each bias risk level was divided into low, high or unclear, and different color blocks represented the results. Two independent researchers conducted the quality assessment.

3. Results

3.1. Search Results and Research Characteristics. A total of 69232 documents were retrieved from different databases, of which 43486 duplicate documents were eliminated. The remaining literature were reviewed and evaluated according to the inclusion criteria, and 10 were finally selected. The specific inclusion and exclusion process is shown in Figure 1. Document characteristics and experimental result data were counted, and a quality review was conducted. See Table 1 for a summary of study characteristics and scores of the modified Jadad scale. A total of 523 Parkinson's disease patients with HY stages 1-3 were included in the study. Eligible research types included aerobic exercise, resistance exercise, and physical therapy-based multidisciplinary rehabilitation. The duration of physiotherapy varied from 6 months to 2 years. In addition, drug treatment status in

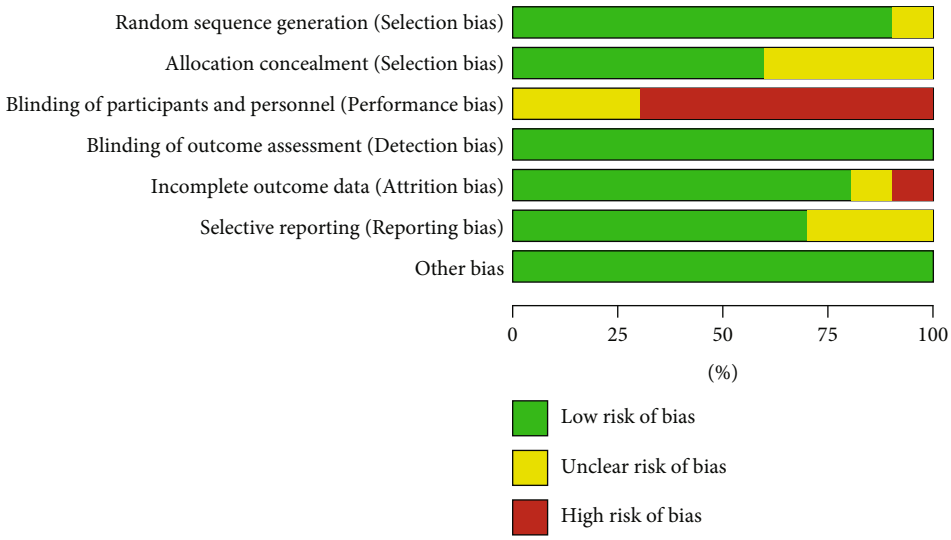


Figure 3: Study bias risk map.

different studies was also distinct. 6 of them were combined with drug treatment, while patients in 2 special studies took the drug part of the time, and the drug was stopped part of the time during the whole experiment (see Table 1 for detailed literature research characteristics).

3.2. Bias Risk and Literature Quality Assessment. Figure 2 is a summary of the bias risk of each literature, and Figure 3 is a bar chart of the bias risk of the included studies. Each study had its limitations or could not be judged. In other words, no investigation was completely low risk. All studies had a low risk of blinding or other bias in outcome assessment. In current meta-analysis, most included studies have low risk in random sequence generation, random scheme hiding, and data integrity. However, most studies had a bias in the blind method for participants, demonstrating a high risk. The improved Jadad scale is also a general tool to evaluate the quality of literature. The literature scores were distributed between 4 and 6, and most of the literature scores were 5. The included literature was of high quality. The studies included in this paper were heterogeneous, so funnel analysis was not applicable.

3.3. Effect of Long-Term Physical Therapy on Motor Symptoms of Patients with Combined Antiparkinson Drugs. 395 patients in 7 RCT studies were included in the analysis [11–13, 21, 22, 25, 26]. During long-term physical therapy, the changes in the MDS-UPDRS motor score before and after using antiparkinson drugs were analyzed. Therefore, the impact of long-term physical therapy on motor symptoms of patients with antiparkinson drugs was evaluated (see Figure 4 for details). The total meta-analysis data are shown in Figure 4(a). The data showed that long-term physical therapy could improve patients' motor symptoms with combined antiparkinson drugs (SMD = −0.47, 95%CI = −0.83, −0.12, Z = 2.61, $P = 0.009$). Meanwhile, $I^2 = 65\%$ indicated significant heterogeneity among the studies. Further, the studies were divided into three types according to the type of physical therapy: aerobic exercise, resistance training, and physical therapy-based multidisciplinary rehabilitation. Subgroup analysis was conducted according to three types, as shown in Figure 4(b). The results failed to show statistically significant results ($Z = 1.53$, $P = 0.13$, $Z = 1.28$, $P = 0.2$, $Z = 0.86$, and $P = 0.39$). The subgroup of aerobic exercise and multidisciplinary rehabilitation group showed significant heterogeneity ($I^2 = 81\%$ and $I^2 = 85\%$).

3.4. Effect of Long-Term Physical Therapy on Motor Symptoms of Patients without Antiparkinson Drugs. A total of 240 patients in 4 RCT studies were included in the analysis [21, 23–25]. The changes in MDS-UPDRS motor score before and after long-term physical therapy in patients who did not use antiparkinson drugs were analyzed. Therefore, the impact of long-term physical therapy on motor symptoms of patients who stopped using antiparkinson drugs was evaluated (see Figure 5 for details). The total meta-analysis data are shown in Figure 5(a). The data showed that long-term physical therapy significantly improved the motor symptoms of patients who stopped using antiparkinson drugs (SMD = −0.86, 95%CI = −1.47, −0.24, $Z = 2.73$, and $P = 0.006$). Furthermore, $I^2 = 77\%$ showed significant heterogeneity among the studies. Subgroup analysis of each study according to each physiotherapy type is shown in Figure 5(b). The multidisciplinary rehabilitation subgroup failed to show a significant positive effect, and the heterogeneity of this subgroup was high, $I^2 = 89\%$. Only one study was about the aerobic group and resistance training. Between them, resistance training showed a positive impact on improving exercise symptoms.

3.5. Effect of Long-Term Physical Therapy on Daily Activities (ADL) of Parkinson's Patients. A total of 474 patients in 9 RCT studies were included in the analysis [11–13, 20–24, 26]. The changes in MDS-UPDRS ADL scores before and after long-term physical therapy were analyzed to evaluate the impact of long-term physical therapy on the daily activities (ADL) of Parkinson's patients (see Figure 6 for details). The total meta-analysis data are shown in Figure 6(a). The

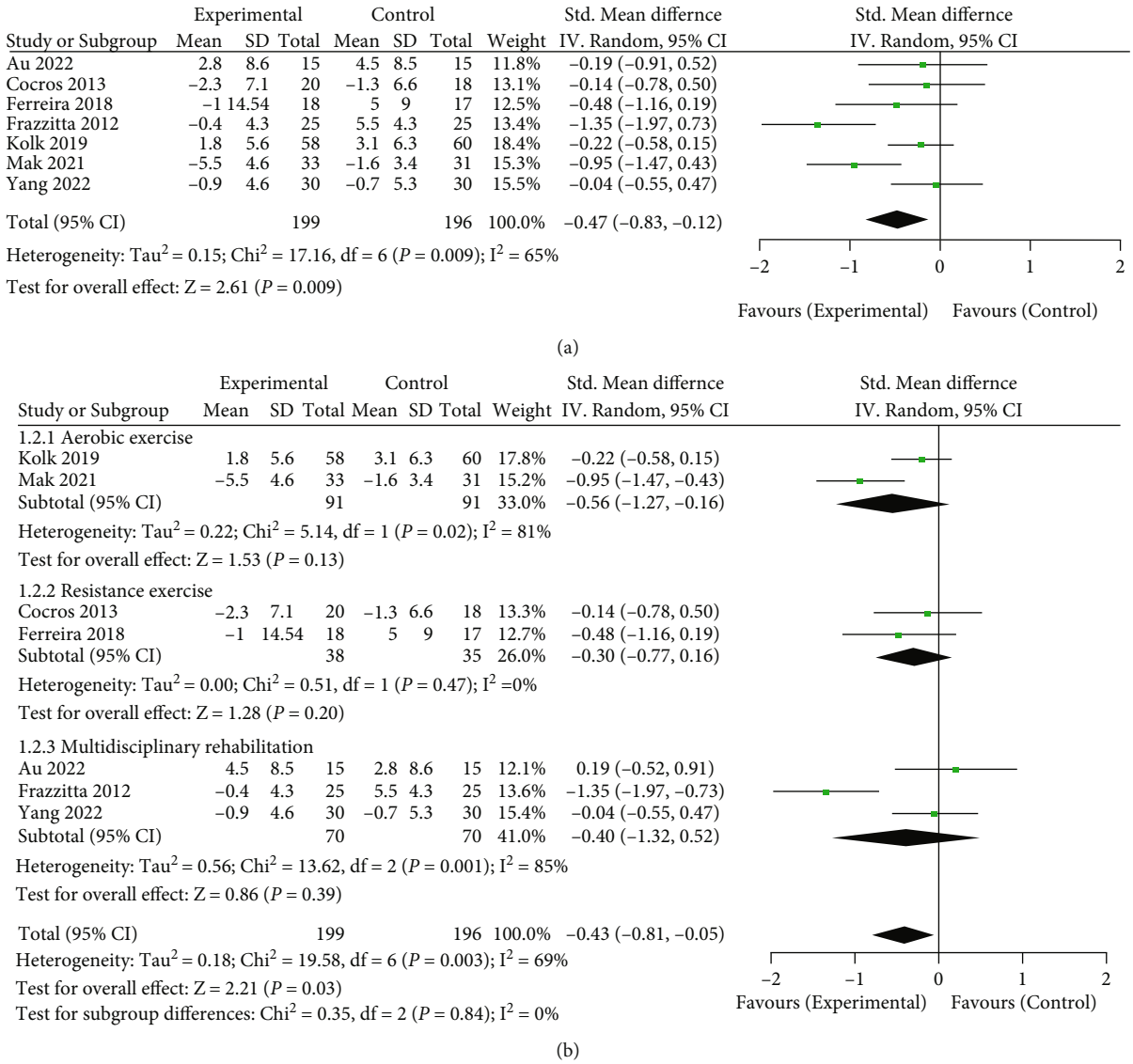


Figure 4: Effect of long-term physical therapy on motor symptoms of patients with combined antiparkinson drugs. (a) Total meta-analysis data and (b) subgroup analysis data by physical therapy type.

data showed that long-term physical therapy had no significant effect on the daily activities (ADL) of Parkinson's patients (SMD = −0.31, 95%CI = −0.70, 0.08, $Z = 1.54$, and $P = 0.12$). In addition, $I^2 = 75\%$ showed significant heterogeneity among the studies. Further subgroup analysis of each physiotherapy type is shown in Figure 6(b). The aerobic exercise and resistance training groups had no significant effect, but the multidisciplinary rehabilitation group showed positive improvement (SMD = −0.67, 95%CI = −1.32, − 0.03, $Z = 2.04$, and $P = 0.04$).

3.6. Effect of Long-Term Physical Therapy on Antiparkinson Drug Dosage (LED) of Parkinson's Patients. A total of 449 patients in 8 RCT studies were included in the analysis [11, 12, 20, 21, 24–26]. Since patients used different Parkinson's drugs, levodopa equivalent dose (LED) was used for unified analysis and measurement to analyze the changes in LED dosage before and after long-term physical therapy. Furthermore, the impact of long-term physical therapy on the antiparkinson drug dosage (LED) of Parkinson's patients was evaluated (see Figure 7 for details). The total meta-analysis data are shown in Figure 7(a). The data showed that long-term physical therapy could reduce the LED dose of Parkinson's patients and the difference was statistically significant (SMD = −0.45, 95%CI = −0.79, − 0.11, $Z = 2.58$, and $P = 0.010$). $I^2 = 67\%$ showed significant heterogeneity among the studies. Further subgroup analysis of each physiotherapy type is shown in Figure 7(b). The aerobic exercise and resistance training groups had no significant effect, but the multidisciplinary rehabilitation group showed a positive impact (SMD = −0.68, 95%CI = −1.25, − 0.11, $Z = 2.35$, and $P = 0.02$).

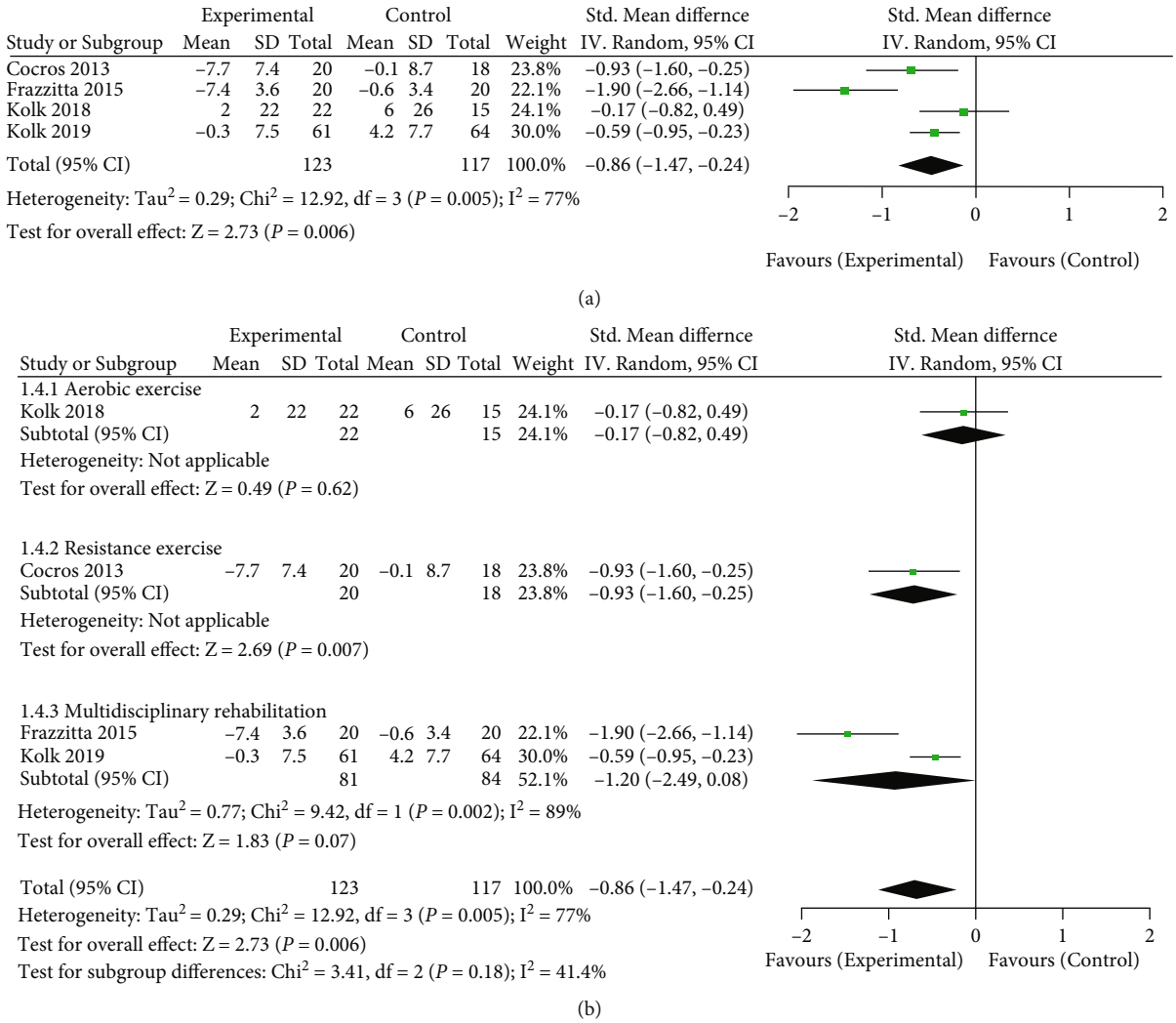
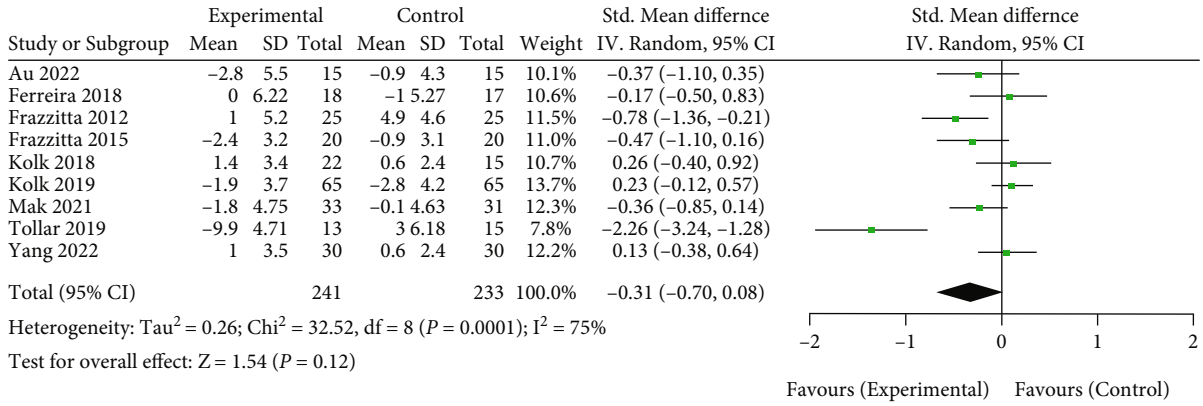


Figure 5: Effect of long-term physical therapy on motor symptoms of patients without antiparkinson drugs. (a) Total meta-analysis data and (b) subgroup analysis data by physical therapy type.

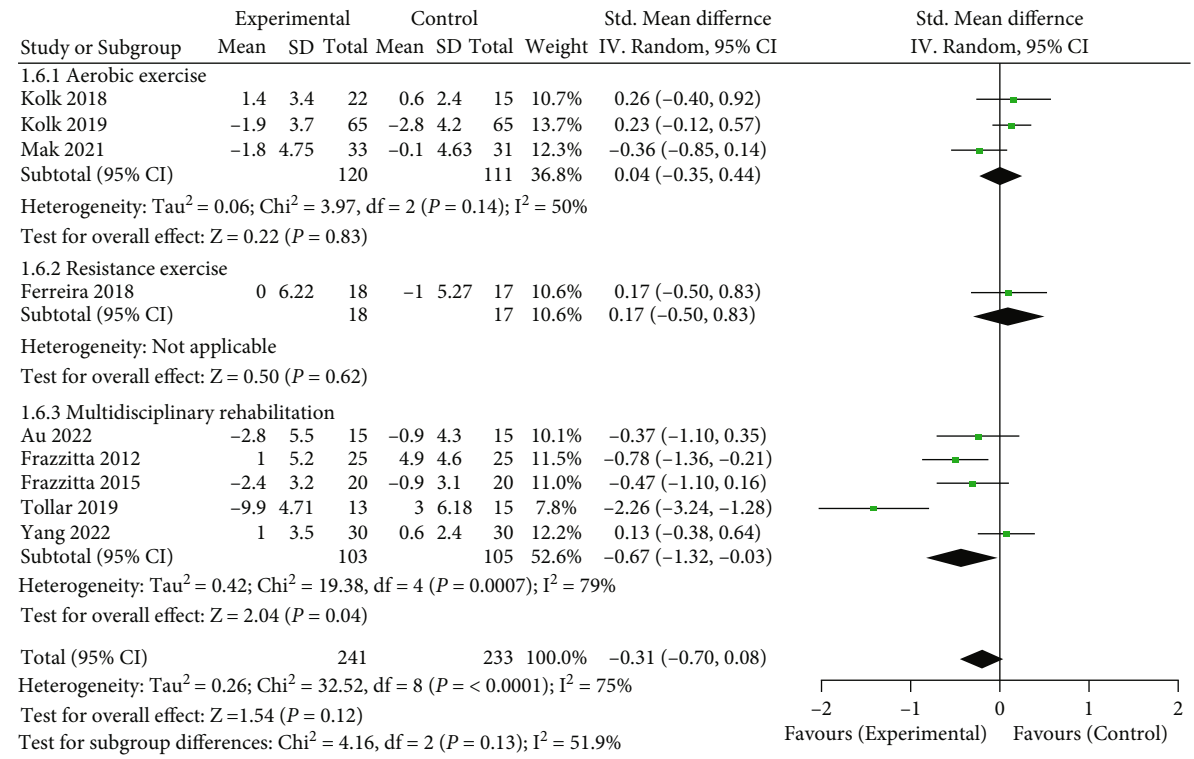
4. Discussion

Currently, there are fewer systematic evaluations and meta-analyses to study the effects of long-term physical therapy on motor symptoms, quality of life, and dosage of antiparkinson drugs in patients with Parkinson's disease. Meanwhile, there is a lack of research evidence of high-quality literature analysis. This paper summarized and analyzed the impact of long-term physical therapy on the results of Parkinson's patients. We divided them into three groups according to the type of physical therapy. We classified and analyzed each subgroup to explore the impact of a specific kind of physical therapy on the results, thus seeking the best treatment type. The analysis results of this study demonstrated that physical therapy for at least 6 months or longer for patients with mild to moderate Parkinson's HY could effectively improve the motor symptoms of Parkinson's patients than the control group, mainly the short-term intervention group of physical therapy, other types of intervention group, or no treatment group, whether or not combined with antiparkinson drugs. Meanwhile, long-term physical therapy could reduce the LED dose of patients treated with drugs. Increasing literature emphasizes the importance of early long-term physical intervention for Parkinson's patients [27, 28], and the conclusion of this paper also supports this view. Although there is little research on long-term physical therapy, this paper still conducted a subgroup analysis according to the type of physical therapy. Among them, the multidisciplinary rehabilitation group showed that it could improve ADL and LED.

To investigate the effect of long-term physical therapy on motor symptoms of patients with combined antiparkinson drugs, we included 7 RCT studies. The analysis showed that long-term physical therapy combined with antiparkinson drugs could improve motor symptoms, and the difference was statistically significant. However, no statistically significant difference was found in each analysis subgroup. On the one hand, the methods of physical therapy were different, the treatment time was also different, and the heterogeneity of methodology was quite considerable, which caused variation in the result. On the other hand, due to the mixed use of antiparkinson drugs and the extended research time,



(a)



(b)

Figure 6: Effect of long-term physical therapy on daily activities (ADL) of patients with Parkinson's disease. (a) Total meta-analysis data and (b) subgroup analysis data by physical therapy type.

it was difficult to analyze whether a specific intervention or the combined use of drugs and exercise was responsible for the result. Moreover, one of the literature included in this study showed a greater effect on improving medication status compared with other literature [26]. Still, other studies did not show significant statistical differences. This result should be carefully considered.

In this paper, 4 literatures were included to analyze the impact of long-term physical therapy on patients who stopped using antiparkinson drugs. The final summary analysis showed that long-term physical therapy had achieved the remission of motor symptoms. But in the subgroup analysis, only one resistance training had a statistically significant effect.

9 studies were included to analyze the effect of long-term physical therapy on daily activities (ADL) of Parkinson's patients. The results showed that there was no statistically significant effect. However, subgroup analysis showed that the multidisciplinary rehabilitation group showed positive improvement. Although the multidisciplinary therapy included in the literature mainly consisted of physical therapy, it also had some visual and auditory guidance training to improve gait and posture [24, 26]. Several RCT experiments showed that multidisciplinary rehabilitation therapy combined with gait and posture management could improve the daily life of Parkinson's patients [29, 30]. Their results also suggested that multidisciplinary therapy, such as physical therapy combined with posture and gait management,

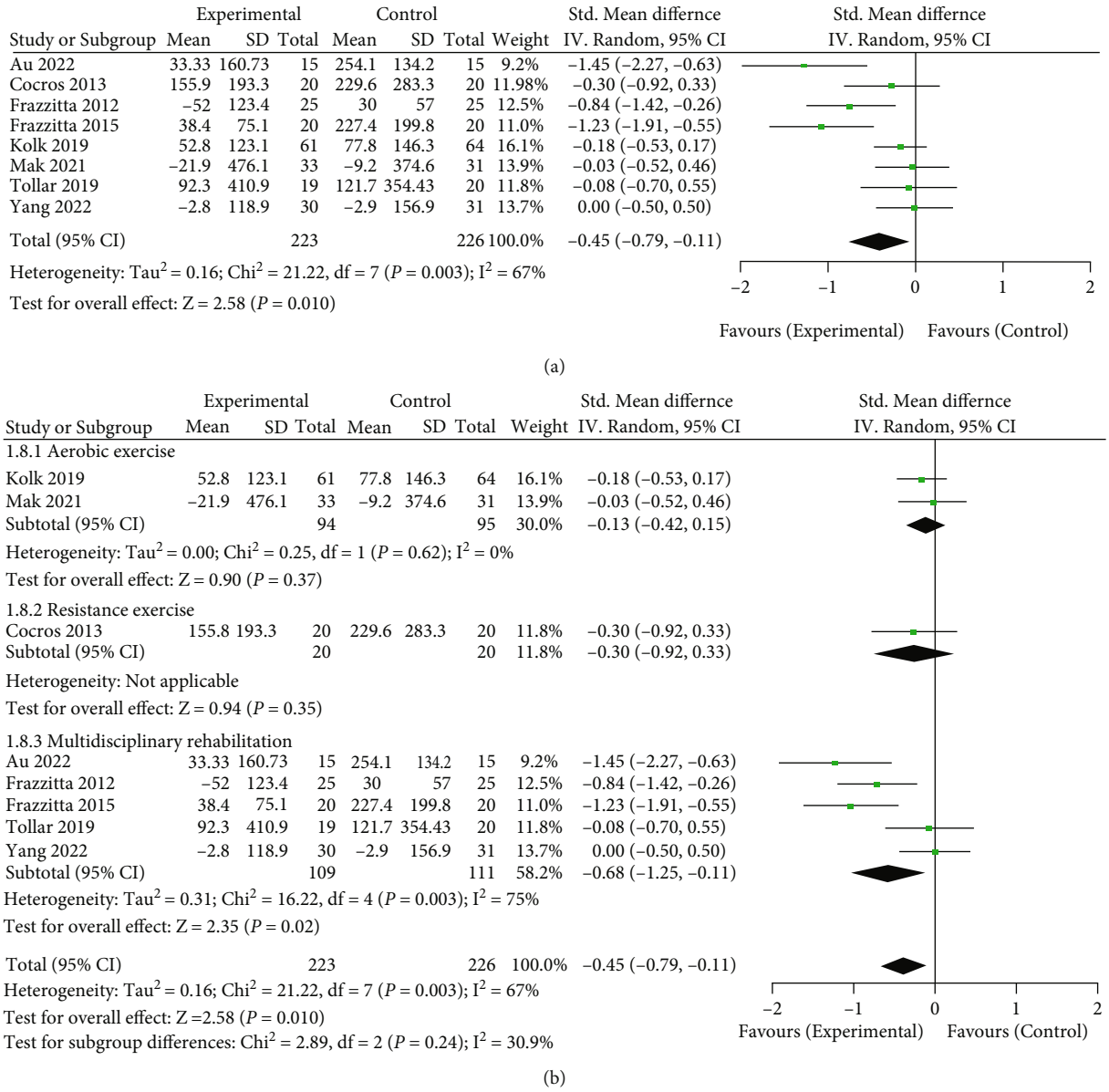


Figure 7: Effect of long-term physical therapy on the dosage (LED) of antiparkinson drugs in patients with Parkinson's disease. (a) Total meta-analysis data and (b) subgroup analysis data by physical therapy type.

had a certain positive significance for improving ADL. In addition, the symptoms of Parkinson's patients also include non-motor symptoms, such as sleep disturbance, mood disorders, and autonomic dysfunction [2], which also widely affect the daily life of patients, and also cause the diversity of reasons for improving patients' daily life. A single change in a patient's motor symptoms was not completely effective in improving the patient's daily living score. The multidisciplinary rehabilitation treatment model has more treatment modes and improves the functional impairment of the patients more widely, which is also the potential reason why the multidisciplinary treatment mode improves the daily life score of Parkinson's patients.

A total of 8 articles were included in the analysis of the impact of long-term physical therapy on the LED dose. Although the research was heterogeneous, the summary analysis results suggested that it was positive and beneficial. However, the subgroup analysis of the five literatures showed that multidisciplinary rehabilitation had a statistically significant impact on ADL, indicating that long-term multidisciplinary rehabilitation based on physical therapy positively affected ADL. The result might suggest that multidisciplinary rehabilitation reduces the drug use of progressive Parkinson's patients.

The study also has limitations. This study mainly focused on a wide range of physical therapy measures and did not focus on a specific treatment type. Therefore, the number of studies of each intervention type was small, so the interpretation of the results of different intervention types was relatively weak. Secondly, low-quality studies and studies with an inaccuracy of medication status or score changes, studies with unknown status, or lack of mean and

standard deviation were excluded to ensure the reliability of research evidence. However, this resulted in a small number of included literatures. In addition, some control groups in the included literature had some short-term physical interventions. Despite the intervention period, the bias caused by these control groups could not be excluded entirely.

The analysis results of this paper showed that physical therapy for at least 6 months or longer for patients with mild to moderate Parkinson's HY could effectively improve the motor symptoms of patients with Parkinson's disease, whether combined with antiparkinson drug therapy or not. Compared with the control group, that is, the short-term intervention group of physical therapy, other types of intervention group, or no treatment group, long-term physical therapy could reduce the LED dose of patients with drug therapy. The results of this study emphasized the importance of persisting in long-term physical therapy, regardless of whether it is in the state of drug treatment, and the necessity of continuous physical therapy from the early and middle stages of the disease [27]. The improvement can boost the confidence of Parkinson's patients and make them pay more attention to and adhere to long-term physical therapy. In addition, reducing drug dose can minimize the risk of exercise complications related to drug dose, thus helping reduce patients' relevant economic burden.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Xiaotian Ji and Danian Lu contributed equally to this work.

Acknowledgments

The study was supported by Sanya people's Hospital, West China (Sanya) Hospital, Sichuan University.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 2986223, 8 pages
https://doi.org/10.1155/2022/2986223

Research Article

Comparison of Needle-Warming Moxibustion and Other Physical Therapies for Lumbar Disc Herniation: A Meta-analysis

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Received 17 June 2022; Revised 13 July 2022; Accepted 16 July 2022; Published 28 July 2022

Academic Editor: Xi Lou

Background. Needle-warming moxibustion (NWM) demonstrates a controversial effect on lumbar disc herniation (LDH). This study is aimed at comparing the efficacy of NWM and conventional acupuncture or other physical therapies on LDH through a meta-analysis. *Methods*. Potentially eligible literatures were retrieved and screened from electronic databases. The subject of the literature was a comparison of NWM and conventional acupuncture or other physical therapies for LDH. The methodological quality was evaluated by the Jadad scale. The chi-square test was used for the heterogeneity test. Subgroup analysis was used to explore the source of heterogeneity. Risk ratio (RR) or mean difference (MD) with 95% confidence interval (CI) was used to describe the effect size. The publication bias was evaluated by Egger's test. *Results*. The effective rate of NWM in the treatment of LDH was significantly higher than that of conventional acupuncture (RR = 1.27, 95%CI [1.18, 1.36], $P < 0.00001$) and lumbar traction (RR = 1.12, 95%CI [1.06, 1.18], $P < 0.0001$) There was no significant difference in the effective rate between NWM and electric acupuncture for LDH (RR = 1.06, 95%CI [0.98, 1.14], $P = 0.17$). VAS of LDH patients treated with NWM was lower than conventional acupuncture (MD = −1.51, 95%CI [−1.70,−1.31], $P < 0.00001$) and lumbar traction (MD = −2.64, 95%CI [−2.79,−2.49], $P < 0.00001$) but statistically insignificant with electric acupuncture (MD = −0.31, 95%CI [−0.72, 0.09], $P = 0.13$). JOA scores of LDH patients treated with NWM were higher than those with conventional acupuncture (MD = 2.24, 95%CI [1.04, 3.45], $P = 0.0003$) and lumbar traction (MD = 10.76, 95% CI [10.45, 11.07], $P < 0.00001$) but statistically insignificant with electric acupuncture (MD = 0.25, 95%CI [−0.95, 1.45], $P = 0.69$). The long-term effective rate of NWM on LDH was higher than that of conventional acupuncture (MD = 3.13, 95%CI[2.12, 4.61], $P < 0.00001$). In this study, no heterogeneity ($P > 0.10$, $I^2 < 50\%$) and publication bias ($P > 0.05$) among the literature were noted. *Conclusion*. The effect of NWM on LDH was superior to traction therapy and conventional acupuncture therapy, but similar to electric acupuncture for LDH. High-quality randomized controlled trials were still needed to confirm the results.

1. Introduction

Lumbar disc herniation (LDH) is a chronic degenerative disease of the lumbar intervertebral disc characterized by rupture of the fibrous ring and protrusion of the internal nucleus pulposus [1]. LDH causes a series of symptoms related to stimulation or compression of the adjacent nerve roots, such as pain, weakness, and numbness in the waist and legs [1, 2]. Bowel dysfunction and paralysis may even occur in severe cases [1, 2]. The incidence of lumbar disc herniation has steadily increased over years [3]. In addition to physical discomforts, LDH could also incur psychological anxiety and depression that has become a serious social health problem [4, 5].

The current treatment for LDH include both surgical and nonsurgical modalities [6–8]. In fact, LDH generally follows a benign natural course and symptoms in most patients can be improved to a certain extent after nonsurgical treatment [9].

Nonoperative treatment included drug application, lumbar traction, manual therapy, epidural injection, massage, acupuncture, moxibustion, and wearing orthopedic braces [10–12]. Both acupuncture and moxibustion have been shown to be effective methods to alleviate lumbar intervertebral disc herniation. The underlying mechanism for the therapeutic efficacy may be related to the fact that the acupuncture or temperature stimulation could induce an analgesic effect by interfering with neurotransmitter transmission and reducing inflammatory reactions through improving the microcirculation of peripheral nerve tissue [13]. Needle-warming moxibustion (NWM) is a combination of acupuncture and moxibustion that has been widely used to treat LDH [10, 12, 14].

However, the efficacy of NWM in the treatment of LDH has been controversial. Some randomized controlled trials (RCT) have confirmed the effectiveness of NWM in treating LDH. For example, Lu et al. [14] observed that NWM can effectively alleviate the pain in patients with LDH and improve lumbar function. However, some studies hold different views. The therapeutic effect of NWM on LDH is similar to that of electric acupuncture [15]. The sample size of individual randomized clinical trials is small, and the level of evidence is low. It is necessary to conduct a meta-analysis to explore the efficacy of NWM on LDH. A previous meta-analysis [16] showed that the therapeutic effect of NWM was better than that of acupuncture. However, this study was limited by small sample size and observation indicators. It had not yet provided positive evidence for the efficacy and safety of NWM in LDH. Moreover, the study was limited to the short-term efficacy and failed to compare the long-term efficacy of the two treatment methods. In recent years, new data on NWM in the treatment of LDH have emerged that provided more references for a relevant systematic evaluation. This study collected the data from RCTs in recent years for meta-analysis to further promote the rational application of NWM in LDH by evaluating its efficacy and safety.

2. Materials and Methods

2.1. Retrieval Strategy. We searched 6 databases, including China biology medicine disc (CBMdisc), China National Knowledge Infrastructure (CNKI), the Cochrane Library, Embase, PubMed, and Web of Science from the establishment of the database to May 25, 2022. There was no restriction on the language of published literature. The search strategy was determined by the combination of search subject words and free words: ("lumbar disc herniation" OR "intervertebral disc herniation") AND ("needle warming moxibustion" OR "warm needle" OR "warming needle moxibustion" OR "needle warming moxibustion").

2.2. Inclusion and Exclusion Criteria. The inclusion criteria were as follows: (1) the subjects were patients with LDH; (2) the control group and experimental group were both included; (3) the experimental group was treated with NWM, whereas the control group was treated with acupuncture or other physical therapy; (4) the observed outcomes included at least one of the following indicators: total effective rate, visual analysis scale (VAS) and Japanese Orthopedic Association (JOA) scores; and (5) the study type was RCT. The exclusion criteria were as follows: (1) retrospective study, (2) case reports or animal experiments, (3) the subjects who received surgical intervention, (4) duplicate publications, and (5) key data which were missing and could not be supplemented.

2.3. Literature Screening, Data Extraction, and Methodological Evaluation. Two researchers conducted literature retrieval independently according to the retrieval strategy. After reading the title and abstract, the literatures were screened, and then the full text was read to determine whether it was eligible for inclusion. The content extracted from the eligible literature mainly included the basic characteristics, such as the year of publication, the author, the country or region, and the demographics of the research subjects, intervention measures, and outcome indicators. The methodological quality of the included RCT was evaluated by two researchers independently according to the Jadad scale that included the generation of random sequence, randomized hiding, blinding method, withdrawal, and dropouts. Disagreements with regard to data extraction and methodological assessment were settled by consultation with a third investigator.

2.4. Statistical Methods. The Revman 5.3 software was used for meta-analysis. The chi-square test was used for the heterogeneity test. The random-effects model and fixed-effects model were used to calculate the combined statistics in the presence ($P < 0.1$ or $I^2 > 50\%$) or absence ($P \geq 0.1$ and $I^2 \leq 50\%$) of interstudy heterogeneity, respectively. Subgroup analysis was used to explore the source of heterogeneity. The categorical and measurement data were expressed by the relative risk ratio (RR) or the mean difference (MD) with 95% confidence interval (CI), respectively. Egger's test was used to evaluate publication bias. Two-way $P < 0.05$ was statistically significant.

3. Results

3.1. Basic Information of Included Documents. According to the search strategy, 1605 articles were collected. According to the screening criteria, 1590 literatures were excluded after reading the title, abstract and full text. Finally, 15 literatures were included in the study [14, 15, 17–29]. The flow chart of literature screening is shown in Figure 1. The 15 publications were all RCTs, of which 14 were published in Chinese and 1 in English. A total of 1381 LDH patients, including 749 in the NWM group and 632 patients in the control group, were included. The basic information of literature and Jadad scores are shown in Table 1.

3.2. Short-Term Effective Rate of NWM Treatment. A total of 15 literatures reported the short-term effective rate of NWM in the treatment of LDH. As shown in Figure 2, no interstudy heterogeneity was noted ($\chi^2 = 6.16, P = 0.63, I^2 = 0\%$). The effective rate of NWM on LDH was higher than that of conventional acupuncture (RR = 1.27, 95%CI $[1.18, 1.36]$, $Z = 6.63, P < 0.00001$). Egger's test showed no publication bias ($P > 0.05$). The treatment for the control group in 4 studies was lumbar traction, and there was no heterogeneity

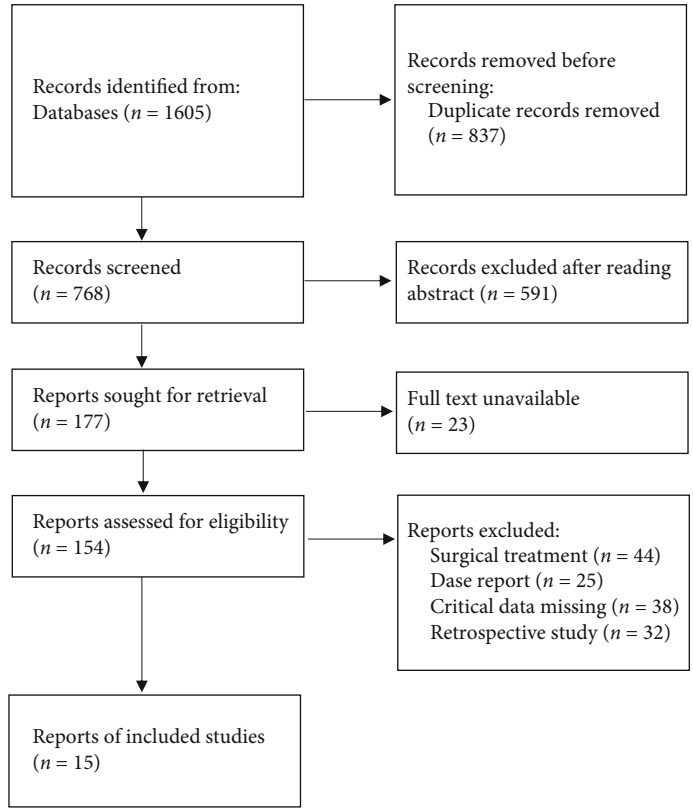

Figure 1: Document screening flow chart.

Table 1: Basic information of included literature and Jadad score.

Author	Year	Study type	Participants		Intervention		Jadad
			Treated	Control	Treated	Control	
Cao [17]	2011	RCT	32	30	NWM	Acupuncture	4
Chen [18]	2017	RCT	35	35	NWM	Acupuncture	6
Duo and Ba [19]	2016	RCT	140	140	NWM	Traction	5
Gao and Liu [20]	2013	RCT	78	70	NWM	Traction	6
He et al. [21]	2007	RCT	39	39	NWM	Acupuncture	6
Huang and Xie [22]	2010	RCT	48	48	NWM	Acupuncture	5
Lin [23]	2020	RCT	40	40	NWM	Acupuncture	4
Liu [24]	2020	RCT	32	32	NWM	Acupuncture	4
Lu et al. [14]	2021	RCT	50	50	NWM	Acupuncture	5
Shen [25]	2019	RCT	38	38	NWM	EA	5
Song et al. [26]	2016	RCT	60	60	NWM	EA	4
Wang [15]	2013	RCT	46	91	NWM	Acupuncture, EA	4
Wu [27]	2020	RCT	43	43	NWM	Traction	5
Zai et al. [28]	2018	RCT	30	30	NWM	Acupuncture	6
Zheng [29]	2018	RCT	45	45	NWM	Traction	4

NWM: needle warming moxibustion; EA: electric acupuncture; RCT: randomized controlled trial.

($\chi^2 = 6.02$, $P = 0.11$, $I^2 = 50\%$). The effective rate of NWM in the treatment of LDH was higher than that of lumbar traction (RR = 1.12, 95%CI [1.06, 1.18], $Z = 4.08$, $P < 0.0001$). Egger's test showed no publication bias ($P > 0.05$). Similarly, no heterogeneity was noted among the 3 literatures that included electric acupuncture for the control group ($\chi^2 = 3.14$, $P = 0.21$, $I^2 = 36\%$). There was no significant difference between NWM and electric acupuncture in the effective rate of LDH (RR = 1.06, 95%CI [0.98, 1.14], $Z = 1.38$, $P = 0.17$). Egger's test showed no publication bias ($P > 0.05$).

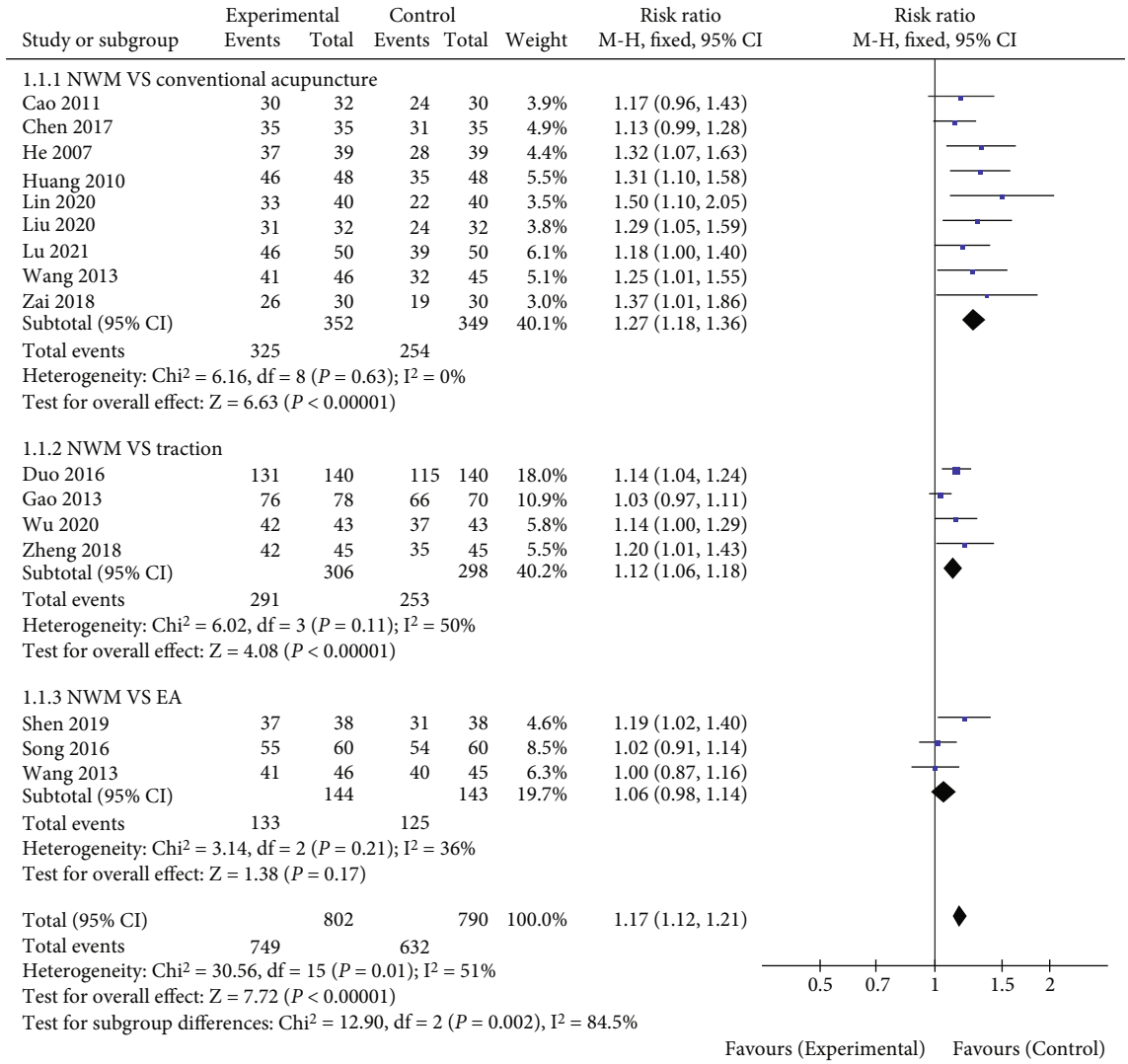

Figure 2: Comparison of short-term effective rate between NWM group and control group. NWM: needle-warming moxibustion; EA: electric acupuncture.

3.3. Effect of NWM Treatment on the VAS Score. A total of 8 articles reported the effect of NWM on the VAS scores in LDH patients. As shown in Figure 3, the treatment method of the control group in the 4 literatures was routine acupuncture, and there was no interstudy heterogeneity ($\chi^2 = 5.98$, $P = 0.12$, $I^2 = 49\%$). VAS of LDH patients treated with NWM was significantly lower than that of conventional acupuncture (MD = −1.51, 95%CI [−1.70,−1.31], $Z = 15.20$, $P < 0.00001$). The treatment method of the control group in the 2 literatures was lumbar traction, and there was no heterogeneity among the literature ($\chi^2 = 0.37$, $P = 0.55$, $I^2 = 0\%$). VAS of LDH patients treated with NWM was lower than that of lumbar traction (MD = −2.64, 95%CI [−2.79,−2.49], $Z = 34.68$, $P < 0.00001$). The treatment method of the control group in the 3 literatures was electric acupuncture, and there was no heterogeneity ($\chi^2 = 1.31$, $P = 0.52$, $I^2 = 0\%$). There was no significant difference in VAS between LDH patients treated with NWM and electric acupuncture (MD = −0.31, 95%CI [−0.72, 0.09], $Z = 1.50$, $P = 0.13$). Egger's test showed no publication bias for all analyses ($P > 0.05$).

3.4. Impact of NWM Treatment on Recent JOA Scores. A total of 7 articles reported the effect of NWM on recent JOA scores in LDH patients. As shown in Figure 4, the treatment method of the control group was routine acupuncture in 3 studies, lumbar traction in 2 studies, and electric acupuncture in another 2 studies. No interstudy heterogeneity was noted for the studies involving routine acupuncture ($\chi^2 = 3.57$, $P = 0.17$, $I^2 = 44\%$), lumbar traction ($\chi^2 = 1.43$, $P = 0.23$, $I^2 = 30\%$), and electric acupuncture ($\chi^2 = 0.66$, $P = 0.42$, $I^2 = 0\%$). JOA score of LDH patients treated with NWM was higher than that of conventional acupuncture (MD = 2.24, 95%CI [1.04, 3.45], $Z = 3.65$, $P = 0.0003$) and lumbar traction (MD = 10.76, 95%CI [10.45, 11.07], $Z = 68.35$, $P < 0.00001$) but statistically insignificant with electric acupuncture (MD = 0.25, 95%CI [−0.95, 1.45], $Z = 0.41$,

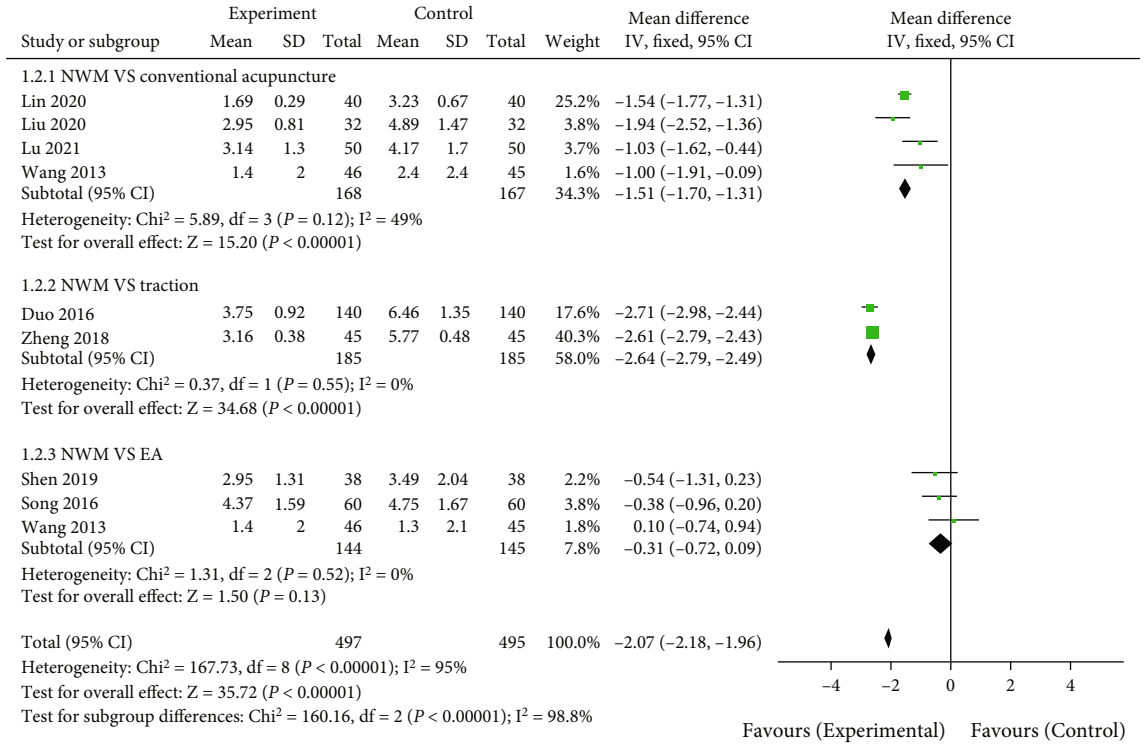

Figure 3: Comparison of recent vas between NWM group and control group. NWM: needle warming moxibustion; EA: electric acupuncture.

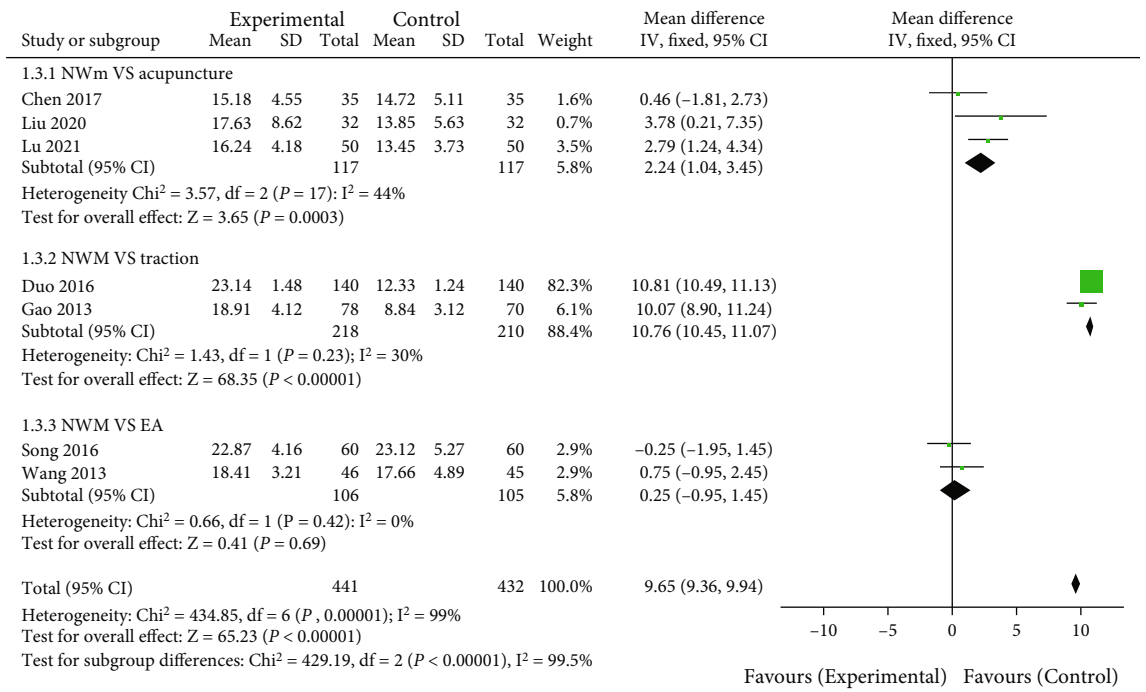

Figure 4: Comparison of JOA scores between NWM group and control group in recent treatment. NWM: needle warming moxibustion; EA: electric acupuncture.

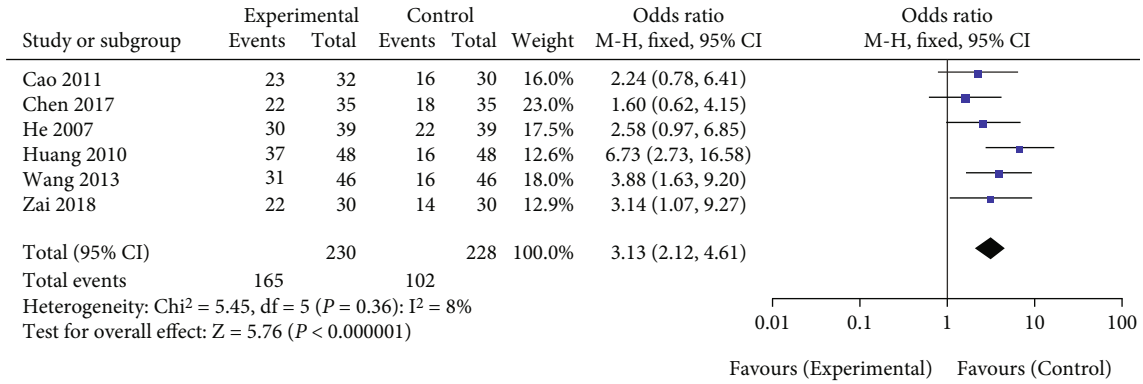

Figure 5: Comparison of long-term effective rate between NWM and acupuncture. NWM: needle-warming moxibustion.

$P = 0.69$). Egger's test all showed no publication biases ($P > 0.05$).

3.5. Comparison of Long-Term Effective Rate between NWM and Conventional Acupuncture. The patients were followed up in 6 literatures, and the long-term effective rate was obtained. There was no heterogeneity among the studies ($\chi^2 = 5.45, P = 0.36, I^2 = 8\%$). The long-term effective rate of NWM for LDH was higher than that of conventional acupuncture (MD $= 3.13, 95\%\text{CI}\,[2.12, 4.61], Z = 5.76$, $P < 0.00001$), as shown in Figure 5. Egger's test showed no publication bias ($P > 0.05$).

4. Discussion

LDH is a common and frequently encountered condition in the clinic. With the acceleration of global aging process and the rapid lifestyle, the incidence of LDH is gradually increasing. It has become a global health problem that cannot be ignored. NWM can relieve the inflammatory reaction by acupuncture combined with thermal stimulation.

We summarized the data from 15 literatures, including a total of 1381 patients with 749 treated with NWM and 632 with other physical therapy. The meta-analysis results showed that NWM was superior to conventional therapy and traction therapy in terms of the effective rate, VAS score, and JOA score. However, the therapeutic effects of NWM and electric acupuncture are similar. NWM and conventional acupuncture still have advantages in terms of long-term effective rate.

In addition to improving the treatment efficacy and relieving pain, some studies have also confirmed the efficacy of NWM in reducing inflammatory factors and improving lumbar function. Lu et al. [14] showed that serum levels of interleukin-6 and tumour necrosis factor α in LDH patients treated with NWM were significantly lower than those treated with routine acupuncture. The Oswestry disability index of the NWM treatment group was lower than that of the conventional acupuncture treatment group. NWM might alleviate patients' pain by reducing the level of inflammatory factors. Zai et al. [28] confirmed by enzyme-linked immunosorbent assay that the serum level of β-endorphin in LDH patients treated with NWM was significantly lower than that in the conventional acupuncture group. They also confirmed that NWM had shown a therapeutic advantage in the early stages of treatment. With additional course of treatment, the therapeutic effect of NWM became more significant than that of conventional acupuncture. NWM and conventional acupuncture treatment did not cause adverse events. Zheng [29] showed that compared with lumbar traction, NWM treatment could reduce the Oswestry disability index in patients with LDH. Wu [27] demonstrated that NWM treatment could reduce the level of inflammatory factors, including interleukin-6 and tumour necrosis factor- α, as compared with traction treatment. NWM treatment is also advantageous in improving patients' quality of life. Lin [23] confirmed that compared with conventional acupuncture treatment, NWM treatment could reduce length of hospitalizations and improve the activity of the lumbar spine. Liu [24] noted that NWM could reduce serum interleukin-6 and the level of peripheral blood neutrophils as compared with conventional acupuncture treatment.

There was no significant difference between NWM and electric acupuncture with regard to treatment efficiency, VAS, and JOA scores in our study. The therapeutic effects of NWM and electric acupuncture on LDH were similar. Song et al. [26] considered that after the first treatment, the VAS of the NWM group was lower than that of the electric acupuncture group. However, there was no significant difference regarding the VAS score after long-term treatment between the NWM and electric acupuncture groups. After one course of treatment, there was no significant difference in VAS, JOA and effective rate between the 2 groups. Song et al. [26] found that the NWM and the electric acupuncture groups were similar in terms of disease recurrence after 1 month follow-up. Nonetheless, the NWM group often presented with an immediate effect and favorable short-term effect. Wang [15] compared the efficacy of conventional acupuncture, electric acupuncture, and NWM on LDH. The three acupuncture methods could reduce the pain of LDH patients and improve lumbar function. The therapeutic effect of NWM was similar to that of electric acupuncture, both of which were superior to that of conventional acupuncture. Shen [25] pointed out that the effective rate of electric acupuncture on LDH was lower than that of NWM. However, electric acupuncture and NWM have similar effects on pain relief.

This study suffers from several limitations. First, the quality of the included literature is low, which may have a certain impact on the results. Second, in terms of long-term efficacy, the effective rate of NWM is higher than that of conventional acupuncture. Due to the limitation of included literature, we cannot compare the efficacy of NWM, traction therapy, and electric acupuncture. Third, the observation indicators in our study are not comprehensive. More indicators, such as Oswestry disability index, straight leg elevation test, and serum inflammatory cytokine levels, are entailed to evaluate the efficacy. Fourth, we did not perform subgroup analysis by stratifying patients into subgroups according to patient age and sex, thus omitting important and clinically relevant conclusions.

In conclusion, the therapeutic effect of NWM on LDH is superior to traction therapy and conventional acupuncture. However, the efficacy of NWM is similar to electric acupuncture for LDH. High-quality RCTs are still needed to confirm the conclusion.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Juan Wang and Chongnan Liang contributed equally to this work.

Acknowledgments

The study was supported by Hainan Provincial Medical and Health Research Project (No. 20A200307).

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 1248577, 9 pages
https://doi.org/10.1155/2022/1248577

Research Article

Efficacy of Low Molecular Weight Heparin in Preventing Perinatal Venous Thrombosis: A Meta-Analysis

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Received 13 June 2022; Revised 5 July 2022; Accepted 14 July 2022; Published 26 July 2022

Academic Editor: Xi Lou

Background. There have been controversies about the preventive effect of low molecular weight heparin (LMWH) on venous thrombosis (VT) in the perinatal period. This study is aimed at exploring the effectiveness of LMWH in preventing perinatal VT through meta-analysis. *Methods*. Databases such as CNKI, China Biology Medicine disc (CBMdisc), Wanfang, PubMed, MEDLINE, Embase, and Central were searched. Inclusion criteria were as follows: (1) subjects: women at high risk of perinatal VT; (2) experimental group and control group; (3) intervention measures: the experimental group was given LMWH, while the control group was given placebo or standard heparin or physical therapy; (4) outcomes: perinatal VT events or bleeding events; and (5) randomized controlled trials (RCTs). Jadad scale was used to evaluate the literature quality. The Mantel-Haenszel method was used to calculate the odds ratio (OR) and 95% confidence interval (CI). The chi-square test was used to analyze the heterogeneity of the included literature. Subgroup analysis was used to explore the source of heterogeneity. Publication bias was evaluated via funnel plot and Egger test. *Results*. The incidence of perinatal VT in the LMWH group was lower than that in the control group (OR = 0.16, 95% CI (0.08, 0.32), $P < 0.00001$). There was no heterogeneity among literatures ($P = 0.77$, $I^2 = 0\%$) and no publication bias. The incidence of postpartum VT in the LMWH group was lower than that in the control group (OR = 0.14, 95% CI (0.07, 0.30), $P < 0.00001$). There was no heterogeneity among literatures ($P = 0.69$, $I^2 = 0\%$) and no publication bias. The incidence of perinatal bleeding in the LMWH group was higher than in the control group (OR = 1.72, 95% CI (1.06, 2.77), $P = 0.03$). There was no heterogeneity among literatures ($P = 0.25$, $I^2 = 26\%$) and no publication bias. *Conclusion*. LMWH can reduce the incidence of perinatal VT in high-risk women but increase the risk of bleeding. The use of LMWH to prevent perinatal VT should be closely monitored.

1. Introduction

Perinatal venous thromboembolism (VT) is the leading cause of maternal death in developed countries [1–3]. The increase in gestational weeks increases the risk of VT [4, 5], and the peak period of VT occurs within 6 weeks after delivery [6]. However, the pathogenesis of VT is not clear. VT is a disease caused by multiple factors [7–9], which may be related to specific gene expression [10, 11]. In addition, pregnancy itself is a high-risk factor for VT [3–5, 12]. Changes in estrogen and progesterone levels during pregnancy lead to vasodilatation of lower limb veins [3, 5]. The enlarged uterus oppresses the pelvic vein and causes blood stasis [4, 5]. Coagulation factors are activated during pregnancy, and the serum level is significantly increased [5]. A series of physiological changes significantly increased the risk of perinatal VT. Besides, the perinatal period is often associated with many other clinical risk factors, such as obesity, braking, history of VT, and cesarean section. When multiple risk factors are superimposed, pregnant women need closer monitoring and timely preventive measures [3].

The anticoagulation effect of low molecular weight heparin (LMWH) is better than that of unfractionated heparin by reducing the risk of bleeding [13–15]. Compared with unfractionated heparin, complications such as osteoporosis and thrombocytopenia are rarer in patients using LMWH

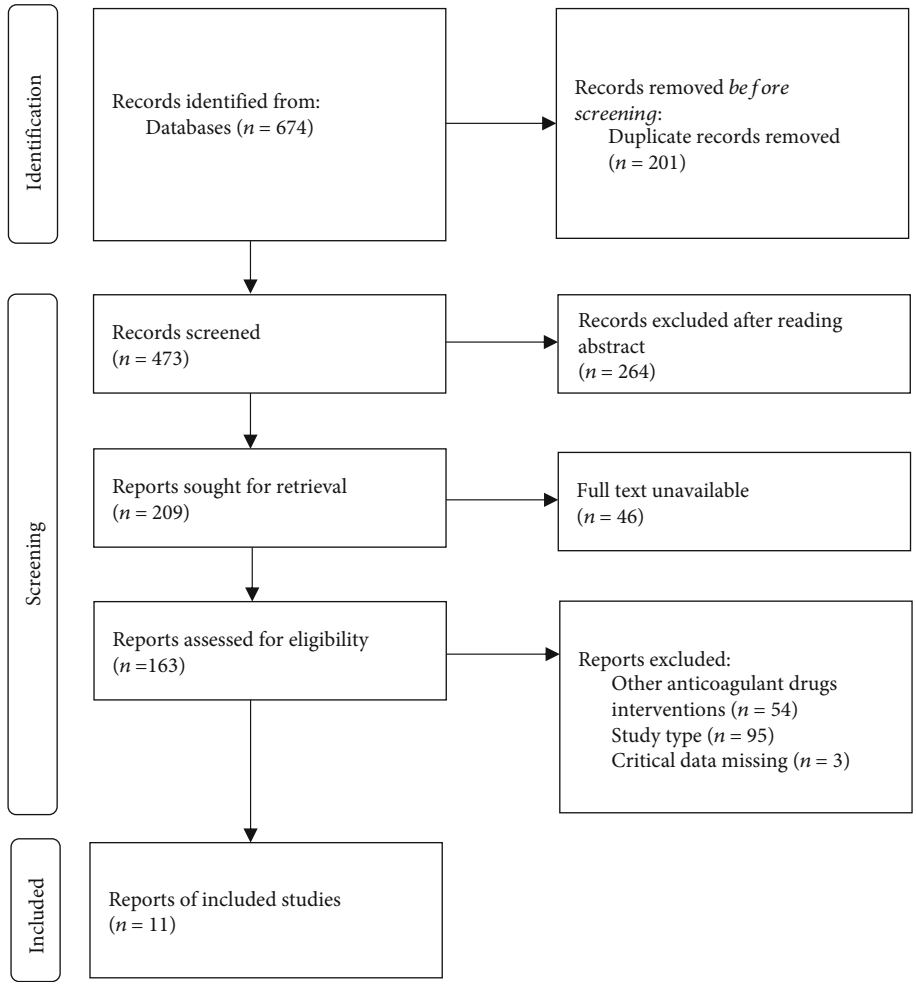

Figure 1: Document screening flow chart.

[15, 16]. Therefore, LMWH is easy to use, with high bioavailability, a long half-life, stable pharmacokinetics, and no need for frequent monitoring [17, 18].

Previous studies have been controversial about the preventive effect of LMWH on perinatal VT. Studies [19] have pointed out that LMWH cannot reduce the incidence of perinatal VT events and may increase the risk of bleeding. Other studies [20] held different views. LMWH could effectively prevent VT events in high-risk pregnant women after cesarean section and reduce fibrinogen levels [20]. Therefore, we conducted a meta-analysis to explore the preventive effect of LMWH on perinatal VT.

2. Materials and Methods

2.1. Literature Search. We searched in CNKI, China Biology Medicine disc (CBMdisc), Wanfang, PubMed, Medline, Embase, Central, and other databases. The search terms included low molecular weight heparin, enoxaparin, nadroparin, dalteparin, tinzaparin, pregnancy, perinatal stage, postpartum, venous thrombosis, thrombogenesis, and thromboembolism. The deadline for the literature search was June 1, 2022. No document language was limited.

2.2. Literature Screening. Inclusion criteria were as follows: (1) subjects: perinatal VT high-risk women. Pregnant women with one or more of the following risk factors are considered to be a population with high risk of perinatal VT: history of thromboembolism, gestational hypertension, diabetes, advanced age, obesity, multiple births, or smoking; (2) the experimental group and the control group were set up; (3) intervention measures: the experimental group was given LMWH to prevent perinatal VT, and the control group was given placebo or unfractionated heparin or physical therapy to prevent perinatal VT; (4) outcomes: including perinatal VT events or bleeding events; and (5) randomized controlled trials (RCTs).

Exclusion criteria were as follows: (1) repeated reports, (2) animal experiments, (3) the subjects received other anticoagulant drugs, (4) observational studies, and (5) the key data in the literature were missing and could not be supplemented.

2.3. Data Extraction and Literature Quality Evaluation. Researchers read the full text and extracted the data. The extracted contents included the number of cases, basic diseases, mode of delivery, intervention measures, drug types,

Table 1: Basic characteristics and Jadad score of included literature.

Author	Year	No. of patients		Study type	Intervention		Outcomes	Jadad
		LMWH	Control		LMWH	Control		
Badawy et al. [21]	2008	170	170	RCT	Enoxaparin sodium (0.2 ml, once daily) + folic acid tablets (0.5 mg daily)	Folic acid tablets (0.5 mg daily)	Hemorrhage	6
Bi [22]	2017	45	45	RCT	LMWH sodium (twice daily) + PT	PT	Postpartum VT	4
Burrows et al. [23]	2001	39	37	RCT	Dalteparin (2,500 IU, once daily)	Normal sodium	Postpartum VT; hemorrhage	6
Gates et al. [24]	2004	78	79	RCT	Enoxaparin (40 mg, once daily)	Placebo (1 ml, once daily)	Perinatal VT; hemorrhage	7
Huang [20]	2018	31	31	RCT	LMWH sodium (200 U/kg, once daily) + PT	PT	Perinatal VT	4
Li et al. [25]	2018	51	51	RCT	Enoxaparin (40 mg, once daily) + obstetrical care	Obstetrical care	Postpartum VT	3
Lin et al. [26]	2021	58	58	RCT	LMWH sodium (5000 U/kg, once daily)	Conventional therapy	Postpartum VT	4
Liu [27]	2020	32	32	RCT	LMWH sodium (4250 U/kg, twice daily) + PT	PT	Postpartum VT	3
Pettilä et al. [28]	1999	50	50	RCT	Dalteparin once daily (mean 4631 IU/day)	Unfractionated heparin twice daily (20569 IU/day)	Perinatal VT; hemorrhage	5
Rodger et al. [19]	2014	146	143	RCT	Dalteparin: 5000 IU once daily + obstetrical care	Obstetrical care	Perinatal VT; hemorrhage	6
Zhang [29]	2013	58	58	RCT	LMWH sodium (5000 U/kg, twice daily)	Conventional therapy	Postpartum VT	4

Note: LMWH: low molecular weight heparin; RCT: randomized controlled trial; PT: physical therapy; VT: venous thrombosis.

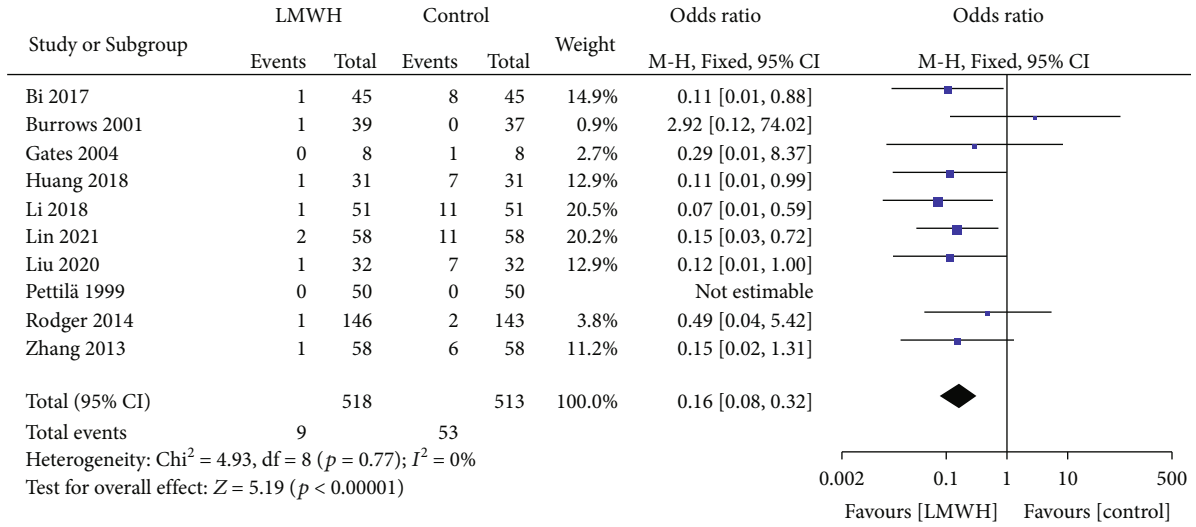

Figure 2: Forest map: comparison of perinatal VT incidence between the LMWH group and control group. LMWH: low molecular weight; VT: venous thrombus embolism.

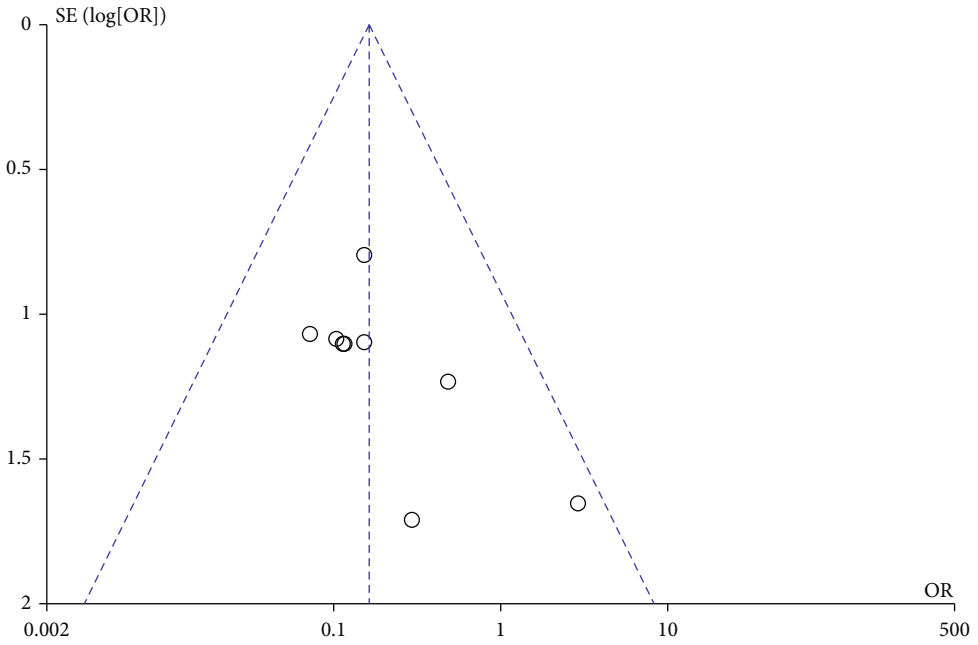

Figure 3: Funnel chart: comparison of perinatal VT incidence between the LMWH group and control group. OR: odds ratio.

drug doses, the incidence of VT, and bleeding events. The Jadad scale was used to evaluate the quality of literature, including the generation of random groups, randomized hidden blind method, implementation of a blind method, loss of follow-up, and withdrawal. Two researchers carried out the above work independently and made crosscomparison after completing the work. If there were differences, the two authors discussed and reached an agreement.

2.4. Statistical Analysis. The results of the included studies were meta-analyzed using the Cochrane software RevMan5.3. Odds ratio (OR) and 95% confidence interval (CI) were used as effect quantities. OR and 95% CI were calculated using the Mantel-Haenszel statistical method. The chi-square test was used to analyze the heterogeneity of the included literature. $I^2 < 50\%$ and $P > 0.10$ indicated no heterogeneity among the literature, and the fixed effect model was used. $I^2 \geq 50\%$ or $P \leq 0.10$ indicated heterogeneity among the literature. Subgroup analysis was used to explore the source of heterogeneity. If it was impossible to clarify the heterogeneity source and eliminate it, the literature results were combined or summarized using the random effect

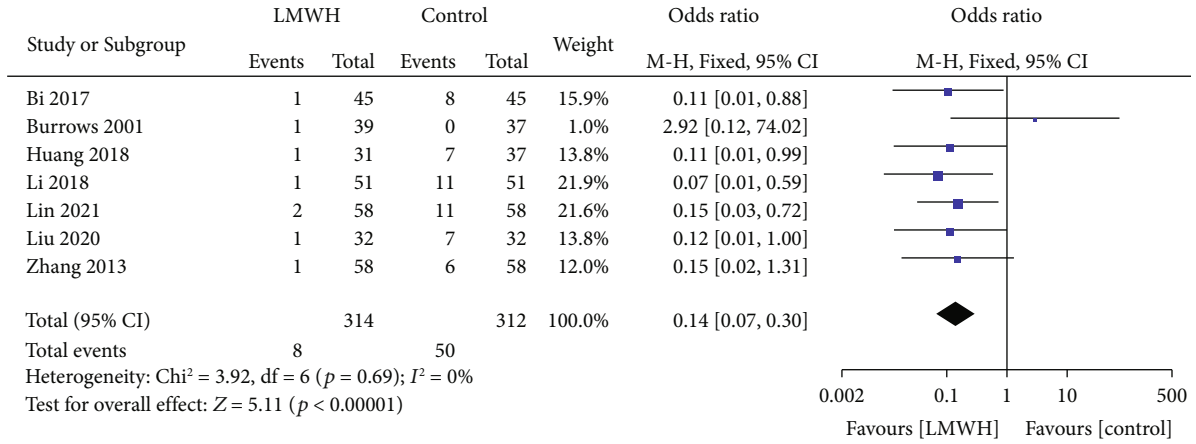

Figure 4: Forest map: comparison of the incidence of postpartum VT between the LMWH group and control group. LMWH: low molecular weight; VT: venous thrombus embolism.

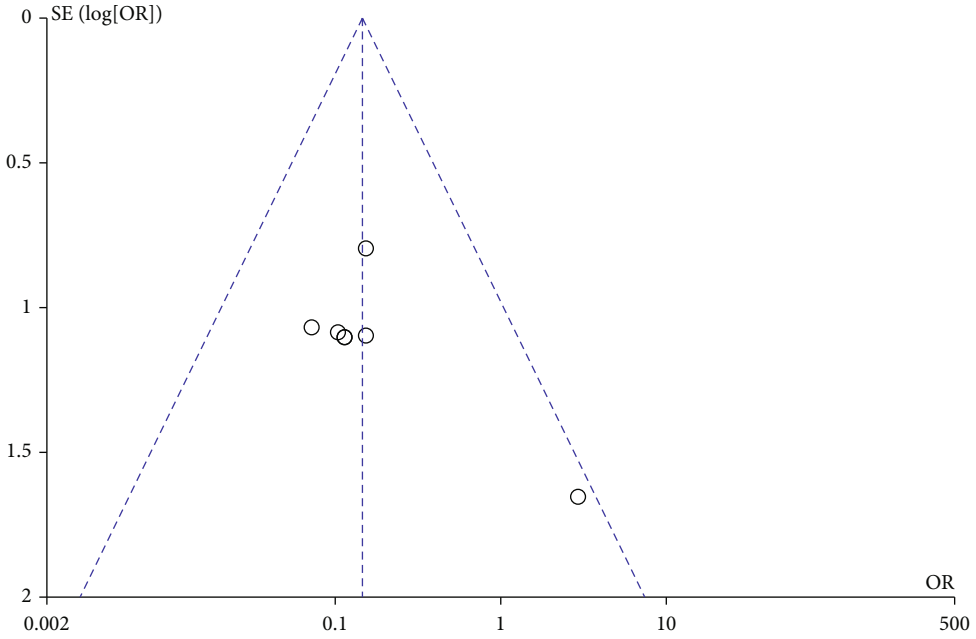

Figure 5: Funnel chart: comparison of the incidence of postpartum VT between the LMWH group and control group. OR: odds ratio.

model. A funnel test was used to evaluate publication bias. Two-way $P < 0.05$ meant statistically significant.

3. Results

3.1. Literature Screening. A total of 674 literatures were retrieved. According to the inclusion and exclusion criteria, 663 literature were excluded, and 11 literature were included in this meta-analysis [19–29]. This study included 1512 high-risk women with perinatal VT, with 758 cases in the LMWH group and 754 cases in the control group. The flow chart of literature screening is shown in Figure 1. The literature characteristics and quality evaluation are shown in Table 1.

3.2. LMWH and the Incidence of Perinatal VT. 10 studies involved the efficacy of LMWH in preventing perinatal VT. There was no heterogeneity among the literature ($chi^2 = 4.93$, $P = 0.77$, $I^2 = 0\%$), and the fixed-effect model was used. The incidence of perinatal VT in the LMWH group was lower than that in the control group (OR = 0.16, 95% CI (0.08, 0.32), $Z = 5.19$, $P < 0.00001$), as shown in Figure 2. The funnel chart showed that the scatter points were distributed within the confidence interval, which was roughly symmetrical, and there was no publication bias, as shown in Figure 3.

3.3. LMWH and the Incidence of Postpartum VT. A total of 7 studies involved the efficacy of LMWH in preventing postpartum VT. There was no heterogeneity among the

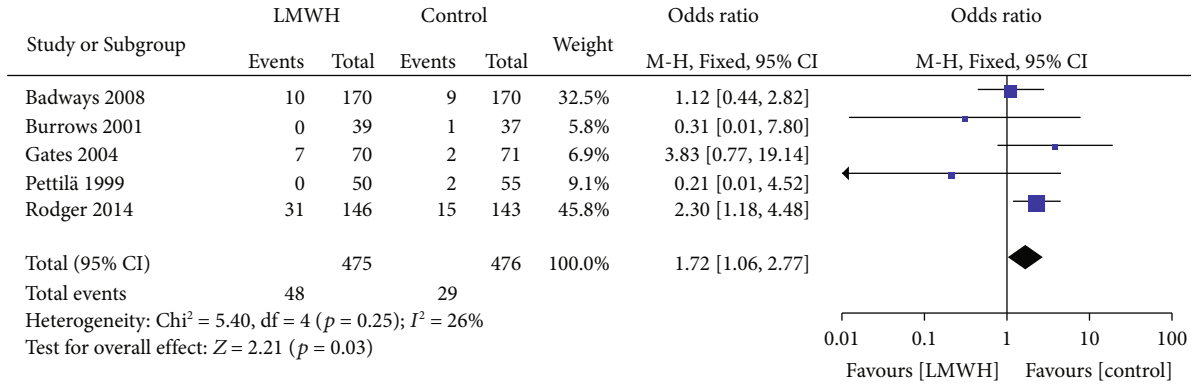

Figure 6: Forest map: comparison of perinatal bleeding rate between the LMWH group and control group. LMWH: low molecular weight; VT: venous thrombus embolism.

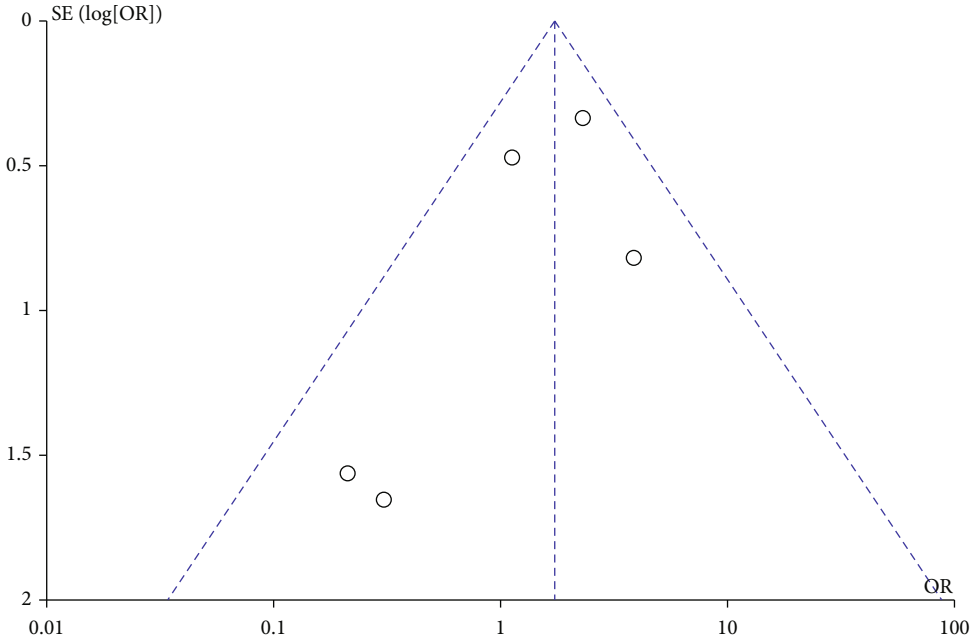

Figure 7: Funnel chart: comparison of perinatal bleeding rate between the LMWH group and control group. OR: odds ratio.

literature ($chi^2 = 3.92$, $P = 0.69$, $I^2 = 0\%$), and the fixed-effect model was used. The incidence of postpartum VT in the LMWH group was lower than that in the control group (OR = 0.14, 95% CI (0.07, 0.30), $Z = 5.11$, $P < 0.00001$), as shown in Figure 4. The funnel chart shows that the scatter points were distributed within the confidence interval, which was roughly symmetrical, and there was no publication bias, as shown in Figure 5.

3.4. LMWH and the Incidence of Perinatal Hemorrhage. A total of 5 studies involved the effect of LMWH on the incidence of perinatal hemorrhage. There was no heterogeneity among the literature ($chi^2 = 5.40$, $P = 0.25$, $I^2 = 26\%$), and the fixed-effect model was used. The incidence of perinatal hemorrhage in the LMWH group was higher than that in the control group (OR = 1.72, 95% CI (1.06, 2.77), $Z = 2.21$, $P = 0.03$), as shown in Figure 6. The funnel chart showed that the scatter points were distributed within the confidence interval, which was roughly symmetrical, and there was no publication bias, as shown in Figure 7.

4. Discussion

Rodger et al. [19] showed that the use of LMWH failed to reduce the incidence of venous thrombosis and abortion. There was no difference in the incidence of major bleeding events between the LMWH group and the control group, but minor bleeding events were more common in the LMWH group. Badawy et al. [21] have shown that LMWH can reduce the incidence of early abortion and late abortion. There was no significant difference between the LMWH group and control group in pregnancy mode, amount of

bleeding during production, and incidence of placental abruption. Their study also pointed out that the average weight of newborns in the LMWH group was higher than that in the control group. They showed that continuous use of LMWH during pregnancy is safe and can reduce the incidence of spontaneous abortion. Burrows et al. [23] conducted a multicenter prospective trial in a pilot study. In this study, patients in the control group were more likely to receive general anesthesia. In addition, the baseline data were balanced. Their results showed that the efficacy of LMWH and the control group in preventing the incidence of VT after a cesarean section was similar. They also pointed out that multicenter RCTs were feasible. Gates et al. [24] showed no difference in the incidence of thromboembolic events and bleeding events between the two groups. Pettilä et al. [28] showed no VT event in the control and LMWH groups. There was no significant difference between the two groups in the incidence of other complications, including osteoporotic fractures, massive bleeding, blood transfusion, spontaneous abortion, and cesarean section. The incidence of minor bleeding events in the LMWH group was lower than in the control group. Pettilä et al. displayed that LMWH has good safety and can be used for VT event prevention. Zhang [29] showed that the possibility of bleeding caused by low molecular weight heparins is lower than that of unfractionated heparin, and the anticoagulation effect is better. LMWH is easy to use, with high bioavailability and fewer adverse reactions. Their results showed that routine subcutaneous injection of low molecular weight heparin sodium after cesarean section in high-risk pregnant women with VT could effectively prevent the occurrence of venous thrombosis in lower limbs. Huang [20] considered that the incidence of deep venous thrombosis of lower limbs in the LMWH group was 3.23%, and that in the control group was 22.58%. There was a significant difference between the two groups. There was no significant difference in platelet count, prothrombin time, and activated partial thrombin time between the LMWH group and control group. The fibrinogen level in the LMWH group was lower than that in the control group. LMWH could effectively prevent VT events in high-risk pregnant women after cesarean section and shorten the rehabilitation time. Bi [22] showed that the incidence of lower limb VT was 17.18% in the control group and 2.22% in the LMWH group. LMWH has a very superior preventive effect on lower extremity deep venous thrombosis in high-risk pregnant women after cesarean section. Liu [27] conducted RCTs to explore the preventive effect of LMWH combined with physical therapy on thrombotic diseases in high-risk pregnant women after cesarean section. The incidence of lower limb VT in the experimental group was lower than that in the control group. The fibrinogen level in the experimental group was lower than that in the control group. Li et al. [25] showed no VT event in the LMWH group. In comparison, 11 patients (21.57%) had deep venous thrombosis in the control group. Therefore, LMWH reduces VT risk. 6 days after cesarean section, the levels of D-dimer and fibrinogen in the LMWH group were significantly lower than those in the control group. They indicated that LMWH has the advantages of no drug monitoring, a long half-life, and no adverse reactions such as bleeding, easy absorption, and moderate price and can effectively prevent the occurrence of deep venous thrombosis after cesarean section. Lin et al. [26] showed that LMWH can improve blood coagulation and hemorheology of high-risk pregnant women after cesarean section, reduce lower limb pain and swelling, restore skin color, and reduce the incidence of lower limb deep venous thrombosis without noticeable adverse reactions.

As can be seen from the above review, the results of our included studies are not completely consistent. In our analysis, there may be some reasons as follows. Firstly, the sample size of the single study is small, which may lead to sample selection bias. Secondly, differences in dose and regimen may influence the results. Finally, the level of local care may influence the perinatal complication rate. We resolved these controversies through meta-analysis. Our meta-analysis showed that LMWH could reduce the incidence of perinatal and postpartum VT and increase the incidence of perinatal hemorrhage in women at high risk of VT.

In addition to preventing VT, some meta-analyses confirmed the efficacy of LMWH in other perinatal diseases. Jiang et al. [30] figured out that LMWH can effectively treat unexplained recurrent abortion. Sirico et al. [31] showed that LMWH does not increase the risk of bleeding and the incidence of blood transfusion during pregnancy. The result was not consistent with ours. This study did not select pregnant women at high risk of VT, but all pregnant women, as subject. Cohort study, case control study, and randomized controlled study were included in this study. This may result in low credibility of the conclusions. Roberge et al. [32] displayed that the combination of LMWH and aspirin can significantly reduce the incidence of preeclampsia and preterm birth.

In conclusion, LMWH can reduce the incidence of perinatal VT in women with high-risk VT but increase the risk of bleeding. When using LMWH to prevent perinatal VT, maternal should be closely monitored.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Yan Huang and Fei Li contributed equally to this work.

Acknowledgments

This project was supported by the Hainan Province Clinical Medical Center.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 7981472, 9 pages
https://doi.org/10.1155/2022/7981472

Research Article

Clinical Diagnosis, Treatment, and Laboratory Detection of 50 Cases of Pulmonary Cryptococcosis

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Received 27 May 2022; Revised 26 June 2022; Accepted 8 July 2022; Published 25 July 2022

Academic Editor: Xi Lou

Objective. This study retrospectively analyzed the clinical diagnosis, treatment process, and laboratory test data of patients with pulmonary cryptococcosis to improve the understanding and diagnosis and treatment ability of the disease. *Methods*. Patients with pulmonary cryptococcosis diagnosed in the First Affiliated Hospital of Dalian Medical University from October 2003 to July 2021 were selected, and their medical records were consulted. The general data, clinical manifestations, laboratory examinations, imaging characteristics, diagnosis, and treatment methods were studied. The software SPSS 22 was used for statistical analysis. *Results*. A total of 50 patients with pulmonary cryptococcosis were included in the study. The ratio of male to female was 1 : 1. The average age was 53.56 ± 11.99 years with a range of 27-82 years. Grouping the patients by age, with 10 years as an age group, we found that 40-60 years was the high-incidence age group. Two patients (4%) had a history of bird contact, and 18 patients (36%) had at least one underlying conditions. Hypertension and cough were the most common underlying condition and clinical manifestation, respectively. The main admission diagnoses were lung shadow (19/50, 38%) and chest/lung mass (15/50, 30%). In the imaging findings, the most common type of lesions was nodule/nodule shadow (29/69, 42.03%). Lesion distribution in the lower lobe, single lobe, and right lung was more frequent than that in the upper lobe, multilobes, and left lung, respectively. Burr sign (12/43, 27.91%) was the most common concomitant sign. Pulmonary ventilatory defect was found in 7 cases. Laboratory test results were largely nonspecific. The pathological examination showed granuloma, with 47 cases (94%) confirmed by postoperative biopsy. Two cases (4%) were confirmed by serology. One case (2%) was diagnosed with *Cryptococcus* smear. 43 cases (86%) were treated with simple surgical resection, 6 cases (12%) were treated with antifungal drugs, and 1 case (2%) was transferred to another hospital for suspicion of pulmonary tuberculosis. *Conclusions*. Pulmonary cryptococcosis is more common in the middle-aged and elderly, and the clinical specificity is low. It can occur in people with normal or impaired immune function. The main clinical and imaging manifestation is cough and pulmonary nodules, which are very easy 5to be misdiagnosed. Surgical resection is the primary treatment.

1. Introduction

Cryptococcus is a genus of basidiomycetous fungi ubiquitously distributed in the environment. Although *Cryptococcus* has more than 30 species, only the *Cryptococcus neoformans* and *Cryptococcus gattii* are related to human diseases [1]. In China, cryptococcal infection is mainly caused by *Cryptococcus neoformans* [2]. This organism is typically found in soil and bird excreta, especially pigeon feces [3]. *Cryptococcus* can infect practically all organ systems, the most common of which are the central nervous system and the respiratory system with resultant cryptococcal meningitis and pulmonary cryptococcosis

[4, 5]. The clinical manifestations of pulmonary cryptococcosis are subtle and nonspecific that renders early diagnosis difficult [6].

Pulmonary cryptococcosis is a type of respiratory mycosis caused by inhalation of *Cryptococcus* spores that can be acute, subacute, or chronic in disease presentation [7]. It has been considered that pulmonary cryptococcosis developed only in HIV-positive people with immune deficiency [8]. Nonetheless, studies reported increasing cases involving patients with normal immune function. According to a retrospective study in China, pulmonary cryptococcosis accounts for 60% of HIV-negative patients with normal immune function [9]. Patients with pulmonary cryptococcosis with different immune states have certain differences regarding clinical manifestations, laboratory test results, and imaging features [10–12]. *Cryptococcus* capsular antigen detection and pathological examination are the main methods for diagnosis, and surgical resection and antifungal medications are usually offered for treatment.

We retrospectively analyzed the clinical data of 50 patients with pulmonary cryptococcosis from the First Affiliated Hospital of Dalian Medical University. We aimed to sum up our experience and improve the understanding of pulmonary cryptococcosis by providing data from our department.

2. Materials and Methods

2.1. Study Subjects. Patients with pulmonary cryptococcosis admitted to the First Affiliated Hospital of Dalian Medical University from October 2003 to July 2021 were retrospectively selected. The study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (no. PJ-KS-KY-2021-276).

2.2. Data Collection. Patient data were retrieved from the electronic medical records. The following information was obtained: patient demographics, history of exposure to pigeons, underlying medical conditions, clinical manifestations, and imaging features on chest computed tomography. Blood test results, such as complete blood counts, erythrocyte sedimentation rate, C-reactive protein, tumor biomarkers carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC), coagulation parameters, viral hepatitis biomarkers, treponema pallidum antibody, human immunodeficiency virus indicator, and biochemical parameters, were also recorded.

2.3. Diagnostic Method. A *Cryptococcus* capsular polysaccharide antigen was detected qualitatively, and ink staining was used for direct microscopic examination. The pathological methods of patients with pulmonary cryptococcosis, including thoracoscopic surgical resection, transbronchial lung biopsies, and percutaneous lung puncture, were recorded.

2.4. Pathological Features. The pathological characteristics of pulmonary cryptococcosis, including pathological type, special staining, and morphological characteristics, were observed under a light microscope.

2.5. Treatments. The treatment method, drug type, dose, administration route, and course of treatment were collected.

Table 1: Age distribution of patients with pulmonary cryptococcosis.

Group	Male	Female	Total
20-29	1 (2%)	0 (0%)	1 (2%)
30-39	2 (4%)	1 (2%)	3 (6%)
40-49	7 (14%)	8 (16%)	15 (30%)
50-59	7 (14%)	9 (18%)	16 (32%)
60-69	4 (8%)	6 (12%)	10 (20%)
70-79	2 (4%)	1 (2%)	3 (6%)
80-89	2 (4%)	0 (0%)	2 (4%)
Total	25 (50%)	25 (50%)	50 (100%)

3. Results

3.1. Patient Demographics. Among the 50 patients included in the study, there were 25 males and 25 females with a male to female ratio of 1 : 1. The age range was 27-82 years, with an average age of 53.56 ± 11.99 years. The highest incidence was noted in patients with age between 40 and 60 years. The age distribution is shown in Table 1.

3.2. Susceptibility Factors

3.2.1. Exposure History. Only 2 out of the 50 patients presented with a history of bird contact history.

3.2.2. Underlying Medical Conditions. A total of 18 cases (36%) had at least one underlying medical condition, of which hypertension was the most common that was noted in 6 cases. The distribution of underlying medical conditions in these 18 patients is shown in Table 2.

3.3. Clinical Manifestations

3.3.1. Types and Incidence of Clinical Manifestations. 22 of the 50 patients had at least 1 of the following clinical manifestations, and the remaining 28 patients had no related clinical manifestations. The number of patients with cough, chest pain, chest tightness, shortness of breath, expectoration, blood in sputum, fever, fatigue, anorexia, pain around the body, dyspnea, and headache is shown in Table 3.

3.4. Preliminary Diagnosis. The 50 patients included in the statistics were not diagnosed accurately at the initial diagnosis. Preliminary diagnoses included lung shadow in 19 (38%), lung or chest mass in 15 (30%), pneumonia in 3 (6%), lung space-occupying lesions in 3 (6%), lung tumor in 2 (4%), pulmonary sarcoidosis in 1 (2%), undetermined shortness of breath in 1 (2%), and pulmonary tuberculosis in 1 (2%). The remaining 5 patients (10%) sought medical service for other diseases, and cryptococcosis was diagnosed at admission. The type and proportion of patients with corresponding preliminary diagnoses at admission are shown in Table 4.

3.5. Imaging Manifestations

3.5.1. Lesion Shapes and Quantity. A total of 48 patients underwent imaging examinations, of which 69 lesions were observed, including nodule/nodule shadow in 29 cases, cord shadow/focus in 10 cases, miliary shadow/focus in 7 cases,

Table 2: Distribution of basic diseases in 18 patients with pulmonary cryptococcosis.

	Underlying medical conditions
Case 1	Hypothyroidism, thyroiditis, metabolic disorder, uremia
Case 2	Hypertension (grade I), coronary heart disease
Case 3	Hypertension (grade II), fatty liver, hyperlipidemia
Case 4	Type 2 diabetes
Case 5	Type 2 diabetes
Case 6	Hypertension (grade II), low incomplete intestinal obstruction
Case 7	Cryptococcal meningitis
Case 8	Diabetes (grade II)
Case 9	Hypertension, diabetes
Case 10	Lung cancer
Case 11	Benign prostate hyperplasia, polycythemia, bone marrow proliferative tumor
Case 12	Serpentine ulcer, lung cancer
Case 13	Pneumonia, tuberculosis
Case 14	Malignant tumor
Case 15	Malignant tumor of lung
Case 16	Hypertension (grade III), rheumatoid arthritis, renal insufficiency, atherosclerosis
Case 17	Type 2 diabetes
Case 18	Hypertension (grade II), hypoxic hypercapnia, asthma, COPD overlap syndrome, malignant tumor

Table 3: Types and incidence of clinical manifestations.

Clinical manifestations	Number of cases	Incidence (%)
Cough	13	26
Chest pain	8	16
Chest tightness	8	16
Shortness of breath	5	10
Expectoration	5	10
Bloody sputum	2	4
Fever	2	4
Weakness	2	4
Poor appetite	1	2
Generalized aches and pains	1	2
Dyspnea	1	2
Headache	1	2

Table 4: Types and proportion of preliminary diagnosis.

Type	Case	Proportion (%)
Lung shadow	19	38
Lung or chest mass	15	30
Pneumonia	3	6
Lung space-occupying lesion	3	6
Lung tumor	2	4
Pulmonary sarcoidosis	1	2
Shortness of breath	1	2
Pulmonary tuberculosis	1	2
Other	5	10
Total	50	100

pulmonary bullae in 5 cases, patch shadow in 4 cases, calcified focus in 3 cases, mass shadow in 3 cases, localized emphysema in 2, space-occupying lesions in 2, patch shadow in 2, mass shadow in 1, and leaf shadow in 1. The types and proportion of patients with varying imaging lesions are shown in Table 5.

3.5.2. Lesion Distribution. Lesion distribution of the 48 patients with pulmonary cryptococcosis in the lower lobe, single lobe, and right lung was more than that in the upper lobe, multilobes, and left lung, respectively. The specific lesion location and distribution are shown in Table 6.

3.5.3. Concomitant Signs. In imaging examination, 28 patients with pulmonary cryptococcosis showed one or more associated signs, including 12 cases of burr (27.91%), 7 cases of pleural thickening (16.28%), 5 cases of mediastinal lymph node enlargement (11.63%), 5 cases of lobulation (11.63%), 5 cases of cavity (11.63%), 3 cases of bronchitis sign (6.98%), 2 cases of pleural effusion (4.65%), 2 cases of vascular cluster sign (4.65%), 1 case of pleural depression sign (2.33%), and 1 case of spinous process (2.33%), as shown in Table 7.

3.6. Pulmonary Function Test. Among the 50 patients, 32 underwent pulmonary function tests, in which 25 (78.125%) were normal, 5 (15.625%) had obstructive ventilatory defect, and 2 (6.25%) had mixed ventilatory defect, as presented in Table 8.

3.7. Laboratory Test Results

3.7.1. Blood Routine Test. The mean white blood cell count was 7.73×10^9/L, in which 11 cases (22%) were high and 39 cases (78%) were normal. The mean lymphocyte count was $1.67 \times$

Table 5: Types and proportion of patients with pulmonary cryptococcus.

Lesion type	Case	Proportion (%)
Nodule/nodule shadow	29	42.03
Cord shadow/focus	10	14.49
Miliary shadow/focus	7	10.14
Pulmonary bullae	5	7.25
Patch shadow	4	5.80
Calcified focus	3	4.35
Mass shadow	3	4.35
Localized emphysema	2	2.90
Seize a seat	2	2.90
Flake shadow	2	2.90
Mass shadow	1	1.45
Leaf shadow	1	1.45
Total	69	100

Table 6: Distribution of lesions in patients with pulmonary cryptococcus.

Position	Left lung	Right lung	Both lungs	Total
Upper lobe	2	4	2	8
Middle lobe		1		1
Lower lobe	4	9	4	17
Multilobes	0	6	16	22
Total	6	20	22	48

Table 7: Imaging concomitant signs in patients with pulmonary cryptococcosis.

Concomitant sign	Case	Proportion (%)
Burrs	12	27.91
Pleural thickening	7	16.28
Mediastinal lymph node enlargement	5	11.63
Lobulation	5	11.63
Cavity	5	11.63
Bronchitis	3	6.98
Pleural effusion	2	4.65
Vascular cluster sign	2	4.65
Pleural depression sign	1	2.33
Spinous process	1	2.33
Total	43	100

10^9/L, in which 1 case (2%) was high, 44 cases (88%) were normal, and 5 cases (10%) were low. The mean neutrophil count was 5.39×10^9/L, in which 15 cases (30%) were high and 35 cases (70%) were normal. The mean lymphocyte proportion was 25.25%, in which 2 cases (4%) were high, 31 cases (62%) were normal, and 17 cases (34%) were low. The mean proportion of neutrophils was 64.56%, in which 12 cases (24%) were high, 35 cases (70%) were normal, and 3 cases (6%) were low, as shown in Table 9.

3.7.2. Inflammatory Indicators. Increased erythrocyte sedimentation rate was detected in 5 of the 29 cases measured (17.24%). Increased C-reactive protein was detected in 3 (25%) of the 12 cases measured, as shown in Table 10.

3.7.3. Tumor Markers. The levels of CEA were measured in 45 of the 50 patients. Increased levels of CEA were found in only 2 cases (4.44%). Similarly, only 3 (11.11%) out of the 27 cases had elevated SCC, as shown in Table 11.

3.7.4. Infectious Disease Inspection. Testing for hepatitis A antibody and hepatitis B surface antigen in 47 and 50 patients was all negative, respectively. In total, 9 cases (19.15%), 3 cases (6.38%), and 12 cases (25.53%) were positive for hepatitis B surface antibody, hepatitis B e antibody, and hepatitis B core antibody, respectively. All patients were negative for hepatitis C, and only 1 patient was positive for HIV (Table 12).

3.7.5. Coagulation Indexes. Coagulation tests and D-dimer measurements were performed in 49 and 15 cases, respectively. Lower APTT, PT, and TT were noted in 4 (8.16%), 0 (0%), and 1 (2.04%), respectively. The mean value of FIB was 2.84 s, which was high in 4 cases (8.16%) and normal in 45 cases (91.84%). The mean value of D-dimer was 0.39 mg/L, which was high in 3 cases (20%) and normal in 12 cases (80%), as shown in Table 13.

3.7.6. Biochemical Indexes

(1) Blood Glucose. Higher blood glucose and lower blood glucose were noted in 11 (22.92%) and 1 (2.08%) case out of the 48 cases tested, respectively (Table 14).

(2) Blood Lipids. As shown in Table 15, abnormal total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein were found in 6 (42.86%), 4 (28.57%), 5 (35.71%), and 4 (28.57%), respectively.

3.7.7. Blood Group Detection. The ABO blood types tested in 35 patients were type A in 15 (42.86%), type B in 9 (25.71%), type AB in 2 (5.71%), and type O in 9 (25.71%). All the tested were Rh-positive (Table 16).

3.7.8. Tuberculosis Antibody Test. Only 4 (18.18%) out of the 22 patients tested were weakly positive for tuberculosis antibody, as shown in Table 17.

3.8. Pathological Findings. Pathological examination predominantly showed granuloma that is histologically composed of multinucleated giant cells and epithelioid cells in a background of chronic fibrosis. Round fungi with transparent halo can be observed. In this study, 47 cases underwent pathological examination after invasive surgery. However, due to the age of the cases, the specific pathological manifestations of some patients were not recorded, and only 33 specific pathological manifestations were queried. The available 33 pathologic examinations were summarized, of which 22 cases (66.67%) reported directly cryptococcus, whereas granuloma

Table 8: Pulmonary ventilation function.

Pulmonary ventilation function	Case	Proportion (%)
Normal pulmonary ventilation function	25	78.125
Obstructive pulmonary ventilation dysfunction	5	15.625
Mixed pulmonary ventilation dysfunction	2	6.25

Table 9: Blood routine examination.

Blood test	Normal value	Average	Higher	Normal	Lower
Leukocyte count	3.5-9.5 (10^9/L)	7.73 (10^9/L)	11 (22%)	39 (78%)	0 (0%)
Lymphocyte count	1.1-3.2 (10^9/L)	1.67 (10^9/L)	1 (2%)	44 (88%)	5 (10%)
Neutrophil count	1.8-6.3 (10^9/L)	5.39 (10^9/L)	15 (30%)	35 (70%)	0 (0%)
Lymphocyte ratio	20-50 (%)	25.25 (%)	2 (4%)	31 (62%)	17 (34%)
Proportion of neutrophils	45-75 (%)	64.56 (%)	12 (24%)	35 (70%)	3 (6%)

Table 10: Examination results of inflammatory indexes.

Inflammatory indicators	Normal value	Higher	Normal
Erythrocyte sedimentation	0-20 (mm/h)	5 cases (17.24%)	24 cases (82.76%)
CRP	0-8 (mg/L)	3 cases (25%)	9 cases (75%)

Table 11: Examination results of tumor markers.

Tumor markers	Normal value	Average	Higher	Normal
CEA	0-5 (ng/mL)	1.89	2 cases (4.44%)	43 cases (95.56%)
SCC	0-2.5 (ng/mL)	1.28	3 cases (11.11%)	24 cases (88.89%)

Table 12: Inspection results of infectious diseases.

Infectious disease indicators	Negative	Positive	Total
Anti-HAV antibody	47 (100%)	0 (0%)	47 (100%)
HBsAg	50 (100%)	0 (0%)	50 (100%)
Anti-HBsAg antibody	38 (80.85%)	9 (19.15%)	47 (100%)
HBeAg	47 (100%)	0 (0%)	47 (100%)
Anti-HbeAg antibody	44 (93.61%)	3 (6.38%)	47 (100%)
Anti-HbcAg antibody	35 (74.47%)	12 (25.53%)	47 (100%)
PreS1	47 (100%)	0 (0%)	47 (100%)
Anti-HCV antibody	50 (100%)	0 (0%)	50 (100%)
Anti-HEV antibody	47 (100%)	0 (0%)	47 (100%)
Anti-TP antibody	50 (100%)	0 (0%)	50 (100%)
HIV	47 (97.92%)	1 (2.08%)	48 (100%)

and cryptococcus-like structures were reported in 6 (18.18%) and 5 cases (15.15%), respectively (Table 18).

3.9. Diagnostic Methods. As shown in Table 19, 47 cases were confirmed by pathological examination, including 43 cases of lobectomy, 1 case of pleural biopsy, 1 case of bronchial biopsy, and 2 cases of percutaneous lung biopsy. The other 3 cases were diagnosed by cryptococcus capsular antigen in 2 cases and cryptococcus smear in 1 case.

3.10. Treatment Plan. A total of 43 cases and 6 cases were treated by surgical resection and antifungal medications that are predominantly composed of fluconazole, respectively (Table 20). The other case was transferred to another hospital for high suspicion of concomitant pulmonary tuberculosis.

4. Discussion

Cryptococci causing human infections are mainly *Cryptococcus neoformans* and *Cryptococcus gattii* [13]. Cryptococcal infection can occur in multiple organs, particularly the central nervous system, the lungs, the skin, and the bones, in a decreasing order of frequency. *Cryptococcus* is widely distributed and can appear in pigeon dung, soil, vegetables, fruits, and air [11]. Close contact with pigeons or pigeon dung is a factor for cryptococcosis. Similar to a previous report, only 2 cases (4%) have a documented history of pigeon contact in this

Table 13: Examination results of coagulation indexes.

Coagulation indexes	Normal value	Average	Higher	Normal	Lower
APTT	19-31 (s)	23.58	0 (0%)	45 (91.83%)	4 (8.16%)
PT	9-13 (s)	10.77	0 (0%)	49 (100%)	0 (0%)
TT	14-20 (s)	16.80	0 (0%)	48 (97.96%)	1 (2.04%)
Fib	1.8-3.9 (g/L)	2.84	4 (8.16%)	45 (91.84%)	0 (0%)
D-dimer	<0.55 (mg/L FEU)	0.39	3 (20%)	12 (80%)	0 (0%)

Table 14: Glucose test results.

Biochemical indexes	Normal value	Average	Higher	Normal	Lower
Glucose	3.9-6.1 (mmol)	5.915	11 cases (22.92%)	36 cases (75%)	1 case (2.08%)

Table 15: Blood lipid test results.

Blood lipids	Normal value	Normal	Abnormal
TC	<5.20 (mmol/L)	8 (57.14%)	6 (42.86%)
TG	<1.70 (mmol/L)	10 (71.43%)	4 (28.57%)
HDL	>1.04 (mmol/L)	9 (64.28%)	5 (35.71%)
LDL	<3.12 (mmol/L)	10 (71.43%)	4 (28.57%)

Table 16: Blood group test results.

Blood types	Cases	Proportion (%)
A	15	42.86
B	9	25.71
AB	2	5.71
O	9	25.71
Rh (+)	35	100

Table 17: TB antibody test results and proportion.

Test results	Cases	Proportion (%)
Negative	18	81.82
Weakly positive	4	18.18

study [14], suggesting that environmental exposure may not be the main cause of pulmonary cryptococcosis. However, the physician should be highly vigilant for pulmonary cryptococcosis in a patient with history of pigeon contact accompanied by clinical symptoms and expectoration.

Similar to the literature [6], most of the underlying diseases were malignant tumors and diabetes, which may be related to their detrimental effect to the integrity of human immunity. At the same time, the literature [15] has shown that diabetes has become an independent factor for mortality in patients with cryptococcosis.

According to immune status, we divided patients into immunocompetent and immunocompromised groups [12, 16, 17]. In the immunocompetent group, no recognized underlying disease exists or the underlying disease does not affect immunity, such as hypertension. The immunocompromised group must meet one of the following medical histories: long-term use of immunosuppressive drugs or glucocorticoid therapy, diabetes, malignancy, HIV infection, decompensated liver cirrhosis, organ transplantation, acquired immunodeficiency syndrome, idiopathic CD4 lymphocytosis, agranulocytosis, and other conditions that cause severe immunosuppression or other systemic diseases (e.g., systemic lupus erythematosus). In this study, we found that 12 (24%) patients with pulmonary cryptococcosis were immunocompromised, and 38 (76%) pulmonary cryptococcosis patients with normal immunity had results similar to those reported in the literature [16]. It shows that pulmonary cryptococcosis can also occur in people with normal immunity, and the incidence is increased in people with normal immunity [10].

In this study, 28 patients had no clinical manifestations, and 22 patients had one or more of the following clinical manifestations: cough, chest pain, chest tightness, shortness of breath, expectoration, blood in sputum, fever, fatigue, anorexia, body pain, dyspnea, and headache. This study found that the clinical manifestations in 22 patients were nonspecific and difficult to be differentiated from tumors, inflammations, and other lesions. It can be concluded that the clinical manifestations of pulmonary cryptococcosis are heterogeneous and nonspecific [10, 18].

The results of this study showed that the lesions of pulmonary cryptococcosis involved the right lung and the lower lobe more frequently than the left lung and the middle and upper lobe, respectively. Single or multiple nodules accounting for 42.03% were the most common imaging findings. The results were consistent with those reported in the literature [10, 18, 19]. The literature [16] showed certain differences in imaging manifestations in patients with different immune status. The chest CT manifestations of patients without clinical symptoms were mostly of localized nodule/mass type, while those in immunosuppressive patients were pneumonia type and mixed type. However, no differences in imaging manifestations of patients with different immune status were found in this study, which is the same as reported in previous reports [20]. This disparity may be related to small sample size, geographic differences, and the extent of immunity compromise. In this study, the pulmonary lesions of 48 patients were of different

Table 18: Pathological manifestations of pulmonary cryptococcosis.

Pathological findings	Cases	Proportion (%)
Cryptococcus was found	22	66.67
Granuloma	6	18.18
Cryptococcus-like structure in multinucleated giant cells	5	15.15

Table 19: Diagnostic methods.

Diagnostic methods	Cases	Proportion (%)
Pathological examination	47	94
Cryptococcus capsular antigen	2	4
Cryptococcus smear	1	2

Table 20: Treatment plan.

Treatment plan	Cases
Resection	43
Antifungal drugs	6

shapes, and no characteristic lesions were found, rendering clinical diagnosis and treatment difficult. Therefore, imaging manifestations have a certain significance for the diagnosis of pulmonary cryptococcosis and should be interpreted with an appropriate clinical scenario. However, it should also be noted that imaging manifestations of pulmonary cryptococcosis needs to be differentiated from peripheral lung cancer, pulmonary metastatic cancer, and pulmonary tuberculosis [18].

In addition to the above imaging findings, pulmonary cryptococcosis also showed burr, pleural thickening, mediastinal lymph node enlargement, lobulation sign, cavity, bronchitis sign, pleural effusion, vascular convergence sign, pleural depression sign, and spinous process, with burr the most common in this study. In addition, it was found that nodular type was mostly accompanied by burr and lobulation. However, this imaging manifestation is similar to that of lung cancer, making differential diagnosis and treatment difficult [18]. Fewer pleural effusions were found in this study, with only 2 cases. The reason may be that the inflammatory granulomatous lesions of the fungus itself do not lead to large-scale inflammation and necrosis, and it is difficult to lead to the production of exudative pleural effusion.

This study showed that the laboratory examination of pulmonary cryptococcosis had no specificity, which is compatible with an earlier report [13]. This study showed that the leukocyte and neutrophil count was increased, which may be explained by the fact that neutrophils have certain phagocytosis and toxic effects on *Cryptococcus* [21]. In our study, erythrocyte sedimentation rate and C-reactive protein were increased in 5 cases (17.24%) and 3 cases (25%), respectively, which may be caused by cryptococcal infection. In this study, it was also observed that the blood lipid of some patients increased slightly, a phenomenon probably related to the advanced age and coexistence of hypertension in this cohort. The blood routine, erythrocyte sedimentation rate, tumor markers, coagulation indexes, biochemical indexes, and other related indexes in most patients were within the normal range. This suggested that cryptococcal infection does not produce an acute response, which can be differentiated from bacterial pneumonia. This study showed that most patients (88.89%) had SCC in the normal range. Literature [22] suggests that the level of SCC in patients with lung cancer is higher than that in patients with benign lung diseases and healthy people, indicating its potential utility for the ancillary diagnosis of lung cancer. The finding that some patients tested positive for the tuberculosis antibody may also be related to a previous infection.

Although 47 patients were diagnosed with pulmonary cryptococcosis by pathological examination, due to the large time span of patient cases, the detailed pathological manifestations of some patients were not recorded, and only the specific pathological manifestations of 33 patients were queried. Among them, 22 cases (66.67%) described seeing *Cryptococcus*. Granuloma (*Cryptococcus*) was described in 6 cases (18.18%). *Cryptococcus*-like structures in multinucleated giant cells were described in 5 cases (15.15%).

Concerning the diagnosis of pulmonary cryptococcosis in this cohort, 47 patients (94%) were diagnosed by "gold standard" pathology [17]. Granulomatous inflammation with light blue or colorless bacteria that were positive for PAS staining suggested cryptococcal infection. Among them, 43 cases underwent lobectomy, 1 case underwent pleural biopsy, 1 case underwent bronchial biopsy, 2 cases underwent percutaneous lung biopsy, 2 cases were confirmed by serology, and a cryptococcal capsular antigen was positive with pulmonary lesions. One case was diagnosed with *Cryptococcus* smear.

Among them, percutaneous lung biopsy is performed under X-ray fluoroscopy, ultrasound, or CT that uses a fine needle to extract lesion tissue for pathological examination. This method is safe, fast, and accurate with a high positive rate and minimal trauma. However, only 4% of the patients were diagnosed by percutaneous lung biopsy in this study. The main reason is that most of the patients were suspected of malignant lung tumors before the operation and underwent surgical resection.

Ink staining is one of the most commonly used methods for the diagnosis of *Cryptococcus*. However, the positive rate is low and limited by mixed cells and fat droplets. Moreover, the sensitivity of ink staining in the early stage is also not high. Thus, it needs to be detected together with other detection methods, which can improve the diagnostic rate. The diagnosis of pulmonary cryptococcosis by ink staining is simple and rapid. Still, its detection sensitivity is easily affected by many factors, such as the number of fungus in the sample, the treatment method (centrifugation speed and time), the experience of the tester, and whether the subject is HIV infected.

Detection of the *Cryptococcus* capsular polysaccharide antigen is carried out using a colloidal gold method. It has the characteristics of low cost, easy operation, fast detection time, and high sensitivity and specificity. The detection of the cryptococcal capsular polysaccharide antigen has high diagnostic and differential diagnostic value in diagnosing and treating pulmonary cryptococcosis [23, 24]. Compared with surgical resection, detecting the *Cryptococcus* capsular polysaccharide antigen has the advantages of simplicity, rapidity, and low damage. The detection of the *Cryptococcus* capsular polysaccharide antigen should be advocated in patients suspected of pulmonary *Cryptococcus* to avoid traumatic biopsy.

In the present study, pulmonary cryptococcosis was not diagnosed initially, and most of the patients were eventually proven to be misdiagnosed as reported previously [23, 25]. Pulmonary cryptococcosis is challenging to diagnose due to the lack of specific clinical symptoms and generally insufficient experience. Some patients were misdiagnosed with lung cancer and underwent surgical resection that caused unnecessary damage. Therefore, it is particularly important to improve the experience and awareness of pulmonary cryptococcosis.

The goal of pulmonary cryptococcosis treatment is to control and prevent the spread of infection. The treatment scheme is determined by the immune status and disease severity. The expert consensus for the diagnosis and treatment of cryptococcal infection recommended that patients with normal immunity and asymptomatic patients must be closely observed or treated with fluconazole, 200~400 mg per day for 3~6 months. Patients with normal immunity and mild to moderate symptoms or those with nonsevere immunosuppression and diffuse lung infiltration or those with involvement of other systems should be treated with fluconazole, 200~400 mg per day for 6~12 months. For patients who cannot tolerate fluconazole, itraconazole, 200~400 mg per day, can be used for 6~12 months. For those who underwent surgical resection due to thoracotomy exploration or misdiagnosis as tumors or other lesions, it is recommended to apply antifungal drugs routinely after the operation. The course of treatment should not be less than 2 months. Most patients in this study, 43 (86%), underwent surgical resection due to thoracotomy or were misdiagnosed with lung cancer or other lesions. The prognosis of all patients after operation was good, the condition was stable, and the clinical symptoms were greatly relieved, mainly because the lesions were simply limited. When antifungal drugs were used for an average of about 13 days, the clinical symptoms of most patients were significantly relieved. According to the results of this study, the main treatment methods for pulmonary cryptococcosis are surgical resection and antifungal drug treatment. The prognosis is favorable with remarkable treatment effect.

Data Availability

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

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This work was supported by the National Key R&D Program of China (No. 2018AAA0100300).

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 9407888, 9 pages
https://doi.org/10.1155/2022/9407888

Research Article

Serum Vitamin D Level and Efficacy of Vitamin D Supplementation in Children with Atopic Dermatitis: A Systematic Review and Meta-analysis

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Received 1 June 2022; Revised 28 June 2022; Accepted 4 July 2022; Published 20 July 2022

Academic Editor: Xi Lou

Background. The relationship between vitamin D and atopic dermatitis (AD) is controversial. This meta-analysis is aimed at exploring vitamin D level and its deficiency in pediatric AD and at evaluating the efficacy of vitamin D supplementation. *Methods*. PubMed, Medline, Embase, Ovid, Cochrane Library, ISI Web of Science, and ClinicalTrials were searched. Binary variables and continuous variables were measured by odds ratio (OR) and mean difference (MD) with 95% confidence intervals, respectively. The modified Jadad scale, Newcastle-Ottawa Scale (NOS), and Cochrane's bias risk tools were used to evaluate study quality and the risk of bias of eligible studies, respectively. *Results*. A total of 22 literature were included in the analysis. Serum 25 (OH) D level in pediatric AD patients was significantly lower than that of the control group with a combined MD value of -8.18 (95% CI: -13.15, -3.22). Patients with AD were more prone to develop vitamin D deficiency with a combined OR value of 2.17 (95% CI: 1.15, 4.11). According to the score of SCORAD, the level of serum 25 (OH) D level in patients with severe AD was significantly lower than that in patients with mild AD (combined MD = 9.23, 95% CI: 6.92, 11.55). Both self-control studies and randomized controlled trials showed improved SCORAD score and EASI score after vitamin D supplementation. *Conclusion*. This meta-analysis showed lower serum 25 (OH) D level and increased risk of vitamin D deficiency in pediatric AD patients as compared with healthy controls. The serum 25 (OH) D level in severe AD patients was significantly lower than that in the mild AD patients. The SCORAD and EASI score improved after vitamin D supplementation, suggesting its beneficial effect to AD patients. At the same time, more homogeneous studies are needed to reduce confounding factors and further evaluate the impact of vitamin D treatment on the outcome of AD patients.

1. Introduction

Atopic dermatitis (AD) is a common chronic and recurrent inflammatory skin disease characterized by pruritus, eczema, and dry skin [1]. Usually, AD represents an allergy to allergens and thus is often accompanied by various other allergic diseases, such as allergic asthma or rhinitis [2]. AD is seen predominantly in children, of which 30% will continue into adulthood [3]. As a common disease, it affects 5%-20% of children globally. The incidence rate of AD gradually rises within the time range, especially in countries with high urbanization rates or high latitude regions in winter [4]. The occurrence of AD is mainly the result of epidermal barrier defects and immune disorders, while bacterial and viral infections such as Staphylococcus aureus or herpes simplex virus will aggravate AD [5]. Traditional drugs for AD treatment are antihistamines and immunomodulators that reduce skin inflammation, such as local or oral corticosteroids or calcineurin inhibitors [6]. However, these medications are limited by considerable side effects and poor patient compliance.

Currently, a host of studies have reported the potential role of vitamin deficiency in AD development. For example, AD deteriorates in winter when the serum 25 (OH) D level is

the lowest [7]. In addition, it was found that the AD symptoms improved after vitamin D supplementation [8]. These studies may also suggest that vitamin D supplementation is a safe and effective alternative therapy for AD. Although several prior investigations have analyzed the relationship between vitamin D and AD, they were limited by a small number of literatures included, low study quality, remote time frame, and mixed results with both children and adult patients included. Currently, there are still debates in terms of the relationship between vitamin D and atopic dermatitis. In addition, effective treatment and unified research conclusions for AD are still lacking [9–11].

We conducted systematic review and meta-analysis of the included literature to determine serum 25 (OH) D levels in pediatric AD patients and explored the relationship between vitamin D deficiency and AD. We also analyzed the relationship between the grading of AD symptoms and serum 25 (OH) D levels by atopic dermatitis index (SCORAD). Finally, we evaluated the effect and efficacy of vitamin D supplementation on AD severity by SCORAD and eczema area and severity index (EASI).

2. Methods

2.1. Literature Retrieval Strategy. The following databases were searched: PubMed, Medline, Embase, Ovid, Cochrane Library, ISI Web of Science, and ClinicalTrials. The search keywords were "pediatrics" or "children" and "calciferol" and "atopic dermatitis" or "eczema." The search for the literature was limited to human research. The search process was in accordance with the PRISMA statement, and differences in the process were resolved by negotiation. The literature retrieval time is up to February 2022.

2.2. Literature Selection. The inclusion criteria were as follows: (1) case-control study or intervention study, including randomized controlled trial (RCT) and self-controlled stud; (2) pediatric AD patients (<18 years old); (3) available data with regard to serum 25 (OH) D levels in patients and control groups, the number of patients with vitamin D deficiency in patients and control groups, the classification of AD symptoms and corresponding serum 25 (OH) D levels; (4) quantitative assessment of the severity of AD by using SCORAD index or EASI score; and (6) the modified Jadad scale score ≥ 4 for RCTs or the Newcastle Ottawa mean scale (NOS) score of ≥7 for a case-control study.

The exclusion criteria were as follows: (1) The types of literature which were review, systematic evaluation, meta-analysis, case report, and editorial article; (2) incorporation of adult (age > 18 years) AD patients; (3) non-English literature; and (4) studies of pregnant women, infants (<1 year old), or umbilical cord blood samples which were included.

2.3. Data Extraction. Data were extracted from all literature by two independent authors and recorded in the corresponding tables. The extracted data and characteristics include the following: literature characteristics (author, year of publication, and study design), patient characteristics (age, serum 25 (OH) D level (ng/mL), SCORAD index, or EASI score), degree of vitamin D deficiency, and dose and timing of vitamin D supplementation.

The SCORAD is the most effective and commonly used method to evaluate the prevalence of AD in clinical research [12]. The severity of AD is divided into mild AD with SCORAD < 25, moderate AD with SCORAD > 25, and severe AD with SCORAD > 50.

According to the seven-level classification of international vitamin D nutritional status [13], a serum 25 (OH) D level < 20 ng/mL was defined as vitamin D deficiency.

2.4. Study Quality Evaluation. The modified Jadad scale, NOS, and Cochrane's risk of bias tool were employed to assess study quality, bias, and risk of eligible studies, respectively [14]. The modified Jadad scale includes random sequence generation (2 points), randomized hiding (2 points), blinding method (2 points), and withdrawal and dropout (1 point), with a total of 7 points. Studies with 1-3 points were deemed to be of low quality, whereas 4-7points were considered to be high-quality. The NOS scoring table includes the selection of objects in the case combination control group (4 points), the comparability of cases and controls (2 points), and the measurement of exposure factors (3 points), with a total of 9 points. The potential study biases were assessed using Cochrane's bias risk tool in accordance with the PRISMA statement, and the map of the risk of bias was generated [15].

2.5. Statistical Analysis. Review Manager software was used for establishing a forest map and funnel map. Binary variables and continuous variables were measured by odds ratio (OR) and mean difference (MD), respectively. 95% confidence intervals were used for each variable. Clinically homogeneous studies were divided into subgroups, and meta-analyses were performed accordingly. Heterogeneity testing was done by a chi-square test. The fixed effects model was used when the homogeneity was low ($I^2 < 50\%$). Otherwise, the random effects model was used. When $P < 0.05$, the difference was considered statistically significant.

3. Results

3.1. Retrieval Results and Literature Quality Evaluation. The process of literature search and screening is shown in Figure 1. A total of 2464 literatures about vitamin D and AD in children were retrieved from the database. After screening according to the inclusion and exclusion criteria, 22 literatures were included in the analysis [16–37], and the basic characteristics and corresponding scores for each document were counted. The diagram of risk of bias for RCTs is shown in Figure 2. The basic characteristics and document quality scores of included documents are shown in Table 1.

3.2. Comparison of Serum 25 (OH) D Levels between AD Patients and Healthy Controls. 14 studies evaluated the comparison of serum 25 (OH) D levels between AD patients and healthy controls. The characteristics of the included literature are shown in Table 2. A total of 1450 patients and 1009 healthy controls were included. Significant interstudy

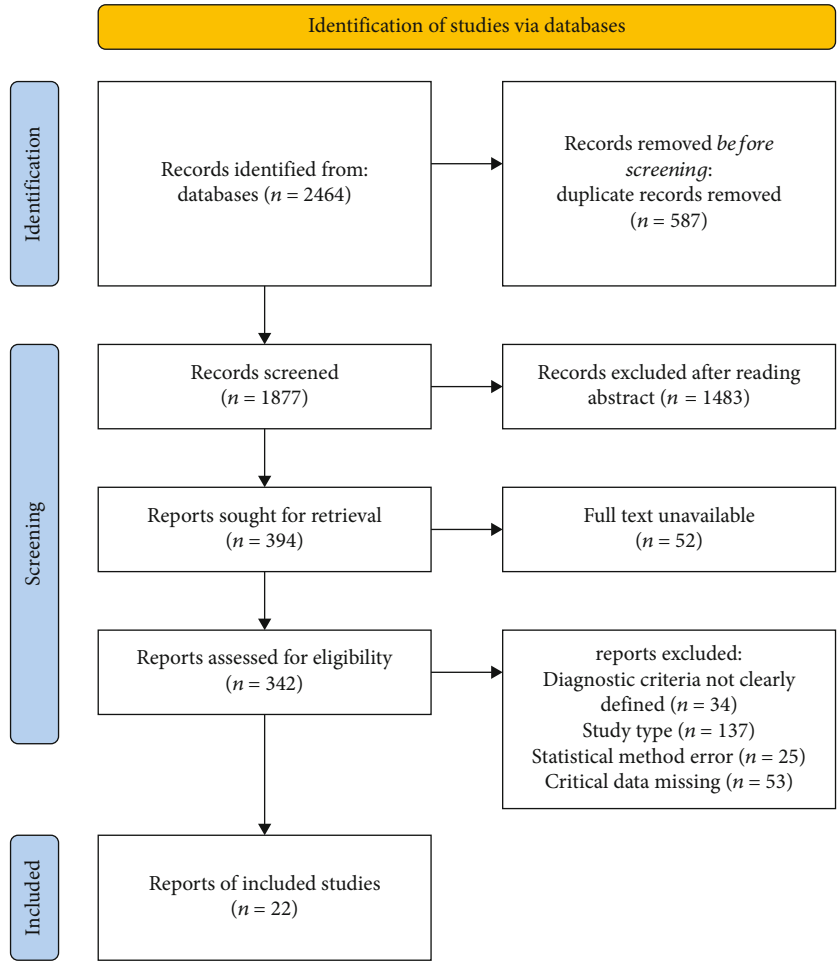

Figure 1: Flow chart of literature screening.

heterogeneity ($P < 0.00001$, $I^2 = 98\%$) were noted, for which the random effects model was used. The combined MD value was -8.18 (95% CI: -13.15, -3.22), and the combined effects amount was $Z = 3.23$ ($P = 0.001$). The results showed that serum 25 (OH) D level in AD patients was significantly lower than those in healthy controls (Figure 3).

3.3. Comparison of Serum 25 (OH) D Deficiency between AD Patients and Healthy Controls. Comparisons of serum 25 (OH) D deficiency between AD patients and healthy controls were reported in 9 studies that included 1096 patients and 765 healthy controls. Significant literature heterogeneity ($P < 0.00001$, $I^2 = 84\%$) was noted, and the random effects model was used. The combined MD value and effect amount Z were 2.17 (95% CI: 1.15, 4.11) and 2.38 ($P = 0.02$), respectively. It showed that the risk of serum 25 (OH) D deficiency in AD patients was significantly higher than that in healthy controls (Figure 4).

3.4. Comparison of Serum 25 (OH) D Levels in Patients with Mild and Severe AD Rated by SCORAD Index. Serum 25 (OH) D levels in AD patients with mild and severe SCORAD index ratings were compared in 9 studies that included a total of 224 patients with mild AD and 196 with severe AD. The combined MD value and effect amount Z calculated by the random effects model was 9.23 (95% CI: 6.92, 11.55) and 7.82 ($P < 0.001$), respectively. The level of serum 25 (OH) D in patients with mild AD was significantly higher than that in patients with severe AD (Figure 5).

3.5. Comparison of SCORAD Scores of Pediatric AD Patients before and after Vitamin D Intervention. The SCORAD score at baseline and after vitamin D treatment in pediatric AD patients was evaluated in 5 studies that included 2 self-control experiments (Table 3). Given that the results of these two reports cannot be statistically integrated with the other 3 RCTs, subgroup analyses were performed. In total, 57 pediatric AD patients received vitamin D treatment in these 2 studies. There was no significant interstudy heterogeneity ($P = 0.48$, $I^2 = 0\%$), for which the fixed effects model was adopted. The combined MD and effect amount Z value were -18.80 (95% CI: -23.18, -14.42) and 8.40 ($P < 0.001$), respectively. The SCORAD scores decreased significantly by 18.8 points after vitamin D treatment in the self-control experiment (Figure 6). For the 3 RCTs, 47 AD patients received vitamin D supplementation. The fixed effects model is adopted. The combined MD and effect amount Z value measured by the fixed effects model ($P = 0.23$, $I^2 = 31\%$) were

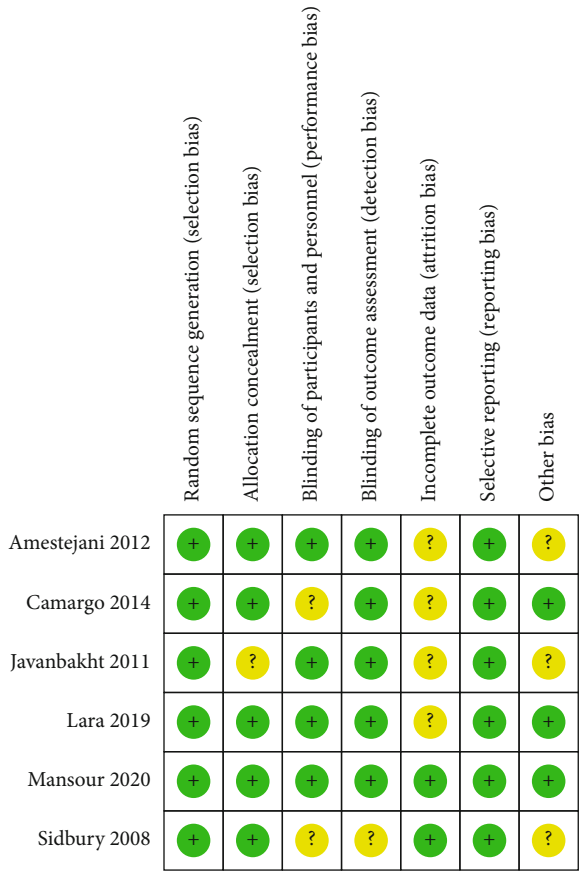

Figure 2: Risk assessment of bias in randomized controlled trials.

Table 1: Basic characteristics and document quality scores of included documents.

Study	Study design	Studies assessment scale
Lipińska, 2021	CCT	7
Ahmed, 2021	CCT	8
Sanmartin, 2020	CCT	7
Raj, 2020	CCT	7
Xiang, 2019	CCT	7
Lee, 2019	CCT	8
Daniluk, 2019	CCT	8
Machura, 2018	CCT	7
Dogru, 2018	CCT	7
Su, 2017	CCT	8
D'Auria, 2017	CCT	9
Sharma, 2017	CCT	7
Cheon, 2015	CCT	8
Di Filippo, 2015	CCT	7
Wang, 2014	CCT	7
El Taieb, 2013	CCT	7
Lara, 2019	RCT	5
Amestejani, 2012	RCT	6
Javanbakht, 2011	RCT	6
Camargo, 2014	RCT	4
Mansour, 2020	RCT	6
Sidbury, 2008	RCT	5

RCT: randomized controlled trial; CCT: controlled clinical trial; studies' assessment scale: RCT study uses the modified Jadad scale; CCT study uses Newcastle-Ottawa scale.

-11.02 (95% CI: -12.63, -9.40) and 13.34 ($P < 0.001$), respectively. The SCORAD score was significantly reduced by 11.02 points after vitamin D treatment (Figure 6). Although the number of studies is small, all studies demonstrated reduced SCORAD and improved clinical symptoms after vitamin D supplementation.

3.6. Effect of Vitamin D Supplementation on EASI Score. Three RCTs evaluated the effect of vitamin D intervention on EASI scores in patients with clinical AD. Study characteristics are summarized in Table 3. A total of 107 AD patients received vitamin D treatment, and 97 AD patients received placebo treatment. There was no significant heterogeneity among the literature ($P = 0.78$, $I2 = 0\%$). The fixed effects model was adopted. The combined MD value was -3.72 (95% CI: -6.25, -1.19), and the combined effect amount was $Z = 2.88$ ($P = 0.004$). After vitamin D treatment, the EASI score of AD patients was significantly lower than that of the placebo treatment group by 3.72 points (Figure 7). Begg's test (Figure 8) showed no publication bias.

4. Discussion

This study comprehensively reviewed and summarized the results of case-control studies and interventional studies. Although it is found that the number of research literature is significant in the preliminary screening, the study quality varied significantly. Therefore, this study only included RCTs with a modified Jadad scale score ≥ 4 or case-control studies with a NOS ≥ 7. The results showed that the serum 25 (OH) D level of AD patients was significantly lower than that of the healthy control group. In addition, serum 25 (OH) D level in patients with severe AD was significantly lower than in patients with mild AD as indicated by the SCORAD. These results suggest that children with AD have a high risk of vitamin D deficiency. Studies have shown that [38] all individuals with vitamin D deficiency should receive serum 25 (OH) D monitoring regularly [13, 39]. Considering the higher risk of vitamin D deficiency in AD patients, vitamin D supplementation in this patient population can be considered in clinical practice.

Emerging studies have shown that the pathogenesis of AD is complicated that included destruction or weakening of epidermal defense barrier, immune dysfunction and gene susceptibility (such as silk protein gene deletion). In addition, allergens and microorganisms are also widely involved in the pathogenesis of AD due to skin barrier defects and innate immune system disorders [40, 41]. Although the exact relationship between vitamin D deficiency and AD remains incompletely understood, previous studies have shown that vitamin D deficiency may be involved in the occurrence and development of AD. Studies have shown

Table 2: Characteristics of included studies on serum 25 (OH) D level between AD patients and healthy controls.

Study	Year	Study population age (AD group/control group) (years)	Study size	Location
Lipińska et al.	2021	Median age (7/8)	75 cases, 37control subjects	Poland
Ahmed et al.	2021	Mean age (11/9.2)	100 cases, 101 control subjects	Egypt
Sanmartin et al.	2020	Age range (0-12/0-12)	134 cases, 105 control subjects	Spain
Xiang et al.	2019	Mean age (5.1/3.2)	81 cases, 65 control subjects	China
Lee et al.	2019	Mean age (8.6/9.4)	135 cases, 65 control subjects	Malaysia
Daniluk et al.	2019	Median age (6/5.5)	29 cases, 22 control subjects	Poland
Machura et al.	2018	Age range (2-14/2-14)	57 cases, 34 control subjects	Poland
Dogru et al.	2018	Mean age (5.6/5.4)	69 cases, 70 control subjects	Turkey
Su et al.	2017	Mean age (6.5/7.4)	60 cases, 37 control subjects	Turkey
D'Auria et al.	2017	Mean age (6.2/6.1)	52 cases, 43 control subjects	Italy
Sharma et al.	2017	Mean age (6.1/6.7)	40 cases, 40 control subjects	India
Cheon et al.	2015	Median age (6/6)	91 cases, 32 control subjects	Korea
Wang et al.	2014	Median age (6/5.5)	498 cases, 328 control subjects	Hong Kong
El Taieb et al.	2013	Mean age (6.1/6.5)	29 cases, 30 control subjects	Egypt

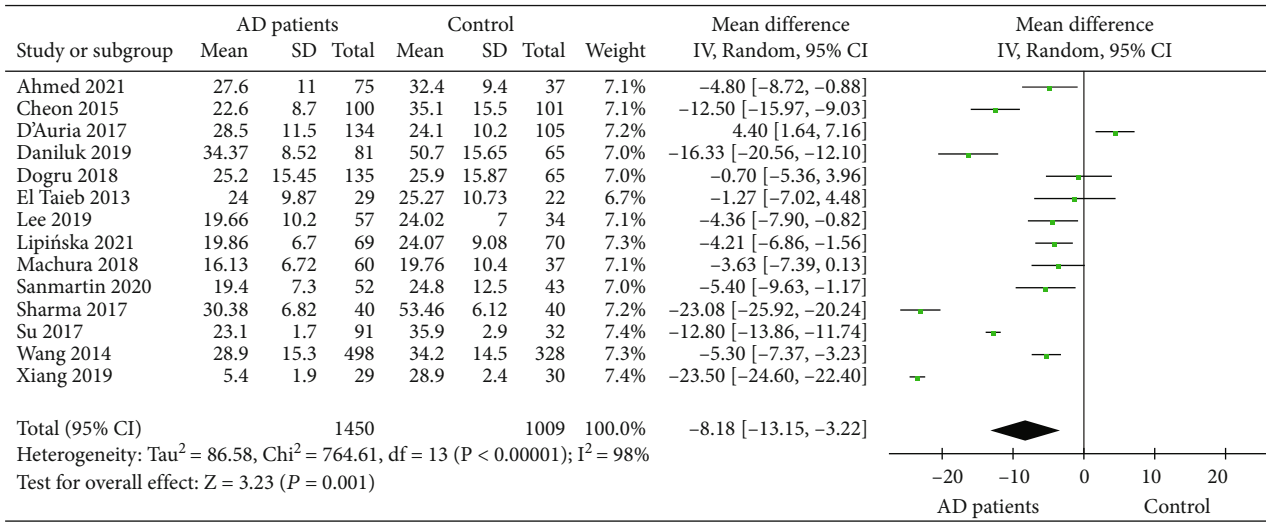

Figure 3: Comparison of serum 25 (OH) D levels between AD patients and healthy controls.

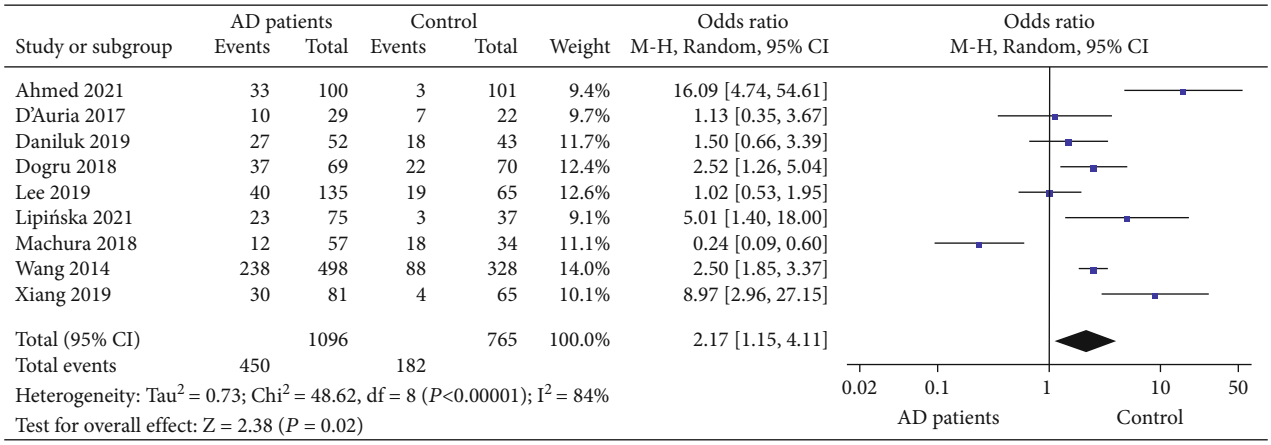

Figure 4: Comparative meta-analysis of serum 25 (OH) D deficiency between AD patients and healthy controls.

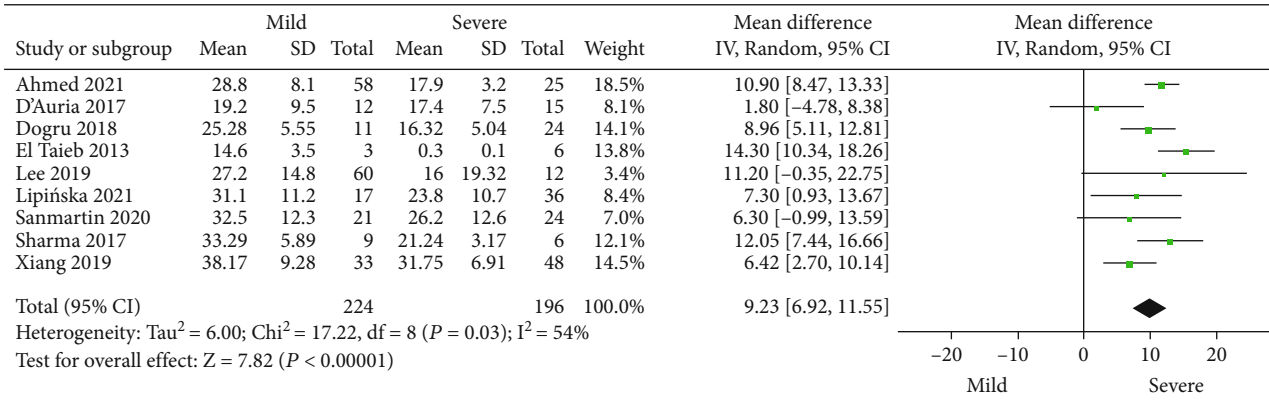

Figure 5: Comparative meta-analysis of serum 25 (OH) D levels in AD patients with mild and severe SCORAD index rating.

Table 3: Summary of characteristics of intervention experiments included in the study.

Study	Year	Study design	Study size	Duration	Dose/daily	Location	AD severity assessment
Raj et al.	2020	RMI	35 cases	3 months	1000 IU	India	SCORAD
Di Filippo et al.	2015	RMI	22 cases	3 months	1000 IU	Italy	SCORAD
Lara et al.	2019	RCT	11 cases, 24 placebos	3 months	1000 IU	Canada	SCORAD
Amestejani et al.	2012	RCT	11 cases, 12 placebos	60 days	1600 IU	Iran	SCORAD
Javanbakht et al.	2011	RCT	24 cases, 26 placebos	60 days	1600 IU	Iran	SCORAD
Mansour et al.	2020	RCT	44 cases, 42 placebos	12 weeks	1600 IU	Egypt	EASI
Camargo et al.	2014	RCT	58 cases, 49 placebos	1 month	1000 IU	Mongolia	EASI
Sidbury et al.	2008	RCT	5 cases, 6 placebos	1 month	1000 IU	USA	EASI

RMI: repeated measure interventions (patients are their own control); RCT: randomized controlled trial; SCORAD: Scoring Atopic Dermatitis; EASI: eczema area and severity index.

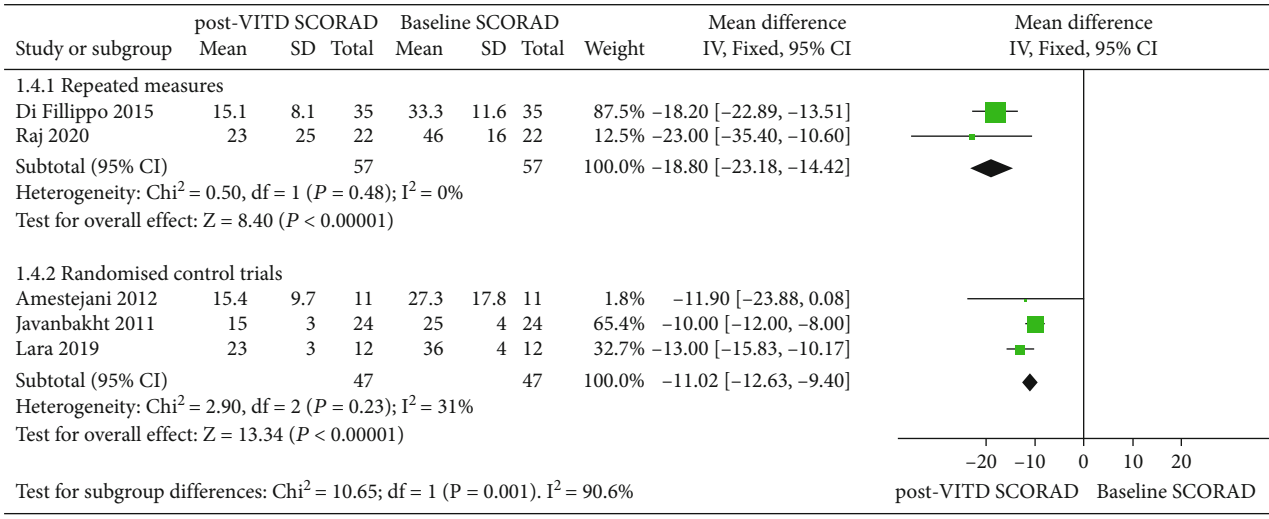

Figure 6: Meta-analysis of SCORAD scores of clinical AD patients before and after vitamin D intervention experiment.

that after vitamin D supplementation, antimicrobial peptides such as catheterin or β-defensin levels increased [42]. After the destruction of the vitamin D receptor, the levels of skin barrier proteins such as outer skin protein and silk fibroin decreased [43]. When the vitamin D level is low, the risk of higher IgE level and fixed value of Staphylococcus aureus in the population increases, while the level of interleukin-37 in the stratum corneum increases fourfold after vitamin D supplementation and reduces the occurrence of herpetic eczema [44]. These reports suggested that vitamin D can regulate immune response and maintain a healthy skin barrier function.

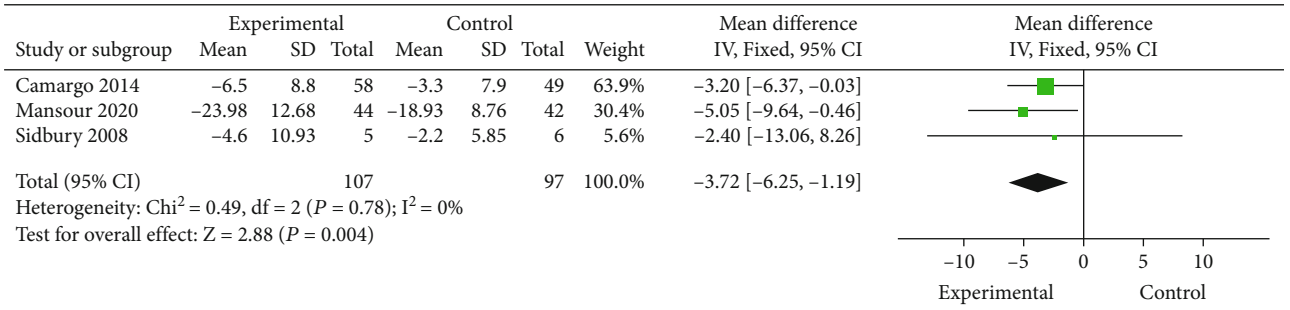

Figure 7: Comparative meta-analysis of the effect of vitamin D intervention experiment on EASI score of clinical AD patients.

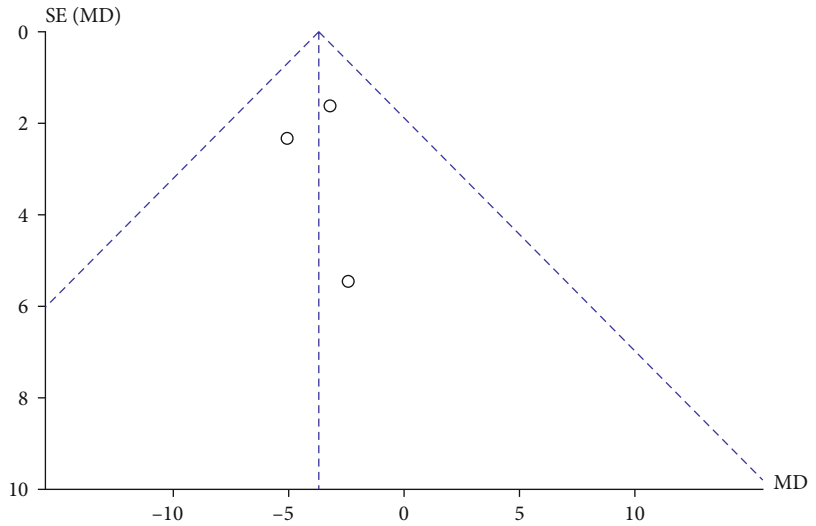

Figure 8: Comparative meta-analysis funnel chart of the effect of vitamin D intervention experiment on EASI score of clinical AD patients.

Our systematic review and meta-analysis that included recent high-quality studies is the latest research on the role of vitamin D in children with AD. This study found that the serum 25 (OH) D level of AD patients was lower than that of the healthy control group, and this reduction was statistically significant. In addition, we also supplemented the relationship between vitamin D deficiency, and patients with AD were more prone to vitamin D deficiency, which has not been mentioned in previous meta-analyses [9]. Due to the difference in sunlight exposure or latitude in various regions, the baseline vitamin D level in different areas varied dramatically. The relatively low vitamin D level does not necessarily mean vitamin D deficiency. This also explains the large heterogeneity with regard to vitamin D levels reported in this study. This study also confirmed that patients with AD have a higher risk of vitamin D deficiency and need continuous monitoring and vitamin D supplementation. The observation that serum 25 (OH) D level in severe AD patients was significantly lower than that of mild AD patients, indicating the decrease in vitamin D level and deficiency may be related to the aggravation of AD.

Self-control experiments and RCTs included in this study showed the improvement of SCORAD and EASI score after vitamin D supplementation. Therefore, vitamin D supplementation is beneficial to AD patients. However, the number of included studies is small, and the interpretation of the results needs to be more cautious. In addition, differences in vitamin D levels during seasonal and latitudinal changes also affect the evaluation of vitamin D supplementation. Moreover, the dose and duration of vitamin D used in different studies vary greatly with many confounding factors that prevented from exploring real impact of vitamin D supplements on children. More large-scale prospective RCT studies with different vitamin D supplement doses and duration are needed to obtain adequate treatment options.

The literatures included in our study are high-quality studies, which is the advantage of this study. Similar literatures have recently compared the effects and efficacy of serum vitamin D levels and vitamin D supplementation on children with AD [45] with similar conclusions. However, we focused on pediatric AD, whereas other studies often presented mixed patient population that included both children and adults. Factors like age create considerable interstudy heterogeneity and reduce the confidence and clinical generalizability of the results. In addition, the evaluation indicators of other studies were single with only the SCORAD score used to evaluate the effect of vitamin D supplementation. In our study, the two indicators are used for comparison, and

more reports are included in the evaluation, making the results more credible. Of note, there are many confounding factors in vitamin D research, such as the latitude, the time of sunlight exposure, and the type, dose, and duration of vitamin D supplements. Due to the wide heterogeneity and lack of homogeneous researches, these potential confounding factors were not considered. This also suggests that a larger sample, multicenter or prospective, highly homogeneous RCTs or cohort studies need to be carried out. A more reasonable and unified result analysis system should be adopted to provide higher-level evidence.

In conclusion, this study systematically summarized and analyzed the evidence of the interaction between vitamin D and children with AD. It showed lower serum 25 (OH) D level and increased risk of vitamin D deficiency in pediatric AD patients as compared with healthy controls. The serum 25 (OH) D level in severe AD patients was significantly lower than that in the mild AD patients. The SCORAD and EASI score improved after vitamin D supplementation, suggesting its beneficial effect to AD patients. At the same time, more homogeneous studies are needed to reduce confounding factors and further evaluate the impact of vitamin D treatment on the outcome of AD patients.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Hongbo Fu and Yanting Li contributed equally to this work.

Acknowledgments

The study was supported by Haikou Maternal and Child Health Hospital.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 3315638, 10 pages
https://doi.org/10.1155/2022/3315638

Research Article

Effect of Prenatal Perineal Massage on Postpartum Perineal Injury and Postpartum Complications: A Meta-Analysis

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Received 27 May 2022; Revised 25 June 2022; Accepted 29 June 2022; Published 14 July 2022

Academic Editor: Xi Lou

Background. The efficacy of perineal massage is controversial. The study was aimed at comparing the effects of perineal massage on perineal injury and complications. *Methods*. PubMed, Embase, the Cochrane Library, and ISI Web of Science were searched for literature on the relationship between prenatal perineal massage and postpartum perineal injury and complications until April 2022. Indicators included postpartum perineal tears, perineotomy, postpartum perineal pain, natural labour, and postpartum incontinence. Finally, RevMan5.4 software was used to analyze the extracted data. *Results*. A total of 6487 subjects in 16 studies were included, with 3211 who received perineal massage and 3276 did not. There was no significant difference in 1-2 degree perineal tearing between the intervention group and the control group (RR = 0.96, 95% CI [0.90, 1.03], $P = 0.30$), and there was no heterogeneity between studies ($P = 0.62$, $I^2 = 0\%$), indicating publication bias. Compared with the control group, prenatal perineal massage significantly reduced the incidence of 3-4 degree perineal tears (RR = 0.56, 95% CI [0.47, 0.67], $P < 0.00001$), and there was no heterogeneity between studies ($P = 0.16$, $I^2 = 30\%$), indicating publication bias. Compared with the control group, prenatal perineal massage reduced the risk of lateral perineal resection (RR = 0.87, 95% CI [0.80, 0.95], $P = 0.001$), and there was no heterogeneity between studies ($P = 0.14$, $I^2 = 31\%$), and there was no publication bias. Compared with the control group, prenatal perineal massage reduced the risk of postpartum pain at 3 months (RR = 0.64, 95% CI [0.51, 0.81], $P = 0.0002$). There was no significant heterogeneity among studies ($P = 0.23$, $I^2 = 31\%$). *Conclusion*. Compared with no prenatal perineal massage, prenatal perineal massage can reduce the risk of perineal injury, the incidence of lateral perineal resection, and the incidence of long-term pain.

1. Introduction

Perineal injury, which refers to the injury that occurs in the genital area associated with laceration during delivery, has a high incidence of 30-85% in vaginal delivery [1]. It can cause perineal pain, difficulty in sexual intercourse, urinary incontinence, and other complications that greatly impact the physical and mental health of pregnant women. Although perineum incision is often offered preemptively to avoid perineum injury, the evidence supporting its efficacy remains elusive. Moreover, the utility of perineal incision is also limited by associated complications and psychologically decreases a woman's sexual desire and esteem. Currently, routine perineum incision is no longer recommended.

Perineal massage is a well-known treatment modality that has been shown [2] to stimulate nerve endings in the skin, enhance perineal blood circulation, improve the elasticity and ductility of perineal tissue, broaden the vaginal opening, reduce the probability of perineal incision, and reduce perineal tear. In addition, it facilitates vaginal delivery and probably reduces the risk of perineal injury by stimulating the child's head during childbirth. Currently, studies [3, 4] about the effect of prenatal perineal massage on the incidence of perineal tears and episiotomy reported inconsistent results. For instance, Ibrahim [5] reported that prenatal perineal massage did not benefit the mother more than Kegel exercises. The efficacy of antenatal perineal massage is controversial. To further explore the impact of prenatal perineal

massage on postpartum perineal injury and postpartum complications, we conducted this systematic review and meta-analysis to update the available evidence to determine whether prenatal perineal massage can reduce the risk of perineal trauma and postpartum complications.

2. Materials and Methods

2.1. Literature Search. PubMed, Embase, the Cochrane Library, ISI Web of Science, and other databases were searched. The search time was set from its establishment to April 2022. Articles and studies about the impact of prenatal perineal massage on postpartum perineal injury and postpartum complications were collected. The search terms were "Antenatal perineal massage", "Perineal trauma", "Episiotomy", and other similar phrases. The joint search was carried out with subject words and free words. References to the target literature were also examined.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria were as follows: (1) study type: randomized controlled studies (RCTs); (2) participants: primipara or postmenopausal women undergoing prenatal care; (3) intervention group: prenatal perineal massage at 34-36 weeks of pregnancy; (4) control group: no perineal massage before delivery; and (5) results: the main results included the risk of perineal tear, the incidence of perineal incision, and natural vaginal delivery. Secondary outcomes were perineal pain (assessed by visual analogue scale (VAS)), urinary incontinence, and fecal incontinence at 3 months postpartum. Exclusion criteria were as follows: (1) nonrandomized trials, in vitro study, or animal study; (2) study overlap; (3) literature with incomplete data or no research indicators; and (4) unrelated studies.

2.3. Data Extraction and Quantitative Evaluation. Two researchers screened the data from the included literature. Controversies emerged were solved through discussion or consultation the third researcher. The extracted data included the first author, publication time and country, the sample size of each group, and the expected primary and secondary results.

We used the Cochrane bias risk assessment tool, which was recommended by the Cochrane manual, to assess the quality of methods included in the study. This tool performed bias risk assessment from six aspects: random allocation method, allocation concealment scheme, blind method, integrity of result data, selection report research results, and other biases. The author's judgment was divided into "low risk," "high risk," and "unclear risk" of bias.

2.4. Statistical Method. RevMan5.4 software was used for meta-analysis. Two-sided $P < 0.05$ indicates that the difference is statistically significant. The risk ratio (RR) and its 95% confidence interval (CI) were used to analyze the dichotomous variables. The heterogeneity test was conducted through I^2. The fixed effect model was in the presence of no obvious interstudy heterogeneity as indicated by $P > 0.05$ and $I^2 < 50\%$. Otherwise, the random effect model was employed for significant interstudy heterogeneity. Subgroup and sensitivity analyses were used to explore the source of heterogeneity. The analysis result was presented by the forest map, and the publication bias was displayed by the funnel map and Egger's test.

3. Results

3.1. Literature Search Results. A total of 1522 English contributions were obtained through database retrieval, of which 826 were included after screening and eliminating duplicate literature. After reading the literature title and abstract, 16 studies [3–18] were finally included. The flow chart is shown in Figure 1.

3.2. Basic Information of the Included Studies. The included studies compared perineal massage versus no perineal massage during prenatal care. All included studies were conducted on pregnant women or their partners at 34-36 weeks of gestation. The included studies were reported from Asia, Europe, North America, Africa, and Oceania. Four studies were from Egypt [3–6], two from Canada [7, 8], and one from Australia [9], Japan [10], Ireland [11], Spain [12], Austria [13], Turkey [14], Iran [15], Nigeria [16], the UK [17], and the United States [18], respectively. The largest sample size was reported from Australia [9], with 1340 cases. A total of 6487 patients were included in the sample, including 3211 in the intervention group and 3267 in the control group. The basic characteristics of the literature and the assessment of risk of bias were shown in Table 1.

3.3. Perineal Tear. A total of 16 literature compared the effect of prenatal perineal massage on the perineal tear. Significant interstudy heterogeneity ($\text{Chi}^2 = 42.15$, $P = 0.0002$, $I^2 = 64\%$) was noted, for which the random effect model was used. Compared with the control group, prenatal perineal massage reduced the risk of perineal tear (RR = 0.82, 95% CI [0.74-0.92], $P < 0.001$) (Figure 2). The funnel plot and Egger's test showed that the scatter points were roughly symmetrically distributed, with no publication bias ($P > 0.05$) (Figure 3). To explore the source of heterogeneity, subgroup analysis was carried out according to the degree of perineal tear. There was no significant difference between the intervention group and the control group (RR = 0.96, 95% CI [0.90, 1.03], $P = 0.30$), and there was no heterogeneity between the studies ($\text{Chi}^2 = 10.84$, $P = 0.62$, $I^2 = 0\%$) (Figure 4). The funnel plot and Egger test showed that the scatter points were biased to the left, and there was publication bias ($P > 0.05$) (Figure 5). Compared with the control group, prenatal perineal massage significantly reduced the incidence of 3-4 degree tear of perineum (RR = 0.56, 95% CI [0.47, 0.67], $P < 0.00001$), and there was no heterogeneity among the studies ($\text{Chi}^2 = 14.23$, $P = 0.16$, $I^2 = 30\%$) (Figure 6). The funnel plot and Egger test showed that the scatter points were biased to the left, and there was publication bias ($P > 0.05$) (Figure 7).

3.4. Lateral Episiotomy. Compared with the control group, prenatal perineal massage reduced the risk of lateral episiotomy (RR = 0.87, 95% CI [0.80, 0.95], $P = 0.001$), and the

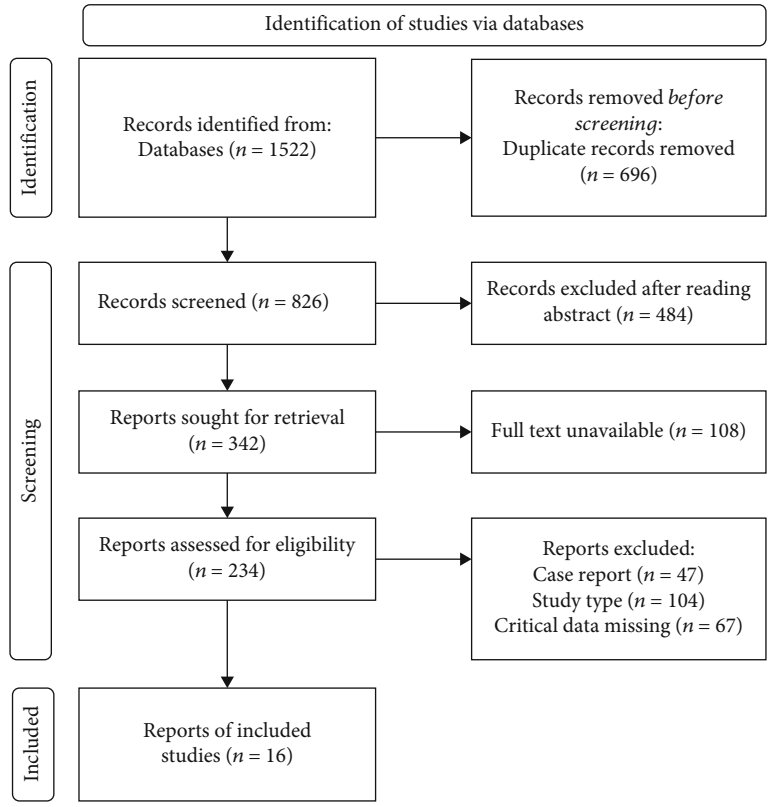

Figure 1: Flow chart of literature screening.

Table 1: Basic characteristics of the literature and assessment of risk of bias.

Author	Country	Year	No. of patients		Risk of basis
			Perineal massage	Control	
Ali H	Egypt	2015	50	70	High
Amira S. Dieb	Egypt	2019	200	200	High
B. Bodner-Adler	Austria	2002	121	410	Uncertain
Dönmez S	Turkey	2015	30	39	High
Elsebeiy	Egypt	2018	37	43	Low
Georgina Stamp	Australia	2001	708	632	Uncertain
Kate Davidson	United States	2000	269	93	Uncertain
Labrecque	Canada	1999	646	658	Uncertain
M. K. Shipman	UK	1997	332	350	Low
Maeve Eogan	Ireland	2006	100	79	High
María Álvarez-González	Spain	2021	60	30	Uncertain
Michel Labrecque	Canada	2000	470	479	Uncertain
Mohamed	Egypt	2011	30	30	Uncertain
Shahoei R	Iran	2016	75	75	Uncertain
Shimada	Japan	2005	30	33	Low
Ugwu	Nigeria	2018	53	55	High

heterogeneity test result was $P = 0.14$, $I^2 = 31\%$ (Figure 8). There was no heterogeneity among the studies. The funnel plot and Egger test showed that the scatter points were roughly symmetrical with no publication bias ($P > 0.05$) (Figure 9).

3.5. Natural Childbirth. Compared with the control group, there was no significant difference in vaginal natural delivery in the prenatal perineal massage group (RR = 1.01, 95% CI [0.97~1.04], $P = 0.69$). There was no heterogeneity between studies ($\text{Chi}^2 = 13.35$, $P = 0.69$, $I^2 = 40\%$) (Figure 10). The

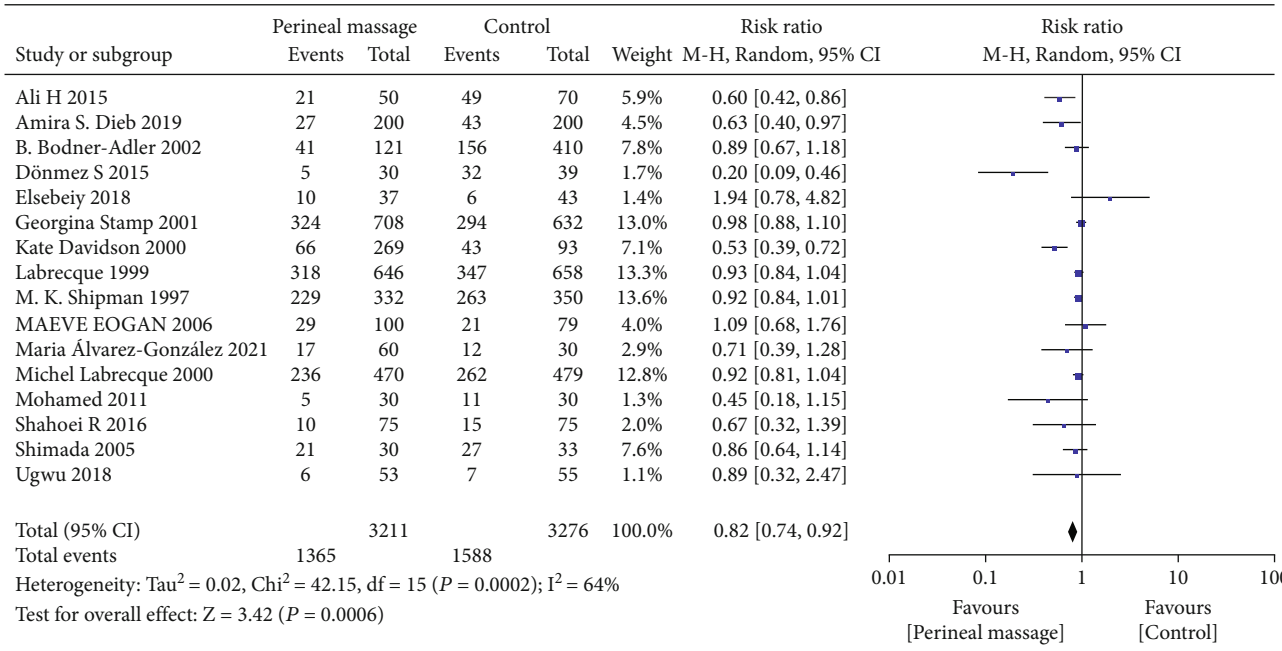

Figure 2: Forest map: effect of prenatal perineal massage on perineal tear.

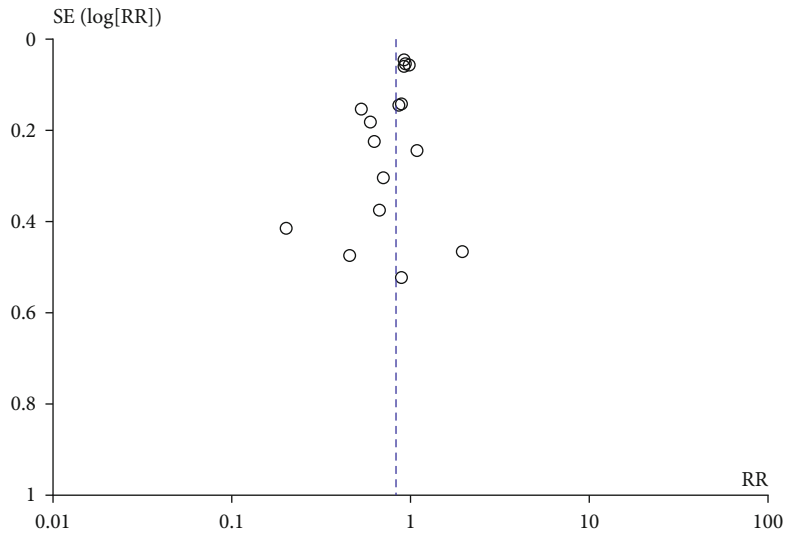

Figure 3: Funnel diagram: effect of prenatal perineal massage on perineal tear.

funnel plot and Egger test show that the scatter distribution is biased to the right, and there may be publication bias ($P > 0.05$) (Figure 11).

3.6. Perineal Pain. We analyzed the perineal pain of parturients at 3 days and 3 months postpartum, respectively. The results showed that prenatal perineal massage reduced the pain risk of parturients at 3 months postpartum (RR = 0.64 , 95% CI [0.51, 0.81], $P = 0.0002$) than the control group. There was no significant heterogeneity among the studies ($\text{Chi}^2 = 2.90$, $P = 0.23$, $I^2 = 31\%$) (Figure 12). Egger's test showed that there was no publication bias among the literatures ($P > 0.05$). There was no significant difference in perineal pain between the intervention group and the control group at 3 days postpartum (RR = 1.00, 95% CI [0.93, 1.07], $P = 1.00$), and there was no significant heterogeneity among the studies ($\text{Chi}^2 = 1.28$, $P = 0.53$, $I^2 = 0\%$) (Figure 13). Egger's test showed that there was no publication bias among the literatures ($P > 0.05$).

3.7. Urinary Incontinence. Compared with the control group, there was no significant difference in urinary incontinence at 3 months postpartum in the prenatal perineal massage group (RR = 0.91, 95% CI [0.79~1.05], $P = 0.21$). There

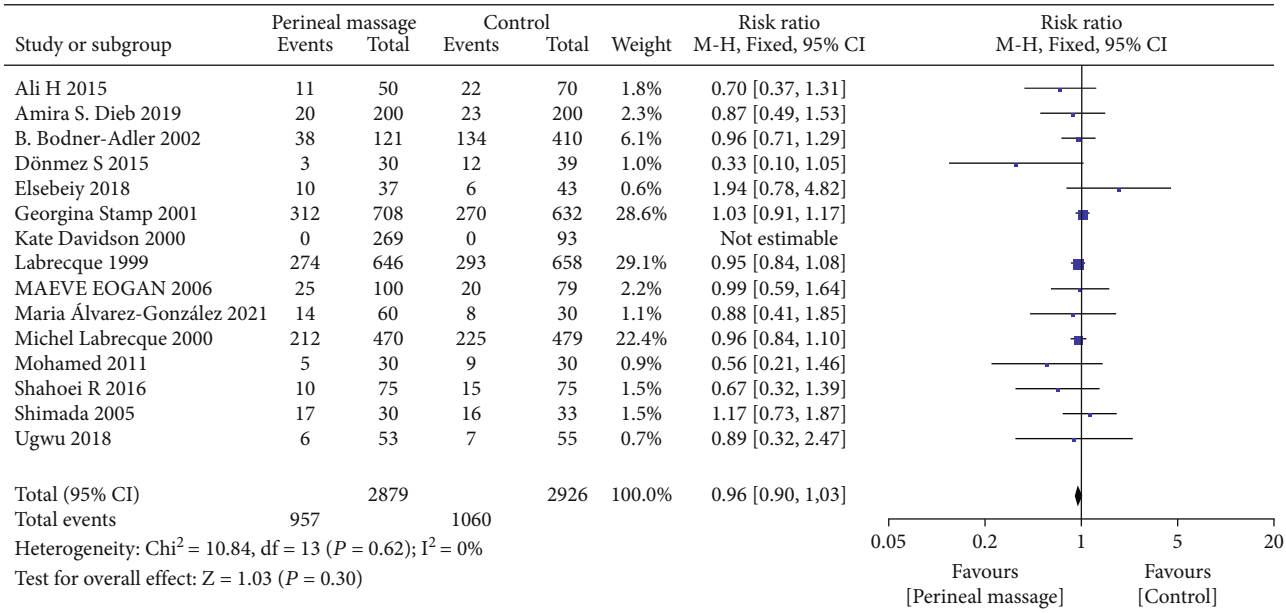

Figure 4: Forest map: effect of prenatal perineal massage on 1-2 degree perineal tear.

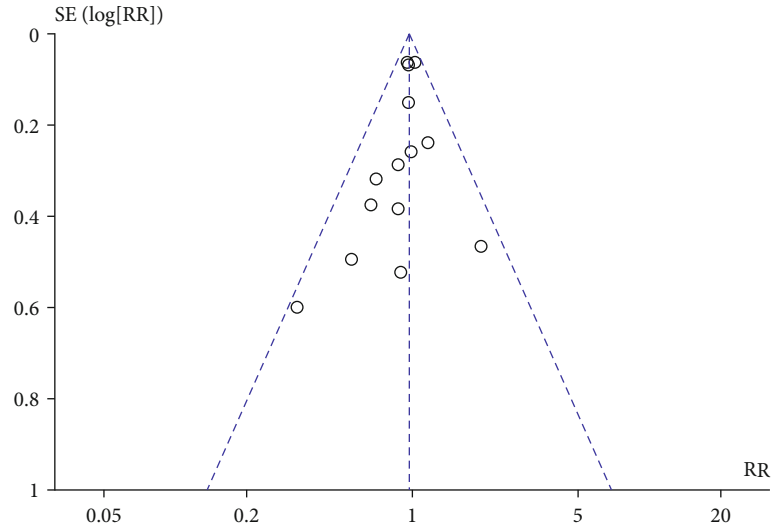

Figure 5: Funnel diagram: effect of prenatal perineal massage on 1-2 degree perineal tear.

was no heterogeneity between studies ($P = 0.94$, $I^2 = 0\%$) (Figure 14). Egger's test showed that there was no publication bias among the literatures ($P > 0.05$).

3.8. Fecal Incontinence. Compared with the control group, there was no significant difference in fecal incontinence at 3 months postpartum in the prenatal perineal massage group (RR = 0.75, 95% CI [0.51~1.11], $P = 0.15$) (Figure 15). There was no heterogeneity between studies ($P = 0.42$, $I^2 = 0\%$) (Figure 15). Egger's test showed that there was no publication bias among the literatures ($P > 0.05$).

4. Discussion

Although perineal injury, a common complication of vaginal delivery, is not life-threatening to both the mother, its associated symptoms such as perineal pain, urinary incontinence, fecal incontinence, and difficulty in sexual intercourse seriously affect the patient's physical and mental health [19]. In this meta-analysis, the authors found that prenatal perineal massage significantly reduced the incidence of perineal tears and episiotomy, especially for 3rd-4th degrees of perineal tears. In addition, prenatal perineal massage could significantly reduce the incidence of perineal pain 3 months after delivery. There was no significant

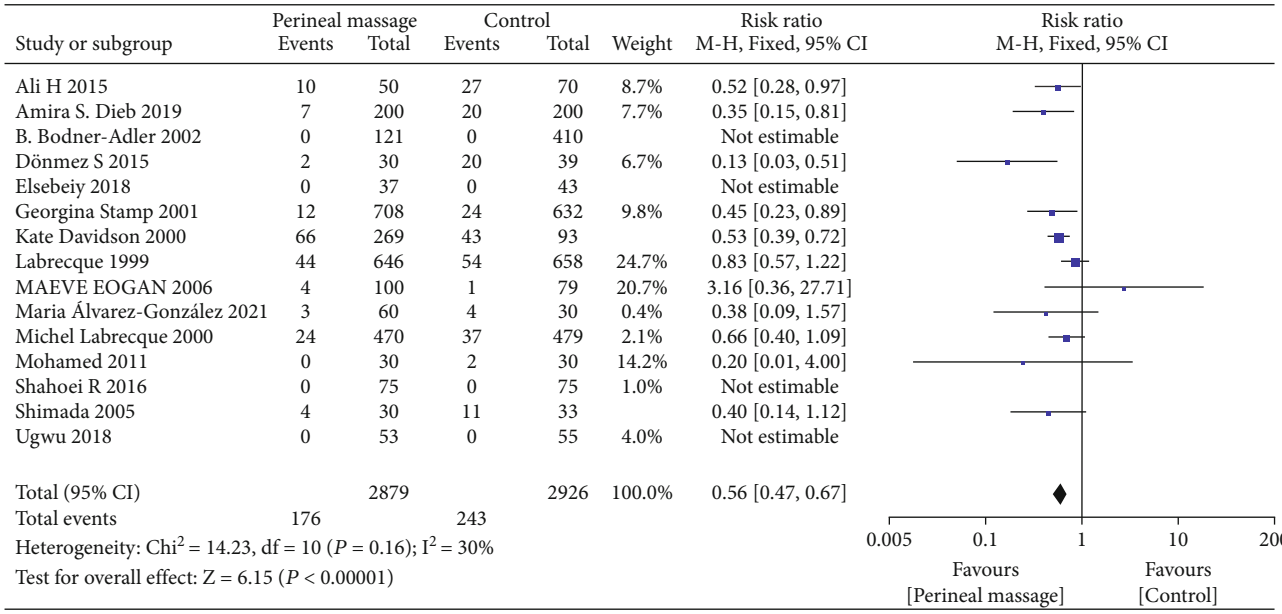

Figure 6: Forest map: effect of prenatal perineal massage on 3-4 degree perineal tear.

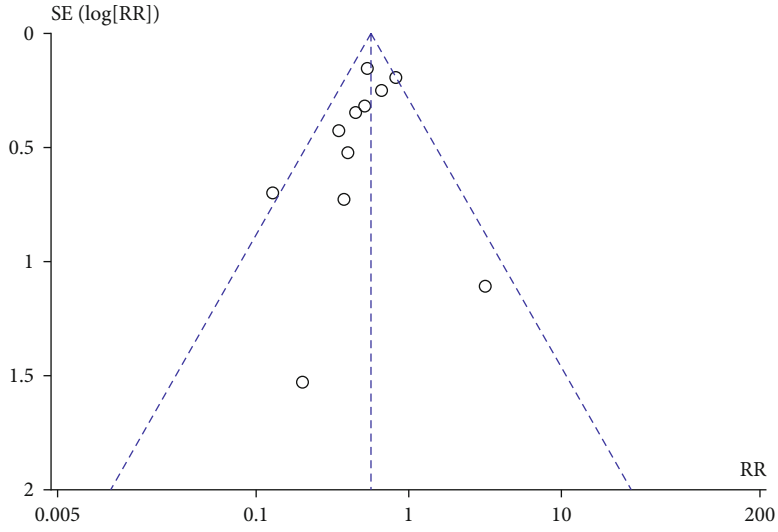

Figure 7: Funnel diagram: effect of prenatal perineal massage on 3-4 degree perineal tear.

difference in terms of incidence of vaginal delivery, perineal pain, urinary incontinence, and fecal incontinence between the prenatal perineal massage group and the control group.

Our study result is consistent with the previous studies [2, 20] that demonstrated that prenatal perineal massage can reduce the incidence of perineal tear and perineal incision. Furthermore, our study demonstrated the beneficial effect of prenatal perineal massage in reducing the risk of third- and fourth-degree perineal tears, which is consistent with that reported by Mohamed et al. [20]. However, in the systematic review of 2008 [21] and 2013 [2] by Beckmann et al., there was no difference in different degrees of perineal tear rate between prenatal perineal massage and the control group. This disparity might be explained by the fact that the study by Beckmann et al. only included 4 studies with a total of 2497 pregnant women, which is obviously much smaller in sample size as compared with the present study. Perineum incision during delivery is also a common cause of perineum injury. Our study showed that prenatal perineum massage could reduce the risk of perineum incision during delivery as compared with the control group, which is consistent with the results by Mohamed et al. and Beckmann et al. Moreover, Aquino et al. [22] even found that perineum massage during delivery could reduce the risk of perineum incision. Theoretically, perineal massage can

Study or subgroup	Perineal massage Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Ali H 2015	17	50	30	70	3.2%	0.79 [0.50, 1.27]
Amira S. Dieb 2019	59	200	77	200	9.9%	0.77 [0.58, 1.01]
B. Bodner-Adler 2002	37	121	111	410	6.5%	1.13 [0.83, 1.54]
Dönmez S 2015	25	39	39	39	5.1%	0.65 [0.51, 0.82]
Georgina Stamp 2001	176	708	170	632	23.3%	0.91 [0.76, 1.09]
Labrecque 1999	146	646	170	658	21.7%	0.87 [0.72, 1.06]
MAEVE EOGAN 2006	38	100	28	79	4.0%	1.07 [0.73, 1.58]
Michel Labrecque 2000	99	470	113	479	14.4%	0.89 [0.70, 1.13]
Mohamed 2011	5	30	8	30	1.0%	0.63 [0.23, 1.69]
Shahoei R 2016	40	75	43	75	5.5%	0.93 [0.70, 1.24]
Shimada 2005	4	30	11	33	1.3%	0.40 [0.14, 1.12]
Ugwu 2018	20	53	32	55	4.0%	0.65 [0.43, 0.98]
Total (95% CI)		2522		2751	100.0%	0.87 [0.80, 0.95]
Total events	666		832			

Heterogeneity: $Chi^2 = 15.94$, df = 11 ($P = 0.14$); $I^2 = 31\%$

Test for overall effect: Z = 3.19 ($P = 0.001$)

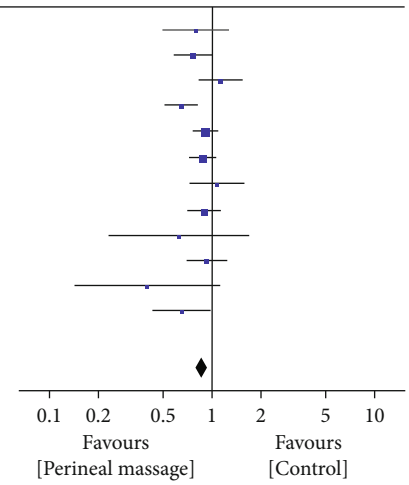

Figure 8: Forest map: effect of prenatal perineal massage on lateral episiotomy.

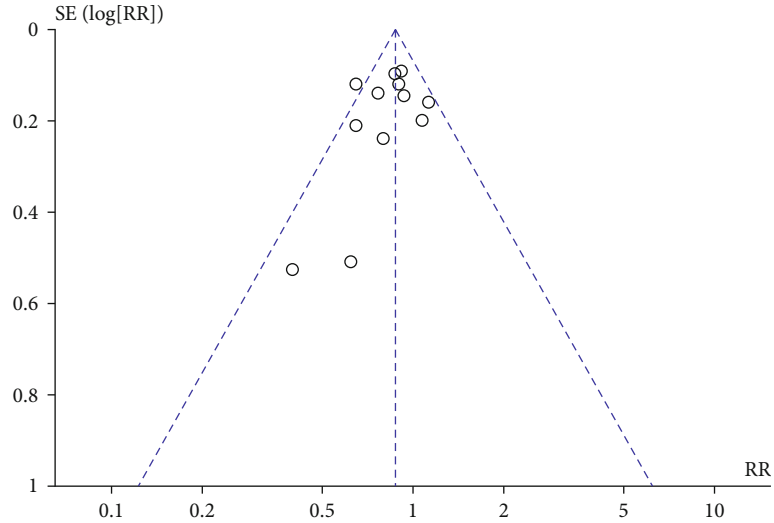

Figure 9: Funnel diagram: effect of prenatal perineal massage on lateral episiotomy.

Study or subgroup	Perineal massage Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
B. Bodner-Adler 2002	111	121	391	410	9.3%	0.96 [0.91, 1.02]
Georgina Stamp 2001	569	708	501	632	27.7%	1.01 [0.96, 1.07]
Labrecque 1999	495	763	516	759	27.1%	0.95 [0.89, 1.02]
M. K. Shipman 1997	217	332	207	350	10.6%	1.11 [0.98, 1.24]
MAEVE EOGAN 2006	68	100	50	79	2.9%	1.07 [0.87, 1.33]
Maria Álvarez-González 2021	52	60	20	30	1.4%	1.30 [0.99, 1.71]
Michel Labrecque 2000	335	470	347	479	18.0%	0.98 [0.91, 1.07]
Mohamed 2011	28	30	25	30	1.3%	1.12 [0.93, 1.35]
Ugwu 2018	35	53	31	55	1.6%	1.17 [0.87, 1.59]
Total (95% CI)		2637		2824	100.0%	1.01 [0.97, 1.04]
Total events	1910		2088			

Heterogeneity: $Chi^2 = 13.35$, df = 8 ($P = 0.10$); $I^2 = 40\%$

Test for overall effect: Z = 0.40 ($P = 0.69$)

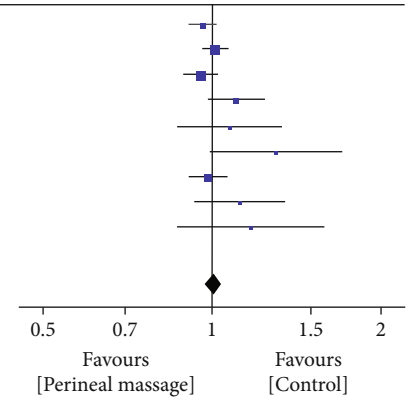

Figure 10: Forest map: effect of prenatal perineal massage on natural delivery.

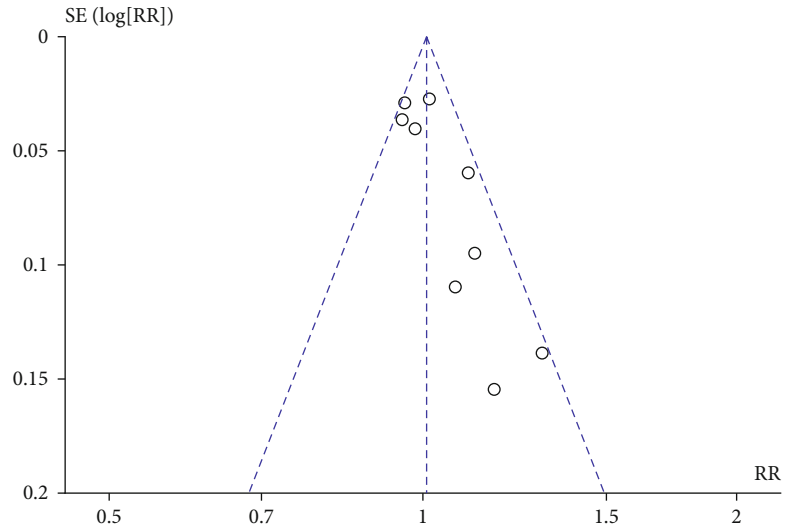

Figure 11: Funnel diagram: effect of prenatal perineal massage on natural delivery.

Study or subgroup	Perineal massage Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Georgina Stamp 2001	43	503	54	436	36.2%	0.69 [0.47, 1.01]
Michel Labrecque 2000	58	460	88	471	54.4%	0.67 [0.50, 0.92]
Shahoei R 2016	4	75	15	75	9.4%	0.27 [0.09, 0.77]
Total (95% CI)		1038		982	100.0%	0.64 [0.51, 0.81]
Total events	105		157			

Heterogeneity: $Chi^2 = 2.90$, df = 2 ($P = 0.23$); $I^2 = 31\%$

Test for overall effect: Z = 3.76 ($P = 0.0002$)

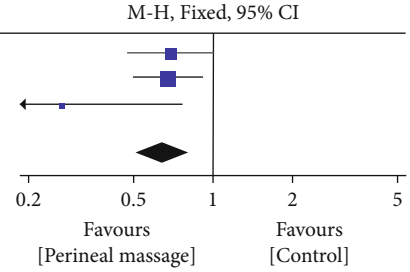

Figure 12: Forest map: effect of prenatal perineal massage on perineal pain 3 days after delivery.

Study or subgroup	Perineal massage Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Georgina Stamp 2001	416	597	359	499	62.7%	0.97 [0.90, 1.05]
MAEVE EOGAN 2006	72	100	55	79	9.8%	1.03 [0.86, 1.25]
Michel Labrecque 2000	179	459	174	473	27.5%	1.06 [0.90, 1.25]
Total (95% CI)		1156		1051	100.0%	1.00 [0.93, 1.07]
Total events	667		588			

Heterogeneity: $Chi^2 = 1.28$, df = 2 ($P = 0.53$); $I^2 = 0\%$

Test for overall effect: Z = 0.00 ($P = 1.00$)

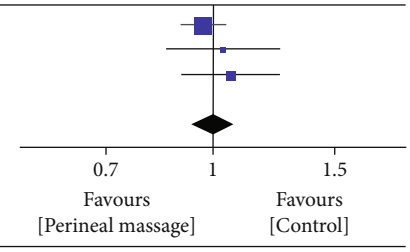

Figure 13: Forest map: effect of prenatal perineal massage on perineal pain 3 months postpartum.

Study or subgroup	Perineal massage Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Georgina Stamp 2001	123	503	115	436	43.3%	0.93 [0.74, 1.15]
Michel Labrecque 2000	138	470	157	479	54.6%	0.90 [0.74, 1.08]
Mohamed 2011	3	30	2	30	0.7%	1.50 [0.27, 8.34]
Ugwu 2018	3	48	4	50	1.4%	0.78 [0.18, 3.31]
Total (95% CI)		1051		995	100.0%	0.91 [0.79, 1.05]
Total events	267		278			

Heterogeneity: $Chi^2 = 0.42$, df = 3 ($P = 0.94$); $I^2 = 0\%$

Test for overall effect: Z = 1.27 ($P = 0.21$)

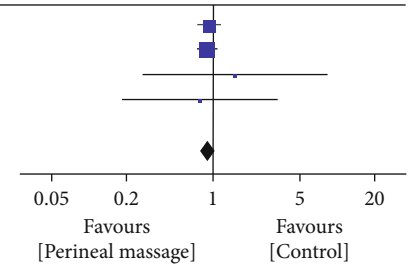

Figure 14: Forest map: effect of prenatal perineal massage on postpartum urinary incontinence.

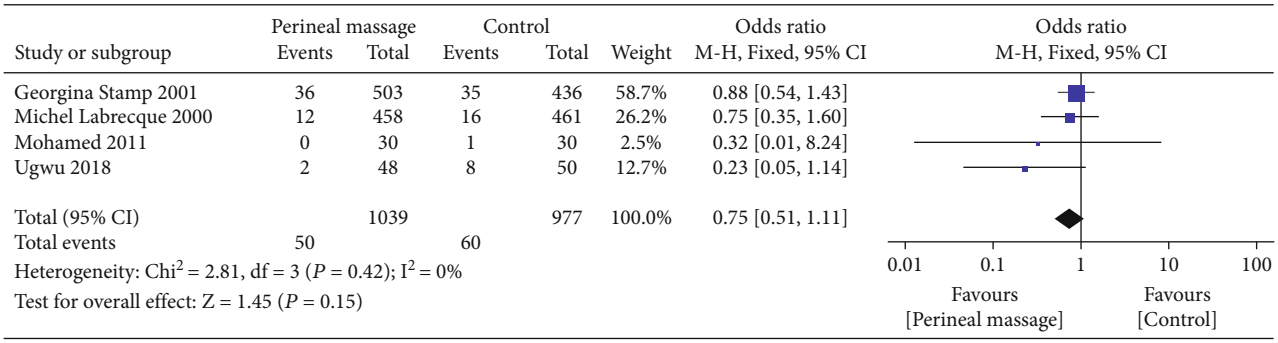

Figure 15: Forest map: effect of prenatal perineal massage on postpartum fecal incontinence.

stimulate skin nerve endings, promote tissue blood circulation, improve the elasticity and ductility of perineal tissue, reduce perineal incision, and improve perineal tear.

Perineal injury during childbirth leads to different complications for women, such as perineal pain. Then, we found that perineal massage could reduce the incidence of perineal pain at 3 months postpartum as compared with the control group. There was no significant difference in the incidence of perineal pain at 3 days postpartum. This is consistent with the results of Beckmann Michael and Stock Owen [2]. The decrease in perineal pain at 3 months postpartum may be related to the fact that prenatal perineal massage can reduce the incidence of perineal injury and perineal incision.

However, there were no significant differences between the two groups with regard to other secondary outcomes, such as the risk of urinary or fecal incontinence at 3 months postpartum and the incidence of spontaneous vaginal delivery. It may be due to the long follow-up time and women's self-esteem. Thus, the follow-up of urinary incontinence or fecal incontinence was difficult, and the data were incomplete. Of the 16 experiments in this study, only 4 reported urinary incontinence or fecal incontinence 3 months after delivery, and the number of samples was relatively small. In the study by Mohamed et al. [20] that analyzed only 3 experiments, prenatal perineal massage reduced the risk of anal incontinence (including fecal incontinence and gas incontinence) but did not reduce the risk of urinary incontinence. Given the relatively small sample size, we believe that additional investigations are entailed to explore the effect of perineal massage on urinary/fecal incontinence.

Reducing perineal injury caused by childbirth is pivotal for enhancing women's physical and mental health [19, 23]. According to our research, prenatal perineal massage can reduce the risk of perineal tear, especially the risk of 3^{rd} -4^{th} degree perineal tear. It can also reduce the risk of perineal incision during delivery and perineal pain 3 months after delivery. Previous studies have confirmed that prenatal perineal massage could benefit pregnant women [2, 8, 20]. However, factors like maternal self-esteem, obesity, and inconvenience make implementation of prenatal perineal massage difficult [24]. Studies have shown that [25] the application of smartphone Apps can better help pregnant women master and apply this helpful technology and enable pregnant women to adhere to the use of prenatal perineal massage from the 34th week of pregnancy to delivery. Obstetrics and gynecology medical staff can learn from this method, publicize and popularize this technology, and encourage and recommend pregnant women to have a prenatal perineal massage before 34 weeks of pregnancy.

The main advantages of this meta-analysis are based on clear definition, strict inclusion and exclusion criteria, a comprehensive retrieval strategy, and a large sample size. According to the retrieval, our research is the most and latest sample in this field. Our limitation is the relatively limited observation indicators included. For example, the effect of prenatal perineum massage on improving postpartum sexual satisfaction and the risk of urinary incontinence and fecal incontinence at 3 months after delivery needs to be further confirmed. These outcomes are directly related to the quality of life of patients and their families that entail continued investigations.

5. Conclusion

Antenatal perineal massage reduces the risk of perineal tears (especially 3^{rd}-4^{th} degree) during vaginal delivery, episiotomy, and perineal pain 3 months postpartum. Therefore, obstetrics and gynecology professionals should consider popularizing prenatal perineal massage.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Qiuxia Chen and Xiaocui Qiu contributed equally to this work.

Acknowledgments

The project was supported by the Hainan Province Clinical Medical Center.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 4977922, 9 pages
https://doi.org/10.1155/2022/4977922

Research Article

The Effect of Different Nutritional Nursing Support on the Nutritional Status and Disease Recovery of Elderly Patients with Gastrointestinal Tumors during the Perioperative Period

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Received 28 April 2022; Revised 12 June 2022; Accepted 16 June 2022; Published 29 June 2022

Academic Editor: Xi Lou

Objective. This study explored the effect of different nutritional nursing support on nutritional status, immune function, postoperative bowel motility, and complications in elderly patients with gastrointestinal tumors during the perioperative period. *Methods*. 300 patients with gastrointestinal tumors treated in the Department of Gastroenterology and anorectal surgery of Hangzhou First People's Hospital Affiliated with the Medical College of Zhejiang University from February 2018 to March 2020 were selected as the research objects in this study. Patients were divided into the early enteral nutrition (EEN) and total parenteral nutrition (TPN) groups (150 cases in each group) according to the principle of odd and even admission numbers. The patients in the EEN and TPN groups were given enteral nutrition nursing support and parenteral nutrition nursing support, respectively. The nutritional status, immune function, postoperative bowel motility, and complication rate of the two groups were evaluated 7 days after the operation. *Results*. The nutritional indexes decreased 3 days after the operation and gradually recovered 7 days after the operation in both groups with different nutritional nursing support. The Hb, TRF, PAB, and ALB indexes in the TPN group were significantly lower than those in the EEN group ($P < 0.01$). On the 7th day after the operation, the indexes of peripheral blood immunoglobulin (IgG, IgM, and IgA) were significantly lower than those in the TPN group, and T lymphocyte subsets (CD4, CD8, and CD4/CD8) demonstrated that the immunological indexes of patients in the EEN group were significantly higher than those in the TPN group ($P < 0.01$). In terms of intestinal peristalsis, the time of first exhaust and first defecation in the EEN group was significantly shorter than that in the TPN group ($P < 0.01$) during the perioperative period. Furthermore, both groups had different degrees of complications, while patients demonstrated a lower complication rate in the EEN group compared to those in the TPN group, suggesting a safer postoperative mode. The results of subgroup analysis showed that the nutritional indexes of the gastric cancer group 7 days after operation were significantly higher than those of the colorectal cancer group under EEN and TPN nutritional support modes. *Conclusion*. Clinical results have suggested that enteral nutrition nursing support can improve the perioperative nutritional status of elderly patients with gastrointestinal tumors by enhancing the immune function and promoting intestinal peristalsis. Meanwhile, the postoperative EEN mode reduces the rate of complications and demonstrates higher safety. Therefore, it has a high clinical application value.

1. Introduction

Gastrointestinal cancer is one of the incidence rates of malignant tumors. Gastrointestinal cancer leads to different effects on the digestive and metabolic functions of the body due to its relatively special location. Therefore, malnutrition and low immune function are commonly seen in gastrointestinal cancer patients, especially the elderly [1, 2]. Relevant studies have shown that postoperative malnutrition can lead to wound infection, abdominal infection, anastomotic fistula, pulmonary dysfunction, poor postoperative wound healing, and other complications [3, 4]. In addition, the stress caused by surgical treatment of gastrointestinal tumors can lead to systemic inflammatory reactions, which

severely impact the prognosis. Therefore, giving necessary early nutritional support and related nursing methods to patients with gastrointestinal tumors after the operation is of great significance to reduce the incidence of postoperative complications, enhance the body's resistance and immunity, improve the nutritional status of patients, and promote the early healing of postoperative incision [5, 6]. At present, total parenteral nutrition (TPN) and early enteral nutrition (EEN) are the two standard nutritional nursing support after gastrointestinal tumor operation. However, it is essential to explore how to minimize the burden and adverse reactions of the digestive tract and promote the effective absorption and utilization of nutrients during the process of nutritional nursing support. There were many studies on perioperative nutritional support for gastrointestinal tumors [7, 8]. The results illustrated that enteral nutrition support was more helpful than parenteral nutrition to improve the nutritional status and immune capacity of patients, thus reducing postoperative complications of the disease and improving patient outcomes. However, relevant studies are limited to older age groups and are mostly limited to random cross-sectional observations. This comparative study evaluates the effects of TPN and EEN nutritional nursing support in elderly patients with gastrointestinal tumors by examining perioperative nutritional status, immune function, postoperative bowel motility, and complications of patients during the perioperative period.

2. Materials and Methods

2.1. Objects and Groups. In this study, 300 elderly patients with gastrointestinal tumors treated in the Department of Gastrointestinal and Anal Surgery of Hangzhou First People's Hospital Affiliated with the Medical College of Zhejiang University from February 2018 to March 2020 were selected as the research objects. The flowchart is shown in Figure 1. All subjects were diagnosed with gastric cancer, colon cancer, and rectal cancer by pathological [9] examination and received radical surgical treatment. Patients were divided into the EEN and TPN groups (150 cases in each group) according to the single and double mantissa of admission numbers in this study. There was no significant difference in general data (such as gender, age, and tumor type) between the two groups ($P > 0.05$), which was in line with the conditions of the clinical control study. This study has been reported to the hospital ethics committee for review and approval. Inclusion criteria include (1) patients with primary gastrointestinal tumor confirmed by clinicopathological diagnosis; (2) patients receiving radical surgical treatment; (3) no serious organic lesions in the crucial organs and no other diseases such as blood, immunity, metabolism, and infectious diseases; (4) no mental disorder or cognitive impairment; (5) ability to well tolerate nutritional support methods used in this study and to complete the whole research process; and (6) voluntary participation of patients and their families in the study and signed informed consent when they knew the purpose, methods, and risks of the study. Exclusion criteria include (1) patients with malignant tumor metastasis or other types of tumor diseases, (2) patients receiving palliative resection, (3) complication of organic lesions of important organs, and (4) those who cannot stand the nutritional support approach adopted in the study or who cannot complete the whole research process.

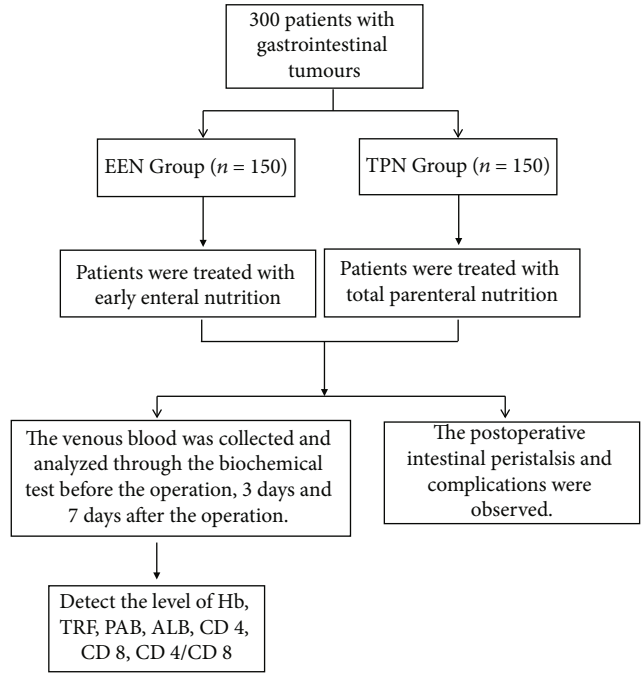

Figure 1: Flowchart of case grouping.

Table 1: Baseline characteristics of the two groups of patients.

Baseline data	EEN group ($n = 150$)	TPN group ($n = 150$)	t/χ^2	P
Age (years)	64.98 ± 4.65	64.66 ± 4.55	0.603	0.547
Gender (male/female)	81/69	83/67	0.054	0.817
Disease duration (years)	8.01 ± 1.99	8.13 ± 3.13	0.396	0.692
BMI (kg/m^2)	24.91 ± 1.74	25.03 ± 2.04	0.544	0.587
Tumor type				
Gastric cancer	63	64		
Colon cancer	54	51	0.152	0.927
Rectal cancer	33	35		

2.2. Nursing Methods. For the TPN group, patients in this group were treated with total parenteral nutrition. For the specific methods, on the first day after the operation, the nutrients required by the body, including glucose, electrolyte, compound amino acids, fat emulsion, water-soluble vitamins, fat-soluble vitamins, trace elements, and other nutrients, were prepared according to the doctor's advice and put into 3 L bags in an all-in-one form. Nutritional support was implemented by intravenous drip. The daily

Table 2: Statistical analysis of nutritional indexes of patients in the two groups before and after nutritional support ($n = 150$, $\bar{x} \pm s$).

(a)

Group	Hb (g/L)			TRF (g/L)		
	Before the operation	3 days after the operation	7 days after the operation	Before the operation	3 days after the operation	7 days after the operation
EEN group	113.3 ± 8.6	105.6 ± 7.7	121.1 ± 9.7	1.73 ± 0.41	1.67 ± 0.33	3.15 ± 0.42
TPN group	112.9 ± 8.8	100.7 ± 8.0	112.9 ± 9.3	1.74 ± 0.39	1.66 ± 0.30	2.12 ± 0.35
t	0.337	5.428	7.545	0.192	0.324	23.088
P	0.736	<0.001	<0.001	0.848	0.746	<0.001

(b)

Group	PAB (mg/L)			ALB (g/L)		
	Before the operation	3 days after the operation	7 days after the operation	Before the operation	3 days after the operation	7 days after the operation
EEN group	199.4 ± 47.0	179.1 ± 57.4	232.2 ± 58.6	29.7 ± 3.3	28.4 ± 3.1	39.0 ± 4.6
TPN group	190.8 ± 46.2	178.2 ± 61.1	201.2 ± 42.5	30.4 ± 3.1	28.1 ± 2.9	31.1 ± 3.0
t	1.605	0.136	5.247	1.740	0.821	17.617
P	0.110	0.892	<0.001	0.083	0.412	<0.001

nutrient supply should be controlled at 25-35 kcal/kg, and the daily infusion time should be controlled at 18 h~24 h. During the treatment, the proportion and amount of nutrients were reasonably adjusted according to the biochemical blood test results. All patients were given parenteral venous nutritional support for one week. After the operation, a liquid diet could be given transiently according to the recovery of gastrointestinal function. For the EEN group, the patients in this group were cared for by early enteral nutrition support. For the specific method, the nasal intestinal tube into the operation was placed, and the position should be able to reach about 25 cm below the trochanter ligament or jejunal output loop. On the first day after the operation, 250 mL of 9% normal saline was slowly input through the nasal intestinal tube. The dropping rate should be controlled at 20 mL/h. During enteral nutrition support, the vital signs of the patient should be closely observed. If the patient does not feel any discomfort, the dropping rate can be appropriately accelerated. On the second day after the operation, 200 mL enteral nutrition emulsion (provided by Huarui Pharmaceutical Co., Ltd., 200 mL/bottle, H20040722)+5% glucose solution can be given. The initial dropping rate should be controlled at 25 mL/h, and the maximum rate should be controlled within 125 mL/h according to the patient's tolerance every 12 h or 24 h. At the same time, a heater was used to maintain the temperature of the nutrient solution at 37-42°C to avoid causing gastrointestinal discomfort. During the nursing period, generally, the solution concentration was from low to high. The infusion and infusion speed were from slow to fast. The number of nutrient solutions for a single infusion was from less to more to strive to realize the acceptable nursing of patients. All patients were given continuous enteral nutrition support for one week, and a liquid diet could be given transiently according to the recovery of gastrointestinal function. The following matters should be paid attention to during enteral nutrition care: (1) The nasal and intestinal tubes were unobstructed and unblocked and washed regularly every day. The tubes were washed with 20 mL warm boiled water once every four hours and once every two hours if necessary. The tubes were sealed with 20 mL warm boiled water with positive pressure. (2) When the tube feeding operation was carried out, the action shall be accurate and gentle to avoid sliding out of the nasal intestinal tube; take good care of the nasal cavity, properly fix the catheter, and carefully check the depth of the catheter in each shift. (3) Pay attention to the principle of aseptic operation, keep the infusion pipeline and nutrient solution clean, and avoid pollution. (4) During the nursing operation of enteral nutrition, the bedside angle (30°~45°) should be raised appropriately to prevent adverse events such as esophageal reflux and aspiration. (5) Control the amount, temperature, and concentration of nutrient solution during infusion, and adjust to the appropriate infusion speed. (6) Observe the complications and the symptoms of diarrhea, abdominal distention, vomiting, and gastric retention. If there is any discomfort, deal with it in time. (7) For psychological intervention, patients with gastrointestinal cancer are prone to different degrees of adverse emotions (such as depression, irritability, and anxiety) due to physiological discomfort after the operation. During enteral

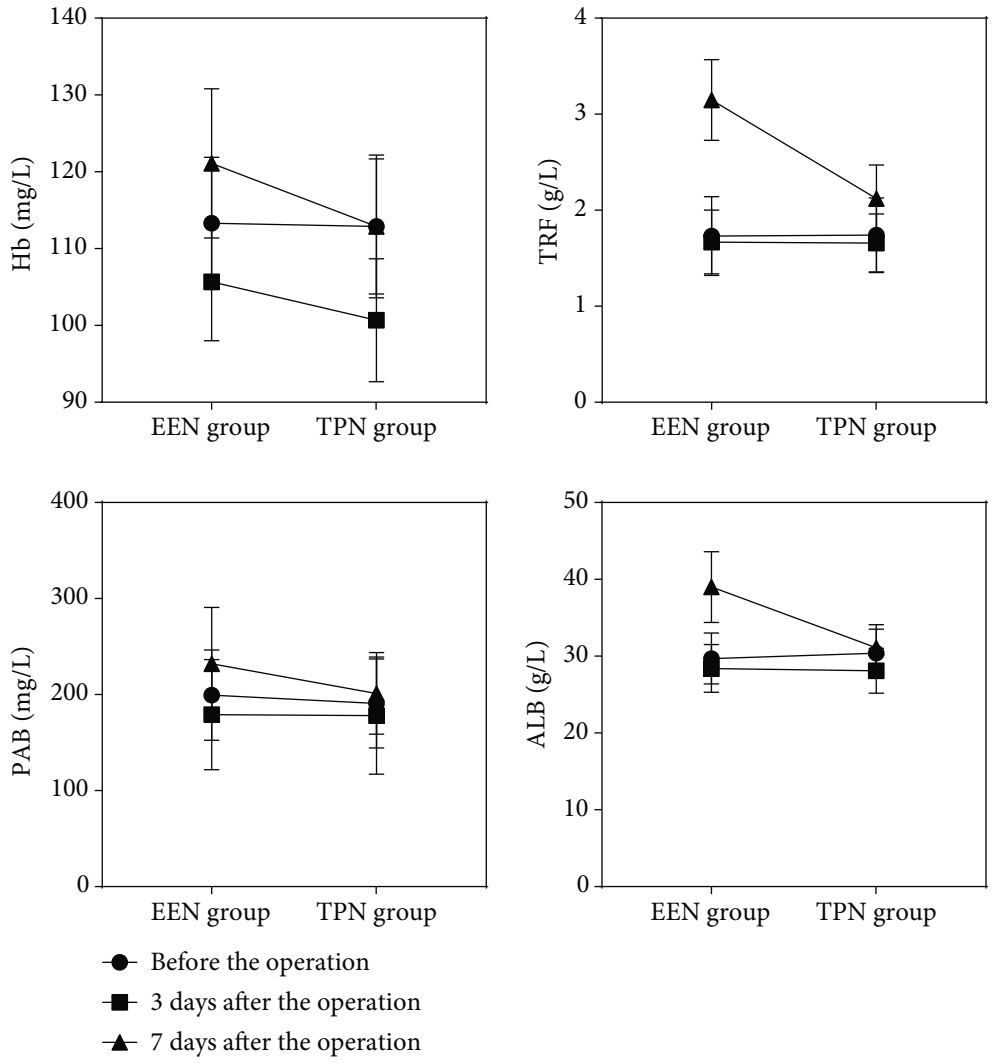

Figure 2: Nutritional indexes (Hb, TRF, PAB, and ALB) of the two groups. Hb of 3 and 7 days after the operation, TRF of 7 days after the operation, PAB of 7 days after the operation, and ALB of 7 days after the operation in the EEN group and the TPN group ($P < 0.001$); the rest of the differences were all $P > 0.05$.

Table 3: Statistical analysis of immune function indexes of patients in the two groups before and after nutritional support ($n = 150$, $\bar{x} \pm s$).

Group	Detection time	IgG (g/L)	IgM (g/L)	IgA (g/L)	CD4 (%)	CD8 (%)	CD4/CD8
EEN group	Before the operation	11.15 ± 2.29	1.97 ± 0.22	1.71 ± 0.34	37.19 ± 6.03	24.09 ± 9.68	1.96 ± 1.28
	7 days after the operation	16.84 ± 2.34	2.65 ± 0.52	2.80 ± 0.53	36.14 ± 2.64	28.37 ± 10.21	1.50 ± 0.77
TPN group	Before the operation	11.26 ± 2.31	1.88 ± 0.24	1.73 ± 0.40	36.89 ± 6.51	25.25 ± 8.22	1.72 ± 1.040
	7 days after the operation	13.80 ± 1.69	2.02 ± 0.77	2.02 ± 0.27	31.15 ± 4.46	22.17 ± 8.23	1.71 ± 1.04
t (before the operation)		0.421	3.407	0.487	0.406	1.116	1.866
P (before the operation)		0.674	0.001	0.627	0.685	0.266	0.063
t (7 days after the operation)		12.876	8.274	16.137	11.783	5.784	2.005
P (7 days after the operation)		<0.001	<0.001	<0.001	<0.001	<0.001	0.046

nutrition support, the placement of the nasal intestinal tube will lead to the patient's resistance. The nursing staff should explain in detail the significance, importance, and implementation method of enteral nutrition, explain that the nutrition tube is an important guarantee for the implementation of early enteral nutrition, actively dredge and appease

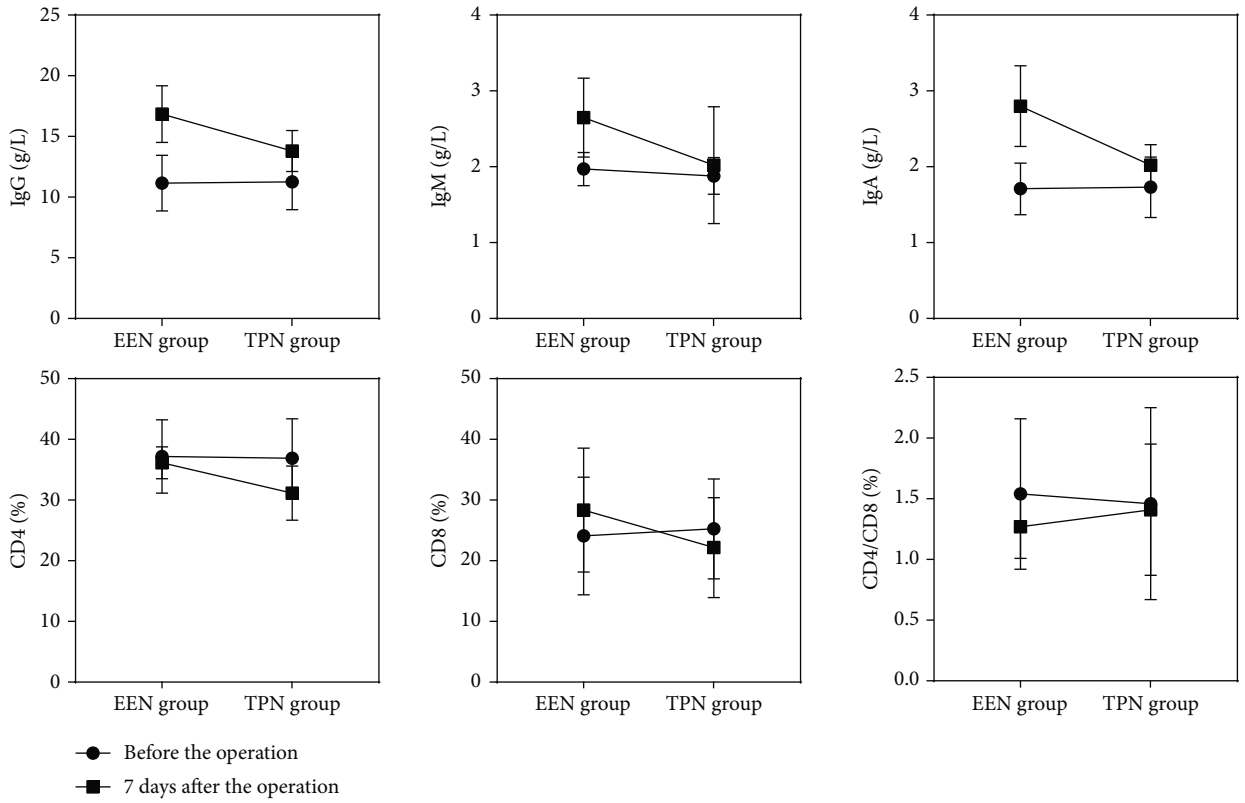

Figure 3: Immune function indexes (IgG, IgM, IGA, CD4, CD8, and CD4/CD8) of the two groups. Before the operation, the difference between the EEN group and the TPN group was $P > 0.05$, and the difference between the two groups at 7 days after operation was $P < 0.05$.

Table 4: Statistical analysis of intestinal peristalsis indexes of patients in the two groups after nutritional support ($n = 150$, $\bar{x} \pm s$, d).

Group	First postoperative exhaust time	First defecation time after operation
EEN group	2.12 ± 0.76	3.07 ± 0.81
TPN group	3.34 ± 0.89	5.36 ± 1.32
t	12.785	18.099
P	<0.001	<0.001

the patients, alleviate the patient's bad mood, and strengthen the patient's trust in the medical staff. It is helpful to improve the nursing compliance of patients.

2.3. Observation Index. The venous blood of the two groups was collected and analyzed through the biochemical test before the operation and 3 days and 7 days after the operation by the laboratory of our hospital. The levels of hemoglobin (Hb), transferrin (TRF), prealbumin (PAB), and serum albumin (ALB) at different stages were statistically analyzed. The venous blood of the two groups was taken before operation and 7 days after the operation to examine peripheral blood immunoglobulin (main indexes are IgG, IgM, and IgA) and T lymphocyte subsets (main indexes are CD4, CD8, and CD4/CD8). The postoperative bowel motility and complications of the two groups were observed.

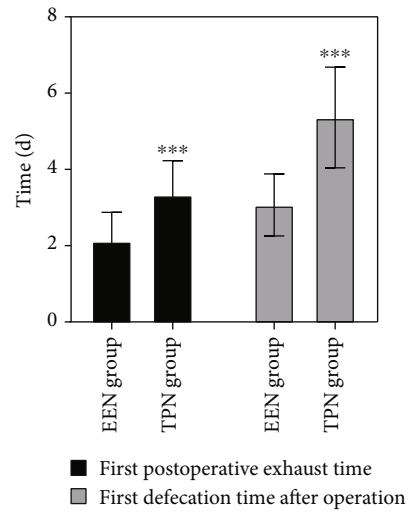

Figure 4: Intestinal peristalsis indexes of the two groups. Compared with the EEN group $^{***}P < 0.001$.

2.4. Statistical Analysis. All statistical data of this study were recorded in Excel form, and SPSS17.0 statistical software was

Table 5: Statistical analysis of complication indexes of patients in the two groups after nutritional support ($n = 150$, n (%)).

Group	Incision infection	Abdominal infection	Pneumonia	Anastomotic fistula	Stomach discomfort	Complication rate
EEN group	4 (2.67)	4 (2.67)	4 (2.67)	0	14 (9.33)	26 (17.34)
TPN group	13 (8.67)	8 (5.33)	9 (6)	15 (10)	22 (14.67)	67 (44.67)
χ^2	5.051	1.389	2.010	15.790	2.020	26.196
P	0.025	0.239	0.156	<0.001	0.155	<0.001

used for statistical analysis. Nutritional index, immunological index, intestinal peristalsis index, and other measurement data were expressed by $\bar{x} \pm s$, and the independent or paired t-test was performed for comparison. The counting data of postoperative complications were expressed in %, and the χ^2 test was performed. There was a significant difference in the statistical data of the evaluation results between the two groups, which was expressed as $P < 0.05/P < 0.01$.

3. Results

3.1. Baseline Characteristics of the Two Groups. There were 81 males and 69 females in the EEN group. The age range was 60-81 years, with an average age of 64.98 ± 4.65 years. The tumor types were 63 cases of gastric cancer, 54 cases of colon cancer, and 33 cases of rectal cancer. There are 83 males and 67 females in the TPN group. The age range was 60-79 years, with an average age of 64.66 ± 4.55 years. The tumor types were 64 cases of gastric cancer, 51 cases of colon cancer, and 35 cases of rectal cancer. There was no statistical difference in baseline data ($P > 0.05$) (see Table 1).

3.2. Nutritional Indexes of the Two Groups. Before the operation, there was no significant difference in Hb, TRF, PAB, and ALB results between the two groups ($P > 0.05$). Three days after giving different nutritional care support, the nutritional indexes of the two groups decreased, and the nutritional indexes gradually recovered seven days after the operation. However, the biochemical test results showed that the indexes of Hb, TRF, PAB, and ALB in the TPN group were significantly lower than those in the EEN group ($P < 0.01$), which showed that the postoperative nutritional status of the EEN group was significantly improved than that of the TPN group (see Table 2 and Figure 2 for the detailed statistical data).

3.3. Immune Function Indexes of the Two Groups. The immunological test showed that there was no significant difference in the indexes of peripheral blood immunoglobulin (IgG, IgM, and IGA) and T lymphocyte subsets (CD4, CD8, and CD4/CD8) between the two groups before the operation, and there was no significant difference between the two groups ($P > 0.05$). The test on the 7th day after the operation showed that the immunological indexes IgG, IgM, IgA, CD4, CD8, and CD4/CD8 of patients in the EEN group were significantly better than those in the TPN group. The comparison between groups was statistically significant ($P < 0.01$), which showed that the immune function of patients in the EEN group was better than that in the TPN group (see Table 3 and Figure 3 for detailed statistical data).

3.4. Intestinal Peristalsis Indexes of the Two Groups. Clinical observation showed that after different nutritional nursing support interventions, patients' first postoperative exhaust and first defecation time in the EEN group were significantly shorter than those in the TPN group. The comparison between groups was statistically significant ($P < 0.01$), which showed that patients' postoperative bowel motility effect in the EEN group was better than that in the TPN group (see Table 4 and Figure 4 for detailed data).

3.5. Indicators of Complications in the Two Groups. After the patients in the two groups were given different nutritional care support after the operation, there were various degrees of complications. Still, the complication rate of the patients in the EEN group was significantly lower than that in the TPN group. The comparison between the groups was statistically significant ($P < 0.01$), which showed that the safety of the postoperative EEN mode in patients with gastrointestinal tumors was significantly better than that in the TPN group (see Table 5 for the detailed data).

3.6. Comparison of Nutritional Indicators of Gastric and Colorectal Cancer in Subgroups of the Two Groups. In order to further clarify the effect of different nutritional support methods on malignant tumors in different parts, we divided the patients into two groups of gastric cancer and colorectal cancer for analysis. The results showed that after EEN support, Hb, TRF, PAB, and ALB in the gastric cancer group were significantly higher than those in the colorectal cancer group at 7 days after operation. After TPN support, Hb, PAB, and ALB in the gastric cancer group were significantly higher than those in the colorectal cancer group on the 7th day after operation (see Table 6 for details).

4. Discussion

Early postoperative enteral nutrition for patients with gastrointestinal tumors is mainly through the perfusion of nutrients through the pipeline. The intestine can selectively absorb nutrients, which can significantly prevent and improve the postoperative malnutrition of patients, effectively regulate the immune function of patients, and improve the inflammatory response, which is of great significance to reduce postoperative complications [10, 11]. Specific

Table 6: Comparison of nutritional indicators between the gastric cancer group and the colorectal cancer group of the two groups.

(a)

Group	Hb (g/L)			TRF (g/L)		
	Before the operation	3 days after the operation	7 days after the operation	Before the operation	3 days after the operation	7 days after the operation
Gastric cancer EEN group	112.6 ± 9.6	107.6 ± 7.0	123.6 ± 8.9	1.71 ± 0.46	1.65 ± 0.33	3.24 ± 0.40
Colorectal cancer EEN group	113.9 ± 7.5	103.8 ± 8.0	118.7 ± 9.9	1.76 ± 0.36	1.70 ± 0.33	3.06 ± 0.43
t	-0.858	3.080	3.176	-0.731	-0.929	2.680
P	0.391	0.003	0.002	0.464	0.355	0.008

(b)

Group	PAB (mg/L)			ALB (g/L)		
	Before the operation	3 days after the operation	7 days after the operation	Before the operation	3 days after the operation	7 days after the operation
Gastric cancer EEN group	202.4 ± 47.1	181.7 ± 61.2	247.6 ± 52.2	29.4 ± 3.7	28.6 ± 3.0	40.1 ± 4.1
Colorectal cancer EEN group	196.5 ± 47.0	176.6 ± 53.8	217.3 ± 60.8	30.0 ± 2.8	28.2 ± 3.2	38.0 ± 4.8
t	0.772	0.543	3.274	-1.041	0.733	2.914
P	0.441	0.587	0.001	0.298	0.465	0.004

(c)

Group	Hb (g/L)			TRF (g/L)		
	Before the operation	3 days after the operation	7 days after the operation	Before the operation	3 days after the operation	7 days after the operation
Gastric cancer EEN group	113.3 ± 7.7	101.4 ± 8.2	115.0 ± 9.1	1.78 ± 0.41	1.64 ± 0.28	2.16 ± 0.32
Colorectal cancer EEN group	112.5 ± 9.9	100.1 ± 7.8	110.7 ± 9.1	1.70 ± 0.36	1.67 ± 0.32	2.08 ± 0.38
t	0.592	1.052	2.888	1.271	-0.590	1.440
P	0.555	0.295	0.004	0.206	0.556	0.152

(d)

Group	PLB (g/L)			ALB (g/L)		
	Before the operation	3 days after the operation	7 days after the operation	Before the operation	3 days after the operation	7 days after the operation
Gastric cancer EEN group	188.1 ± 47.7	173.1 ± 63.2	210.8 ± 41.3	30.5 ± 3.2	27.9 ± 3.1	31.7 ± 2.9
Colorectal cancer EEN group	193.5 ± 44.8	183.3 ± 58.8	191.7 ± 41.8	30.3 ± 3.0	28.3 ± 2.6	30.6 ± 3.1
t	-0.721	-1.020	2.818	0.459	-0.816	2.318
P	0.472	0.309	0.005	0.647	0.416	0.022

nutrients can be perfused through EEN, which can play a certain pharmacological role and can be used as one of the later rehabilitation treatment methods. Enteral nutrition support can not only effectively stimulate the rapid secretion of digestive juice from the gastrointestinal tract, promote intestinal peristalsis, and increase the blood flow of visceral organs but also is more in line with human physiological processes [12]. Meanwhile, it retains the structure and function of intestinal mucosa to the greatest extent and protects the intestinal mucosal barrier, thus preventing or reducing

entheogenic infection [13]. Relevant studies [8, 14] showed that enteral nutrition was of great significance for improving nutritional status and immunity.

The results showed that the postoperative indexes of Hb, TRF, PAB, and ALB in the EEN group were significantly better than those in the TPN group. The immunological indexes of IgG, IgM, IgA, CD4, CD8, and CD4/CD8 in the EEN group were significantly better than those in the TPN group, the first postoperative exhaust and first defecation time in the EEN group were significantly shorter than those in the TPN group, and the complication rate in the EEN group was significantly lower than that in the TPN group. Studies [15, 16] reported that giving reasonable and effective nutritional nursing support to patients with gastrointestinal tumors after the operation can significantly improve their nutritional status. In the study on the recovery of gastrointestinal mucosal immune function, Becker and others [17] suggested that enteral nutrition support could effectively promote S-IgA secretion in intestinal mucosa after gastric cancer surgery, increasing the immune barrier effect of the intestinal mucosa. In addition, nutrients can change the immune status of the body by affecting the secretion of antibodies and cytokines by immune effector cells [18]. In this study, the postoperative immune globulin levels in the EEN group were significantly higher than those in the TPN group, suggesting that enteral nutrition can better improve the immune status of patients and reduce complications such as infection, which is similar to the previous report [19]. In addition, Chen et al. [20] confirmed that the presence of an appropriate amount of arginine and other immune enhancers in enteral nutrition solutions can promote the postoperative rehabilitation of patients. Studies [21, 22] showed that enteral nutrition support for patients with gastric cancer after the operation could significantly reduce the rate of postoperative complications, especially in abdominal abscess, anastomotic fistula, and mortality, and significantly shorten the length of hospital stay. Besides, it is important to pay attention to psychological counselling which can stabilize the patient's mood, eliminate concerns, and make them actively cooperate with the treatment. The recovery of postoperative intestinal function can be promoted by adjusting the temperature and infusion speed of nutrient solution. The prevention of complications can speed up the rehabilitation process of the disease. The results of subgroup analysis showed that the nutritional indexes of the gastric cancer group 7 days after operation were significantly higher than those of the colorectal cancer group under EEN and TPN nutritional support modes, suggesting that nutritional support had a better effect on postoperative nutritional recovery of gastric cancer patients.

In conclusion, enteral nutrition nursing support can improve the perioperative nutritional status of elderly patients with gastrointestinal tumors by improving the immune function and promoting intestinal peristalsis. The reduction in the complication rate and high safety suggest that enteral nutrition nursing support has a significant value in clinical application. In clinical practice, the choice of enteral/parenteral nutrition for some patients needs to be determined according to the condition, which cannot be completely randomized. Therefore, prospective, multicenter, and fully randomized studies are needed to confirm this conclusion in the future.

Data Availability

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

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This work was supported by the general project of education and teaching reform of Zhejiang University of traditional Chinese medicine in 2020 (XT20006).

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 5759233, 12 pages
https://doi.org/10.1155/2022/5759233

Research Article

Efficacy and Safety Evaluation of Intramedullary Nail and Locking Compression Plate in the Treatment of Humeral Shaft Fractures: A Systematic Review and Meta-analysis

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Received 17 May 2022; Accepted 16 June 2022; Published 28 June 2022

Academic Editor: Xi Lou

Objective. The surgical treatment scheme of humeral shaft fracture is still controversial with no consensus reached. This meta-analysis was aimed at comparing the efficacy and safety of intramedullary nail (IMN) and locking compression plate (LCP) in the treatment of humeral shaft fractures. *Methods*. PubMed, Medline, Embase, Ovid, Cochrane Library, ISI Web of Science, Clinical Trials, and Chinese databases, including China National Knowledge Infrastructure Project, Wanfang database, and China biomedical abstracts database, were used to search the literature. Review Manager software was employed for statistical analysis and establishing forest and funnel maps. Categorical variables were measured by relative risk (RR), and standardized mean difference (SMD) was used to measure continuous variables. 95% confidence intervals were used for each variable. The modified Jadad scale, Newcastle-Ottawa scale, and Cochrane's bias risk tools were used to evaluate the bias and risk of eligible studies. *Results*. A total of 14 studies were included in the analysis with a total of 903 patients with humeral shaft fracture. Significant differences with regard to operation time (Std = −1.18, 95% CI: -2.14, -0.22, $Z = 2.41$, $P = 0.02$), blood loss (Std = −2.97, 95% CI: -4.32, -1.63, $Z = 4.34$, $P < 0.001$), and postoperative infection rate (RR = 0.32, 95% CI: -0.15, 0.68, $Z = 2.98$, $P = 0.003$) were noted between the IMN group and LCP group. In addition, the American Shoulder and Elbow Surgeon (ASES) score (Std = −0.22, 95% CI: -0.44, 0.01, $Z = 2.08$, $P = 0.04$) and the rate of shoulder and elbow function limitation (RR = 1.88, 95% CI: 1.06, 3.33, $Z = 2.17$, $P = 0.03$) between the 2 groups were also statistically significant. There were no significant differences in the rate of radial nerve injury, nonunion, delayed healing, and secondary operation between the two groups. *Conclusion*. IMN is superior than the LCP in terms of the operation time, intraoperative bleeding, and postoperative infection, suggesting its superiority in the humeral shaft fracture fixation. However, IMN is inferior to LCP in ASES score and shoulder elbow function limitation rate, indicating poor early postoperative functional recovery. More studies are required to evaluate and analyze the clinical efficacy between IMN and LCP regarding long-term function after artificial graft removal.

1. Introduction

Humeral shaft fractures are common in adult fractures, accounting for about 3% of all adult fracture types [1]. Controversies still exist about whether surgical intervention is needed for humeral shaft fractures. Surgical treatment is generally recommended for fractures with large displacement angles, multiple fractures, comminuted fractures, and fractures complicated with vascular and nerve injury [2, 3]. However, the failure rate and complications of the traditional plate and screw incision and internal fixation are high [4]. With the continuous improvement of surgical techniques and internal fixation implants, intramedullary nails (IMN) and locking compression plates (LCP) are widely

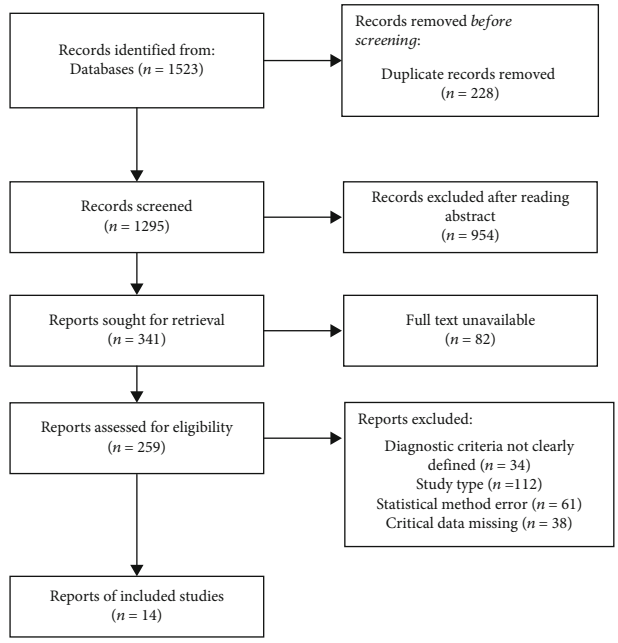


Figure 1: Flow chart of literature screening.

Table 1: Basic characteristics and document quality scores of included documents.

Study	Study design	Study assessment scale	IMN amounts	LCP amounts	Total amounts
Akalın et al. [11]	RCT	6	30	33	63
Bisaccia et al. [8]	CCT	7	26	32	58
Zhao et al. [7]	CCT	8	59	63	122
Fan et al. [2]	RCT	4	30	30	60
Zhang et al. [12]	RCT	4	50	50	100
Wali et al. [13]	RCT	4	25	25	50
Wang et al. [14]	RCT	4	22	23	45
Chaudhary et al. [15]	RCT	6	50	50	100
Li et al. [16]	RCT	4	22	23	45
Singisetti et al. [17]	RCT	5	25	20	45
Putti et al. [18]	RCT	4	16	18	34
Changulani et al. [19]	RCT	5	23	24	47
Mccormack et al. [20]	RCT	4	21	23	44
Chapman et al. [21]	RCT	4	38	46	84

RCT: randomized controlled trial; CCT: controlled clinical trial; study assessment scale: RCT study uses the modified Jadad scale; CCT study uses Newcastle-Ottawa scale.

used in the internal fixation of humeral shaft fractures with studies showing favorable clinical efficacy in both [5].

Several studies have compared the clinical efficacy of LCP and IMN with inconsistent results [6–8]. In addition, previous studies were limited by small study sample, suboptimal study quality, and inclusion of remote studies. The postoperative functional recovery results of this study were evaluated by the American Shoulder and Elbow Surgeon (ASES) score [9]. This study systematically assessed and meta-analyzed the literature on the efficacy of IMN and LCP in the treatment of humeral shaft fractures published in recent 20 years to better evaluate and compare the efficacy of these two schemes and provide a theoretical basis for clinical decision-making.

2. Materials and Methods

2.1. Literature Retrieval Strategy. Three independent researchers selected the database for literature retrieval following the principle of Cochrane. A total of 8 databases, including PubMed, Medline, Embase, Ovid, Cochrane Library, ISI Web of Science, Clinical Trials and China National Knowledge Infrastructure Project, Wanfang database, and China biomedical abstracts database, were employed for literature retrieval.

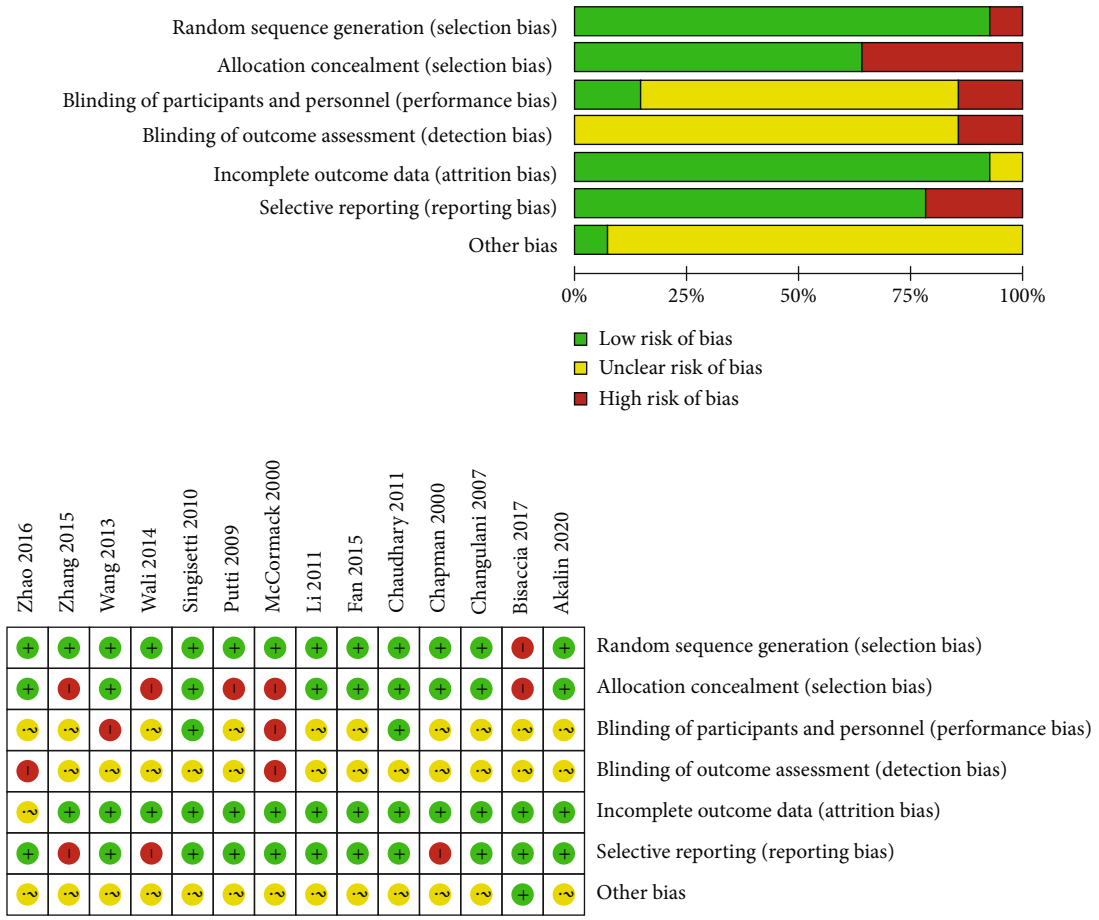
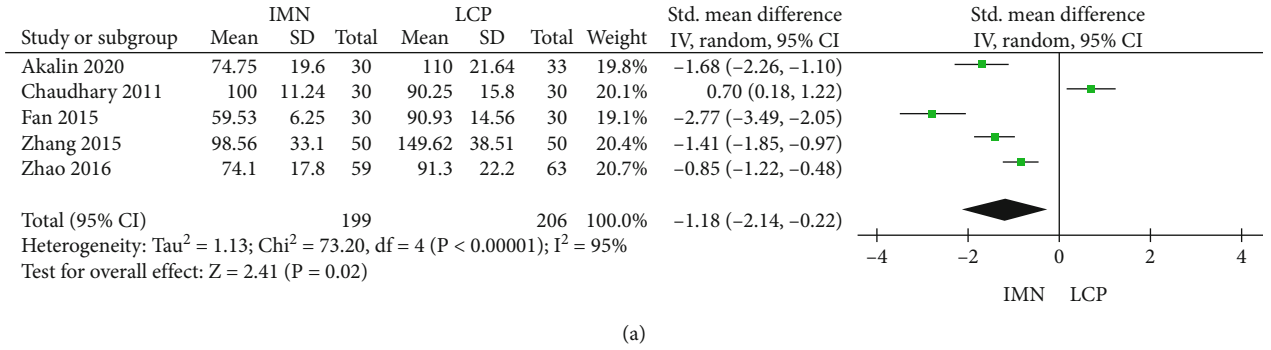
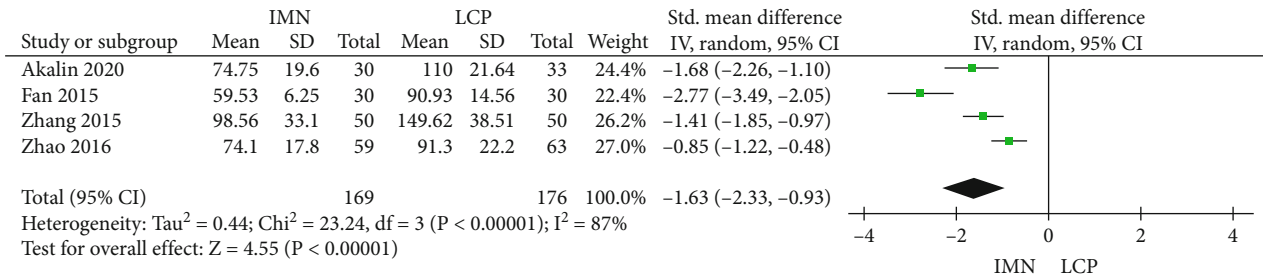


Figure 2: Quality of research methodology and risk assessment of bias included in the literature.



(a)



(b)

Figure 3: Meta-analysis forest of operation time. (a) Meta-analysis forest of operation time in the IMN group and LCP group. (b) Meta-analysis forest of operation time in the IMN and LCP groups in recent ten years.

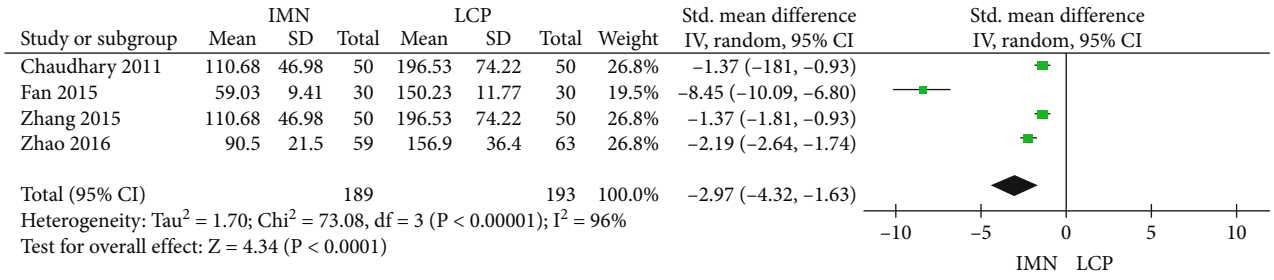


Figure 4: Meta-analysis of intraoperative blood loss in the IMN group and LCP group.

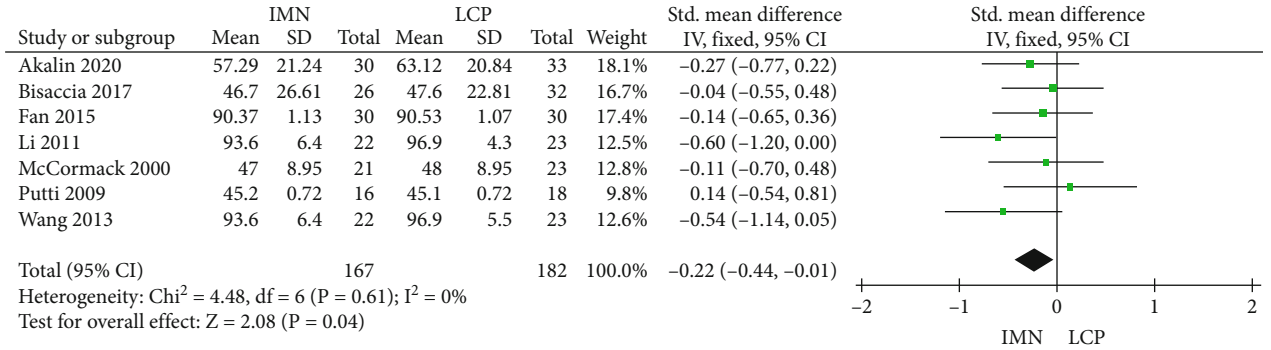


Figure 5: Meta-analysis of ASES scores in the IMN group and LCP group. (a) Forest figure. (b) Funnel figure.

The search terms, including "humeral shaft", "humeral diaphyseal", "humeral diaphysis", "intramedullary nail", and "plate", were used individually or in combination. Any differences were settled through consultation and discussion.

2.2. Literature Selection. The inclusion criteria were as follows: (1) randomized controlled experimental studies or case-control studies published in 2000 or later; (2) LCP or IMN were used to treat humeral shaft fractures; (3) modified Jadad scale score ≥ 4 for randomized controlled trials or the Newcastle Ottawa mean scale (NOS) score ≥ 7 for case-control studies; (4) age ≥ 18 years; (5) the clinical data of patients are complete; and (6) there are corresponding data in the literature to calculate RR and STD values.

The exclusion criteria were as follows: (1) the types of literature were review, systematic evaluation, meta-analysis,

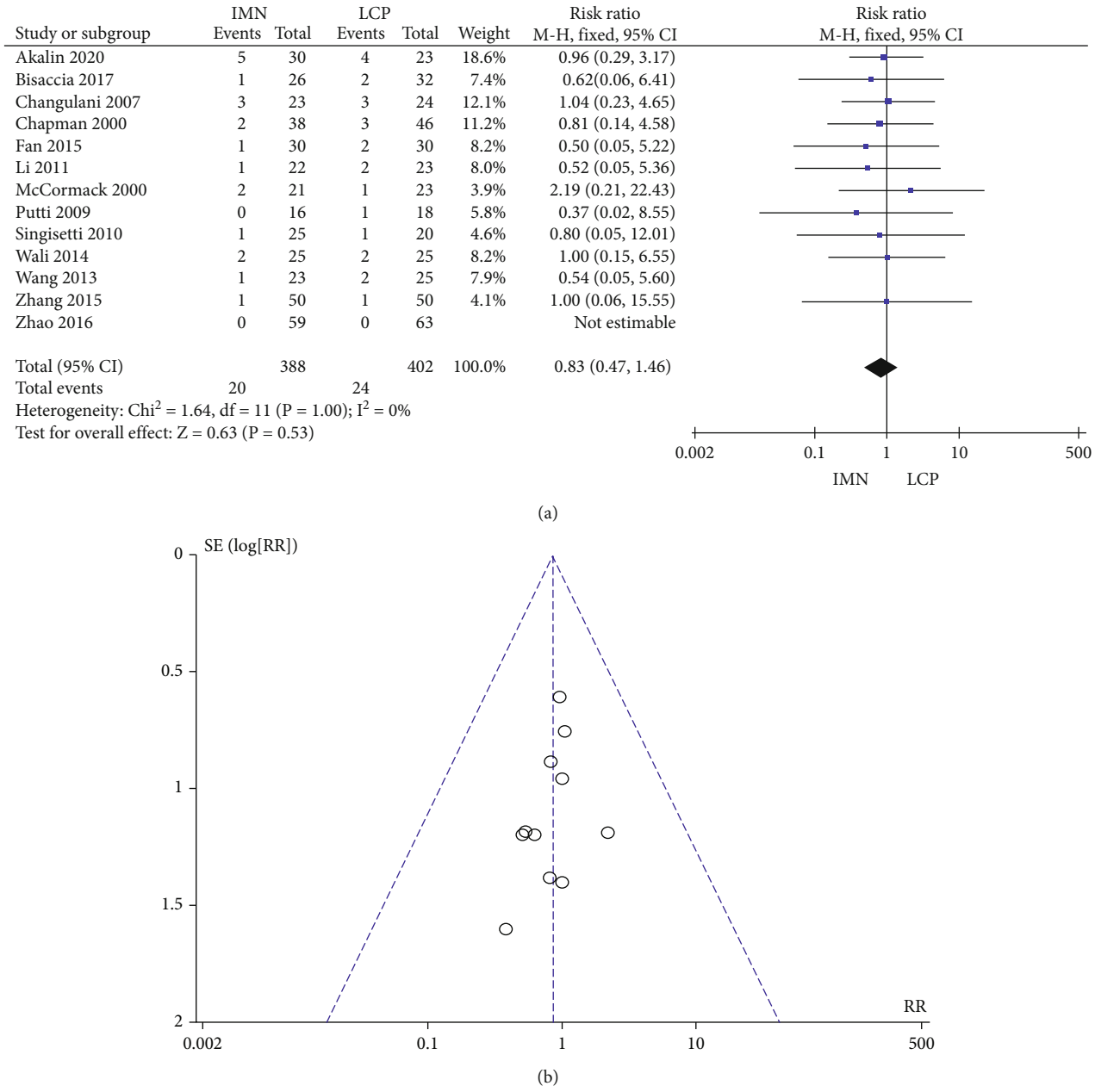


Figure 6: Meta-analysis of the incidence of bone nonunion in the IMN group and LCP group. (a) Forest figure. (b) Funnel figure.

case report, or editorial; (2) inclusion of patients <18 years old; and (3) nonprimary humeral shaft fractures, such as pathological fractures and old fractures after bone nonunion.

2.3. Data Extraction. In this study, two researchers independently extracted and screened data meeting the inclusion criteria for basic information and data extraction. The extracted data and characteristics included the following: literature title, first author, publication year, intervention measures, number of cases, operation time, intraoperative blood loss, complications, and ASES score. Data were extracted based on a broad selection of primary and secondary clinical outcomes from the literature included in this article. The third researcher checked the information and proofread the data to ensure the accuracy of the collected data.

2.4. Quality Evaluation. The modified Jadad scale, NOS, and Cochrane's bias risk tools were used to evaluate the bias and risk of eligible studies, as previously reported [10]. Study quality was evaluated with the modified Jadad scale that provides a semiquantitative rating from low quality (1-3 points) to high quality (4-7 points) based on summative score of 4 items, namely, randomization (2 points), concealment (2 points), blinding method (2 points), and withdrawal and dropouts (1 point). Similarly, the NOS scoring system had a total of 9 points, including selection of subjects (4 points),

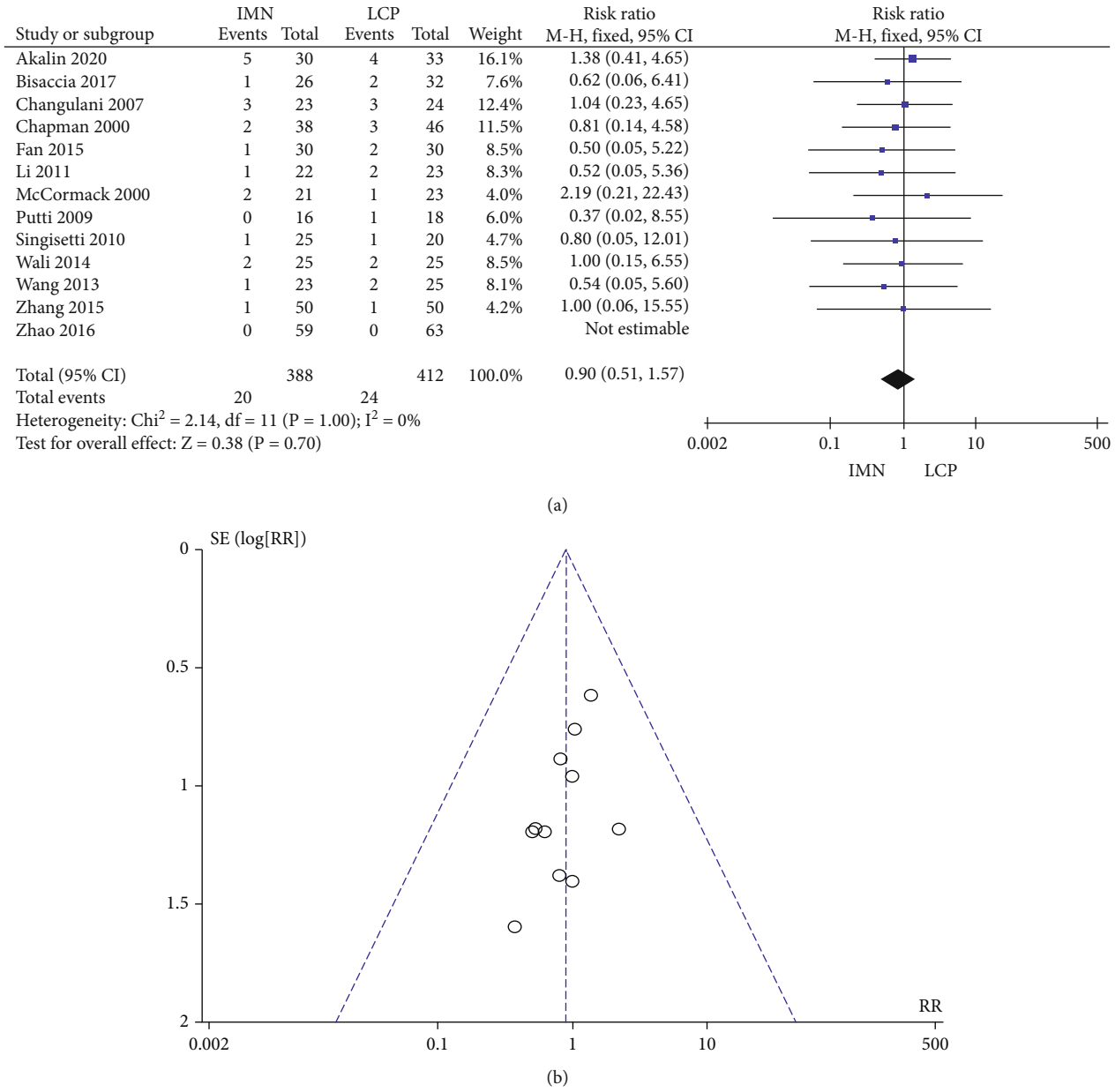


Figure 7: Meta-analysis of the incidence of radial nerve injury in the IMN group and LCP group. (a) Forest figure. (b) Funnel figure.

the comparability (2 points), and the measurement of exposure factors (3 points). The risk bias map was generated using Cochrane's bias risk tool.

2.5. Statistical Analysis. Review Manager software (version 5.4 of the Nordic Cochrane Centre, Copenhagen, Denmark) was used for statistical analysis and generation of the forest map and funnel map. Categorical variables were measured by relative risk (RR), and standardized mean difference (SMD) was used to measure continuous variables. 95% confidence intervals were used for each variable. Meta-analysis was conducted on the data included in the literature. The studies with clinical heterogeneity, which was assessed with the chi-square test and inconsistency index statistic (I^2), were divided into subgroups. The test standard was $I^2 < 50\%$, $P > 0.05$. The fixed-effect model was used when the heterogeneity was low ($I^2 < 50\%$, $P > 0.05$). Otherwise, the random effect model was adopted. When I^2 was inconsistent with the P value, the P value was used as the standard for selecting the processing model. A $P < 0.05$ denoted statistical significance.

3. Results

3.1. Search Results and Literature Quality Evaluation. The process of literature search and screening is shown in Figure 1. This study retrieved 1523 literature on IMN and plate internal fixation of humeral shaft fractures from the database. After screening according to the inclusion and exclusion criteria, 14 literatures were included in the analysis with a total of 903 patients, including 437 patients treated

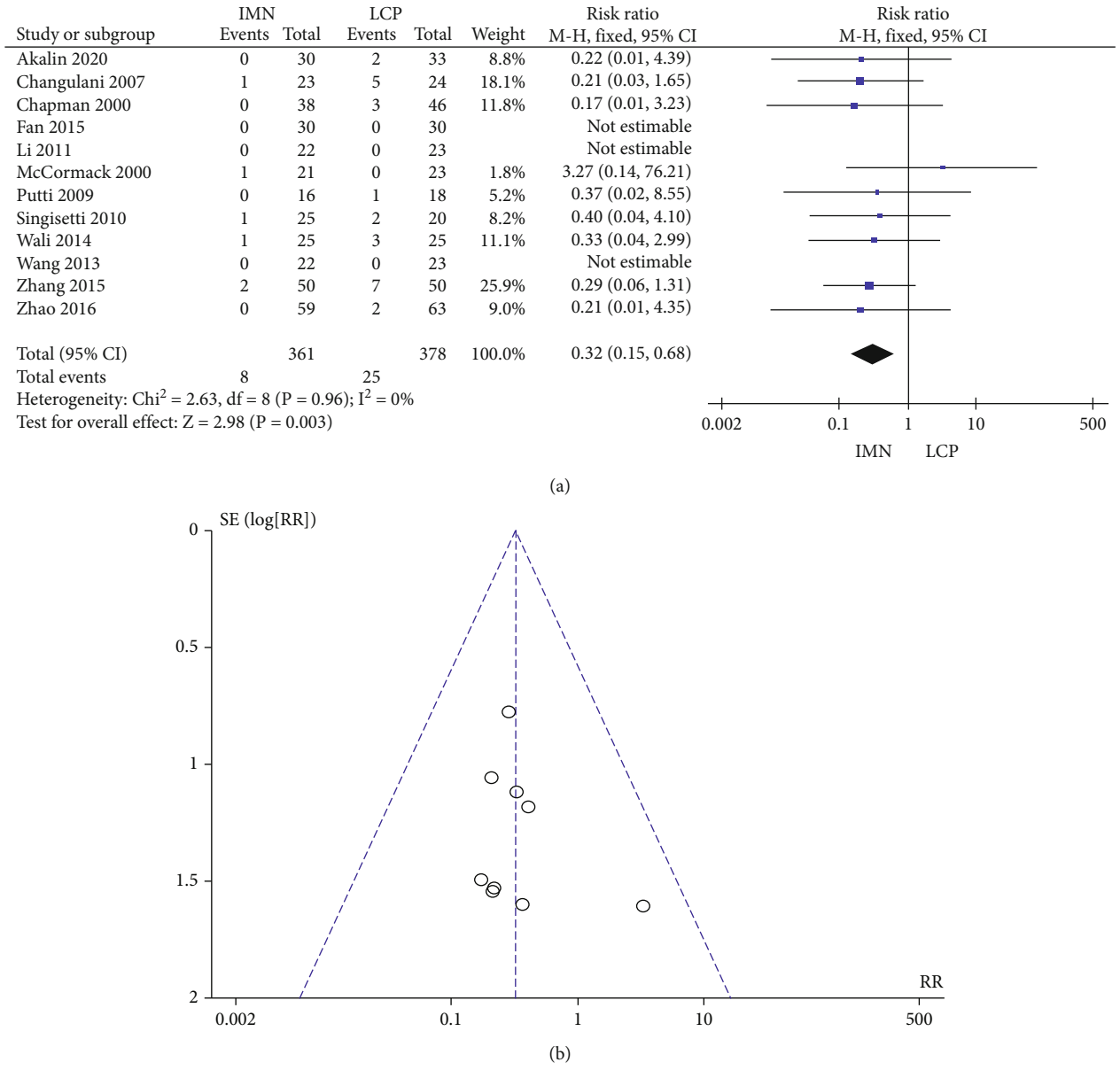


Figure 8: Meta-analysis of postoperative infection rate in the IMN group and LCP group. (a) Forest figure. (b) Funnel figure.

with IMN and 466 with LCP. Study quality is summarized in Table 1, and the risk bias diagram and summary are presented in Figure 2. A total of 12 RCT and 2 controlled clinical trials (CCT) were included in this study.

3.2. Operation Time. A total of 5 literature reported the operation time, and there was significant heterogeneity among the literature ($P < 0.001$, $I^2 = 95\%$). Therefore, a random-effect model was used. The combined Std, 95% CI, and effect amount Z were -1.18, (-2.14–0.22), and 2.41 ($P = 0.02$), respectively. As shown in Figure 3(a), the operation time of the IMN group was significantly shorter than that of the LCP group. Considering the large heterogeneity, the literature was screened for the latest 10 years and analyzed again. There was still significant heterogeneity among the literature ($P < 0.001$, $I^2 = 87\%$); thus, the random-effect model was used. The combined Std value, 95% CI, and combined effect amount Z were -1.63, -2.33–0.93, and 4.55 ($P < 0.001$), respectively. The operation time in the IMN group was shorter than that in the LCP group in recent ten years (Figure 3(b)).

3.3. Intraoperative Blood Loss. Four studies reported intraoperative blood loss, and there was significant heterogeneity among the literature ($P < 0.001$, $I^2 = 96\%$). The combined Std value was -2.97, 95% CI was (-4.32, -1.63), and the combined effect amount Z was 4.34 ($P < 0.001$). The results showed that the intraoperative blood loss in the IMN group was less than that in the LCP group (Figure 4).

3.4. American Shoulder and Elbow Surgeon (ASES) Score. Seven studies reported the ASES score, and no significant

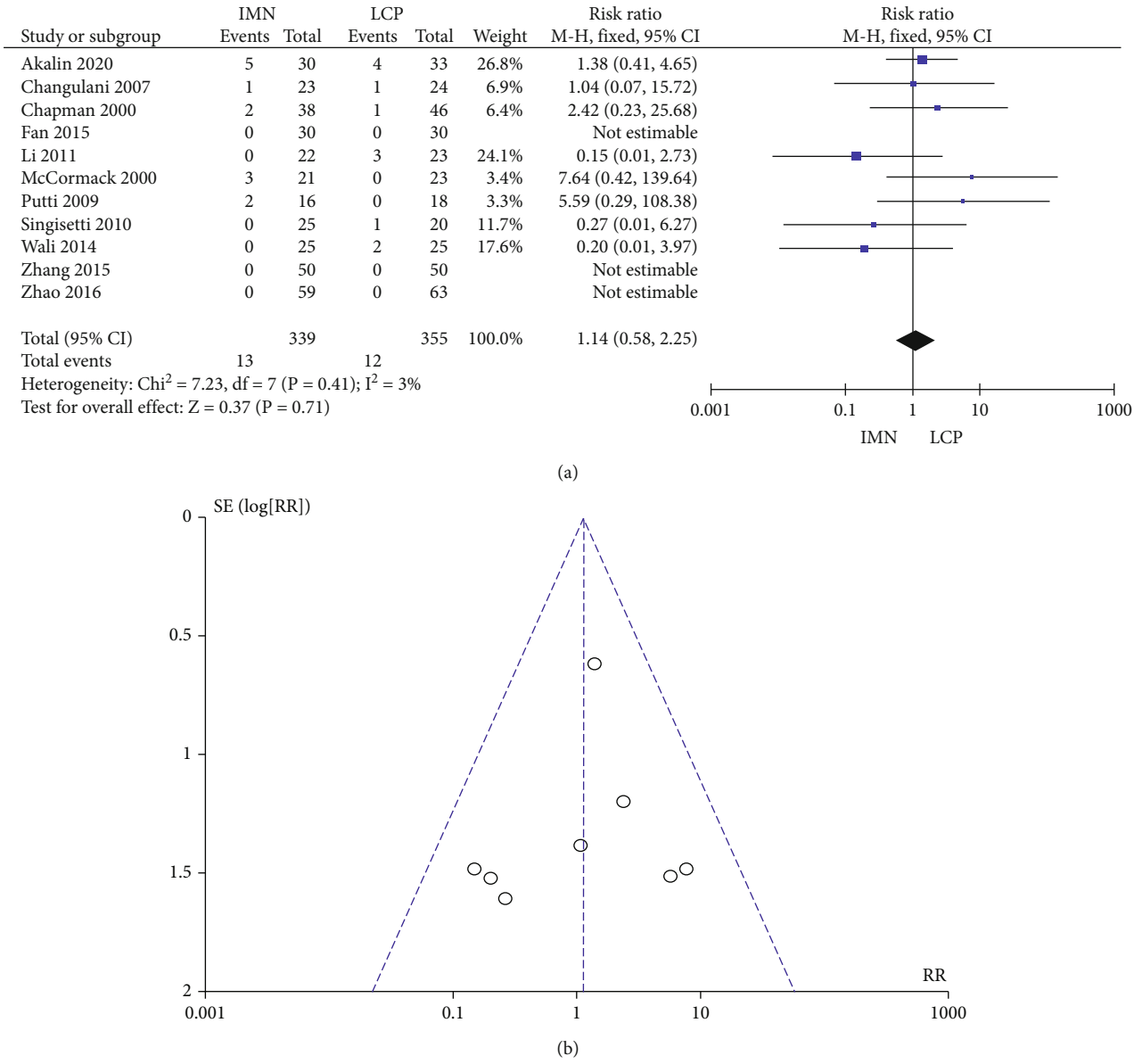


Figure 9: Meta-analysis of the incidence of secondary surgery in the IMN group and LCP group. (a) Forest figure. (b) Funnel figure.

heterogeneity was found among the literature ($P = 0.61$, $I^2 = 0\%$). The combined Std value was -0.22, 95% CI was (-0.44, 0.01), and the combined effect amount Z was 2.08 ($P = 0.04$). The ASES score of the IMN group was statistically lower than that of the LCP group (Figure 5(a)). Begg's test showed no publication bias, as shown in Figure 5(b).

3.5. Incidence of Nonunion. The incidence of bone nonunion was reported in 13 studies with no significant heterogeneity ($P = 1.00$, $I^2 = 0\%$). The combined RR value was 0.83, 95% CI was (0.47, 1.46), and the combined effect amount Z was 0.63 ($P = 0.53$). No significant difference in the incidence of bone nonunion between the two groups was noted (Figure 6(a)). Begg's test showed no publication bias (Figure 6(b)).

3.6. Incidence of Radial Nerve Injury. The fixed model was adopted since all the 13 studies that reported the incidence of radial nerve injury showed no significant heterogeneity ($P = 1.00$, $I^2 = 0\%$). The combined RR value was 0.90, 95% CI was (0.51, 1.57), and the combined effect amount $Z = 0.38$ ($P = 0.70$). There was no significant difference with regard to the incidence of radial nerve injury between the two groups, as shown in Figure 7(a). Begg's test showed no publication bias (Figure 7(b)).

3.7. Incidence of Postoperative Infection. No significant heterogeneity was found in the 12 literature ($P = 0.96$, $I^2 = 0\%$) that reported the incidence of postoperative infection. The combined RR, 95% CI, and effect amount Z was 0.32, 0.15-0.68, and 2.98 ($P = 0.003$), respectively. The postoperative

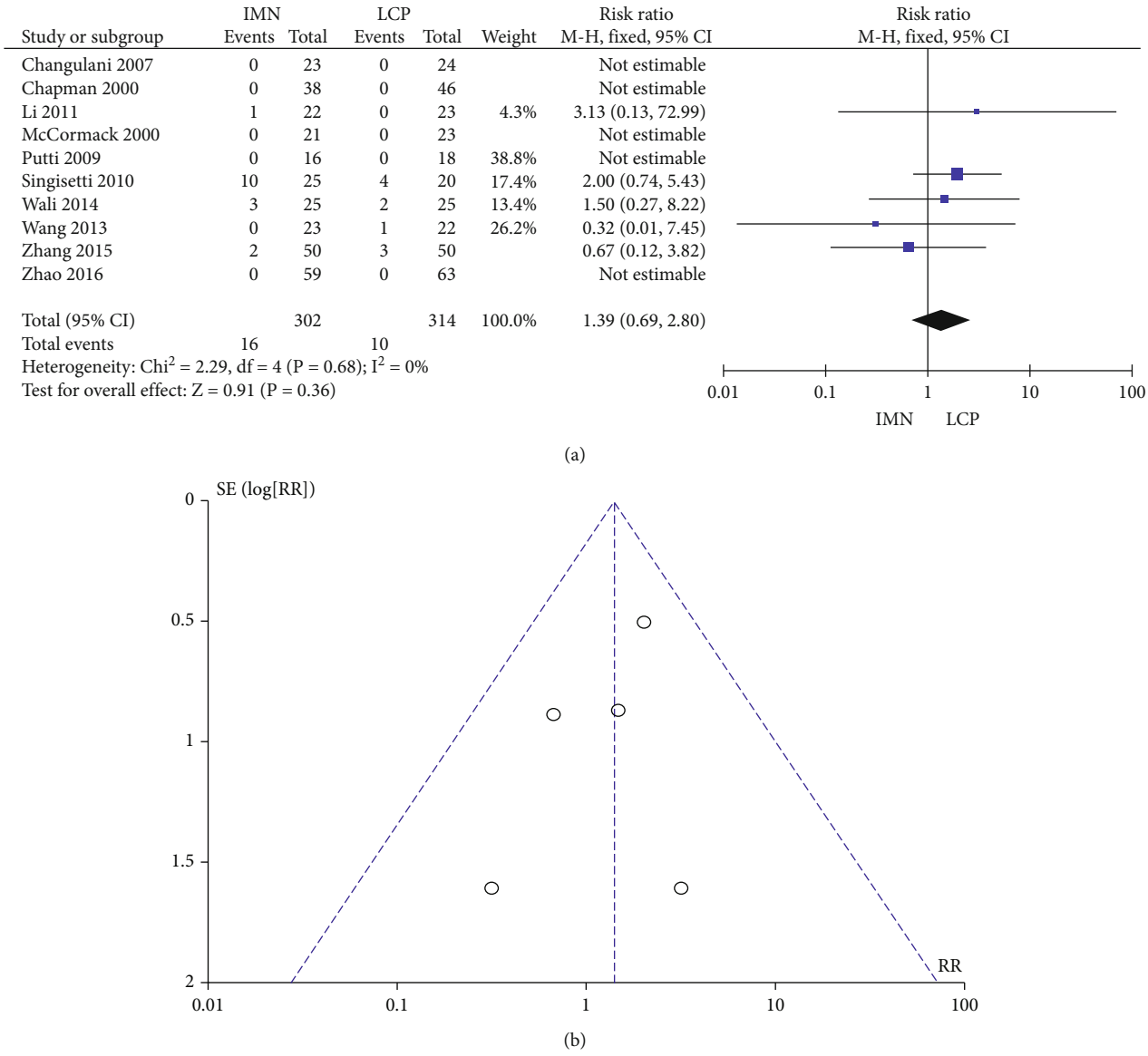


Figure 10: Meta-analysis of delayed healing rate in the IMN group and LCP group. (a) Forest figure. (b) Funnel diagram.

infection rate of the IMN group was significantly lower than that of the LCP group (Figure 8(a)). Begg's test showed no publication bias (Figure 8(b)).

3.8. Incidence of Reoperations. No significant heterogeneity was found in the 11 literature ($P = 0.41$, $I^2 = 3\%$) that reported the incidence of reoperations. The combined RR value was 1.14, 95% CI was (0.58, 2.25), and the combined effect amount $Z = 0.37$ ($P = 0.71$). Figure 9(a) shows no significant difference in the incidence of secondary surgery between the two groups. Begg's test showed no publication bias (Figure 9(b)).

3.9. Incidence of Delayed Healing. A total of 10 studies reported the incidence of delayed healing, and no significant heterogeneity was found ($P = 0.68$, $I^2 = 0\%$). The combined RR value was 1.39, 95% CI was (0.69, 2.80), and the combined effect amount $Z = 0.91$ ($P = 0.36$). No significant difference in the incidence of delayed healing was observed between the two groups, as shown in Figure 10(a). Begg's test shows no publication bias (Figure 10(a)).

3.10. Incidence of Shoulder/Elbow Joint Limitation. No significant heterogeneity was found in the 9 literature ($P = 0.21$, $I^2 = 30\%$) that reported the incidence of should/elbow joint limitation. The combined RR value was 1.88, 95% CI was (1.06, 3.33), and the combined effect amount $Z = 2.17$ ($P = 0.03$). The incidence of shoulder/elbow joint limitation in the IMN group was significantly higher than that in the LCP group (Figure 11(a)). Begg's test showed no publication bias (Figure 11(b))].

4. Discussion

Patients with humeral shaft fracture are often complicated by neurovascular injury, open fracture, combined elbow

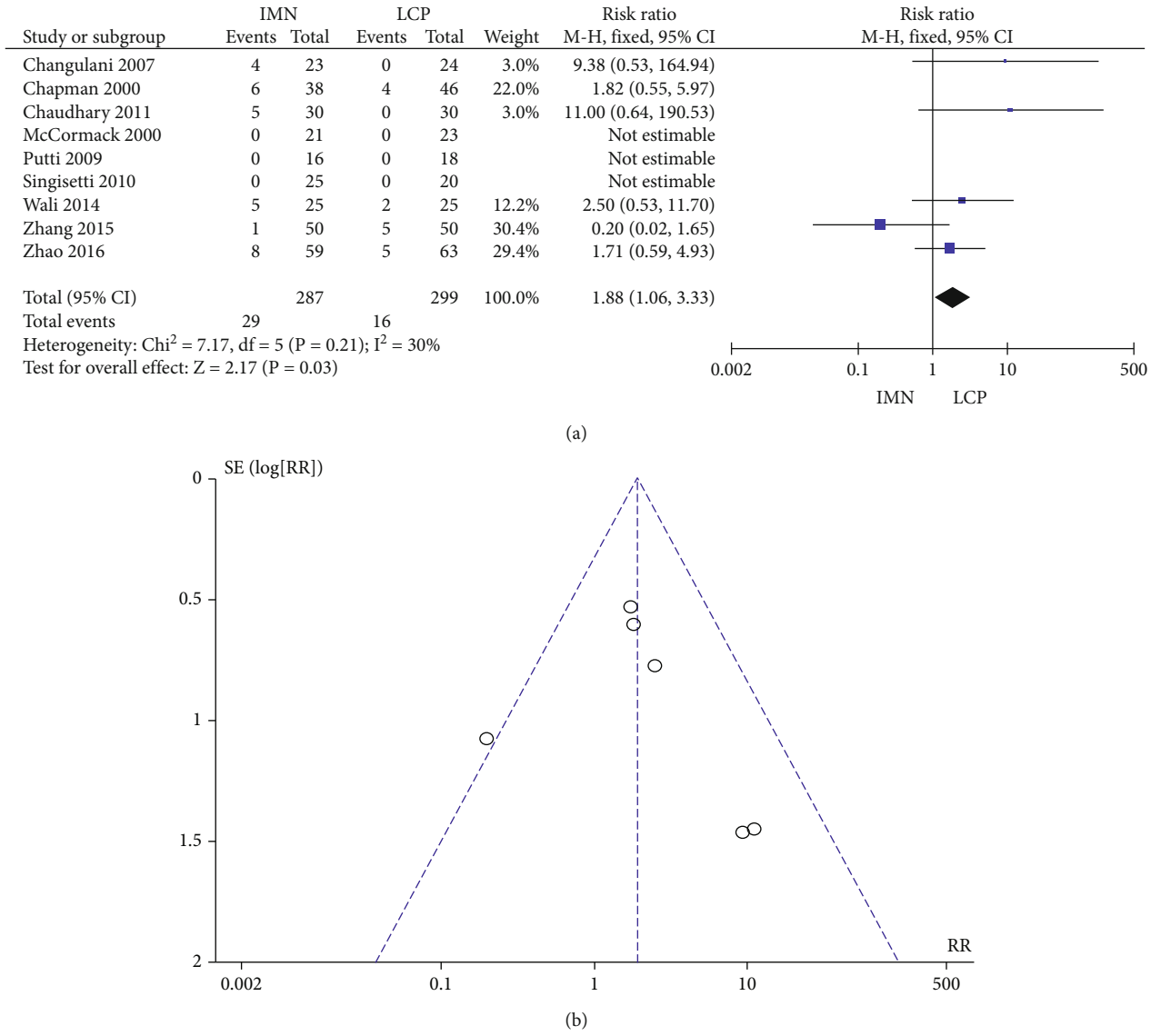


Figure 11: Meta-analysis of the incidence of shoulder elbow joint limitation in IMN group and LCP group. (a) Forest figure. (b) Funnel figure.

forearm fracture, and compound multiple injuries [22, 23]. There are still debates about the optimal management scheme for humeral shaft fracture in the clinic. At present, the main surgical methods include open reduction and internal fixation and intramedullary nail fixation. LCP is widely used in open reduction and internal fixation [5]. Some systematic evaluations and meta-analyses have compared the treatment of humeral shaft fractures with LCP and IMN with inconsistent findings [24–27]. Ozan et al. found that IMN was safer and more applicable and effective than steel plate in treating type A humeral shaft [28]. In a meta-analysis published in 2010 by Heineman et al., it was noted that there were no significant differences in the incidence of postoperative complications, bone nonunion, postoperative infection, radial nerve injury, and reoperations [29]. A plausible explanation for the inconsistencies is that the studies included in the meta-analysis are of mixed quality. Therefore, this study included only RCTs with a modified Jadad scale score ≥ 4 or CCT with a NOS ≥ 7.

The main comparative parameters of the two groups included the incidence of nonunion, iatrogenic radial nerve injury, and postoperative infections. According to relevant research reports, the incidence of bone nonunion was as high as 3-20% [30]. In a study of 325 surgically treated adult humeral shaft fractures, Claessen et al. [31] found that the surgical approach, especially the open approach, was significantly related to iatrogenic radial nerve injury. Ma et al. found no significant difference between IMN and LCP with regard to the success rate of fracture healing, incidence of radial nerve injury, and postoperative infection [24]. This study demonstrated that IMN reduced postoperative infection as compared with LCP, but there were no significant differences in bone nonunion and radial nerve injury. We also reported increased rate of postoperative infections in

the LCP group than that in the IMN group, which may be attributed to the fact that the LCP approach is more traumatic with increased intraoperative blood loss and longer operation duration. The similar success rate of fracture healing and incidence of radial nerve injury also support the application of IMN. However, many controversies still exist about the postoperative infection rate and fracture healing rate between the two. For example, Heineman et al. suggested that applying steel plate to humeral shaft fracture is more likely to reduce the incidence of complications [32], whereas Ozan et al. reported that the incidence of bone nonunion in the IMN group was lower in only one patient [28]. Therefore, future high-quality clinical research should be carried out to strengthen reporting homogeneity during follow-up.

The parameters of efficacy evaluated included operation time, delayed fracture healing, reoperation rate, and intraoperative blood loss. The analysis of this study showed that IMN was superior to the LCP group in operation time and blood loss. Although the included studies have high heterogeneity in operation time and blood loss, which may be related to the significant fluctuation of clinicians' technical level, the analysis results still supported that IMN was advantageous in operation time and blood loss. Interestingly, when only studies published in the recent ten years were included, the operation time of the IMN group was significantly shorter than that of the LCP group, which is different from that reported previously by Wen et al. These discrepancies may be related to the application of IMN and rapid development of surgical techniques [27]. Although the difficulty of open internal reduction is reduced under direct vision, the preparation time is generally much longer. After the widely used intramedullary nail in the clinic, the technology is mature. Although IMN reduction is technically more challenging than LCP, skilled surgeons could still perform the operation with dramatically reduced time as compared with that of the ten years ago. IMN is also characterized by small incisions with reduced intraoperative blood loss. This study also found no significant difference in delayed fracture healing and reoperation rate, which was consistent with previous studies.

This study showed that the IMN group was inferior to LCP group in terms of ASES score and shoulder/elbow limitation rate. This is consistent with the results of the previous meta-analysis that have also shown that using steel plates reduces the probability of postoperative shoulder joint limitation. Meanwhile, it has been suggested that IMN was more likely to cause apparent shoulder joint dysfunction in elderly patients [33, 34]. However, these studies are limited by short follow-up time, and few studies have compared and analyzed the functional recovery of the latter after removing artificial grafts.

Our study strength was inclusion of high-quality studies. A total of 14 studies with 927 subjects were included in this paper, which was the most systematic and comprehensive analysis so far. In addition, the updated clinical research has also brought additional research and analysis conclusions from previous studies. The heterogeneity of some data was wide, suggesting that the clinical results are constantly adjusted with the progress of technology. In the future, it is still necessary to carry out multicenter prospective randomized controlled trials with large sample size to conclusively determine the efficacy and safety of IMN vs. LCP for treating humeral shaft fractures.

To sum up, although IMN is superior to LCP in the fixation of humeral shaft fracture, it is limited by suboptimal early postoperative functional recovery. In the future, additional studies are entailed to evaluate and analyze the clinical efficacy between IMN and LCP with regard to long-term function after artificial graft removal.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Yong Hu and Tianhui Wu contributed equally to this work.

Acknowledgments

The study was supported by Danzhou People's Hospital.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 6846079, 6 pages
https://doi.org/10.1155/2022/6846079

Research Article

Effect of Different General Anesthesia Methods on the Prognosis of Patients with Breast Cancer after Resection: A Systematic Review and Meta-analysis

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Received 21 May 2022; Accepted 15 June 2022; Published 28 June 2022

Academic Editor: Xi Lou

Background. The effect of total intravenous anesthesia (TIVA) and inhalation anesthesia (IA) on the prognosis of breast cancer patients has been controversial. The study is aimed at exploring the effects of different anesthesia methods on the postoperative prognosis of breast cancer patients. *Methods*. Literature retrieval was conducted in PubMed, EMBASE, MEDLINE, Embase, CENTRAL, and CNKI databases. The literature topic was to compare the effects of TIVA and IA on the prognosis of patients undergoing breast cancer resection. Two researchers extracted data from the literature independently. This study included randomized controlled trials that evaluated for risk of bias according to the "Risk assessment Tool for Bias in Randomized Trials" in the Cochrane Manual. The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in observational studies. The chi-square test was used for the heterogeneity test. Publication bias was assessed using funnel plots and Egger's test. If heterogeneity existed between literature, subgroup analysis and sensitivity analysis were used to explore the source of heterogeneity. Sensitivity analysis was performed by excluding low-quality and different-effect models. Data were statistically analyzed using the Cochrane software RevMan 5.3. Hazard ratio (HR) and 95% confidence interval (CI) were used for statistical description. *Results*. Seven literatures were selected for meta-analysis. There were 9781 patients, 3736 (38.20%) receiving TIVA and 6045 (61.80%) receiving inhalation anesthesia. There was no significant difference in overall survival (OS) between TIVA and IA breast cancer patients (HR = 1.05, 95% CI (0.91, 1.22), $Z = 0.70$, $P = 0.49$). There was no difference in the literature ($\chi^2 = 6.82$, $P = 0.34$, $I^2 = 12\%$), and there was no obvious publication bias. There was no significant difference in recurrence-free survival (RFS) between TIVA and IA patients (HR = 0.95, 95% CI (0.79, 1.13), $Z = 0.61$, $P = 0.54$). There was no heterogeneity in the literature ($\chi^2 = 5.23$, $P = 0.52$, $I^2 = 0\%$), and there was no significant publication bias. *Conclusion*. There is no significant difference in OS and RFS between TIVA and IA patients during breast cancer resection. The prognostic effects of TIVA and IA were similar.

1. Introduction

Breast cancer is one of the most common malignant tumours and the leading cause of female cancer death. Surgical resection is the main treatment plan [1], but the stress, anesthesia, and narcotic drugs caused by surgery adversely affect postoperative recovery and anticancer immunity [2]. General anesthesia is the primary anesthesia method for breast surgery, including total intravenous anesthesia (TIVA) and inhalation anesthesia (IA) [3]. These two general anesthesia methods have different side effects on patients and immune status because of the differences in

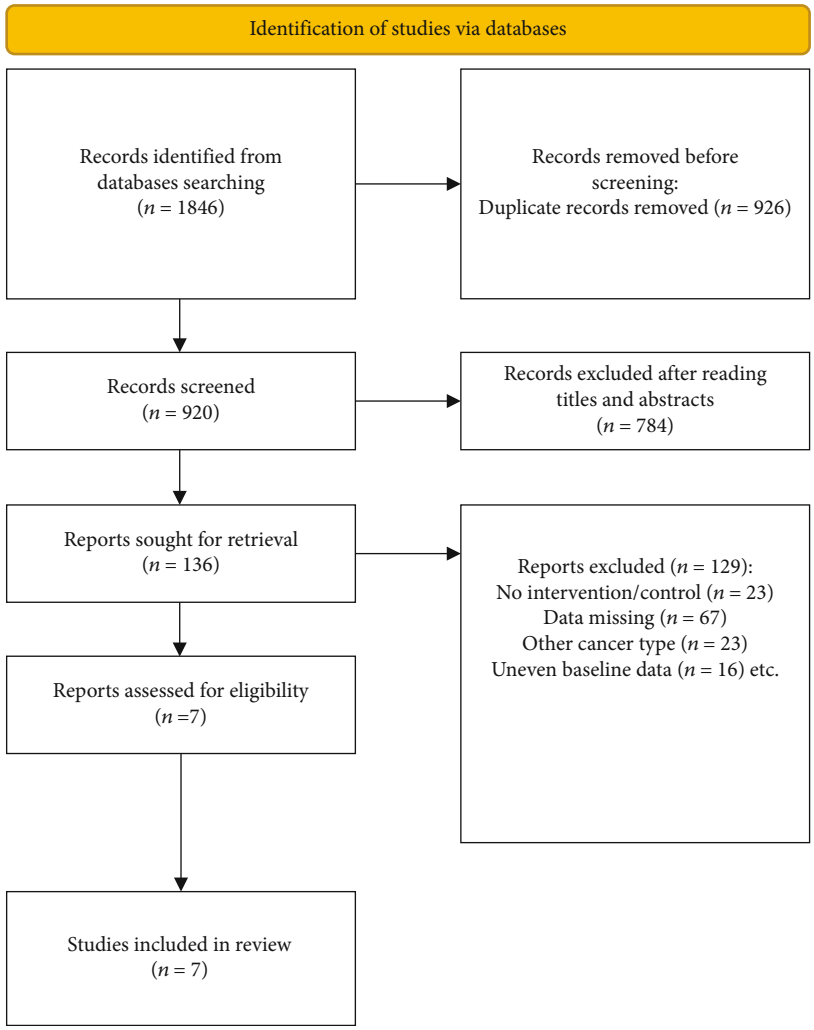

Figure 1: Flow chart of literature screening.

Table 1: Risk of bias assessment.

Study	Study design	No. of patients		Risk of bias assessment
		TIVA	IA	
Cho et al. [11]	RCT	25	25	Low risk of bias
Hong et al. [13]	Retrospective	154	475	NOS score 7
Huang et al. [12]	Retrospective	334	632	NOS score 6
Kim et al. [14]	Retrospective	56	2589	NOS score 7
Yan et al. [15]	RCT	40	40	Low risk of bias
Yan et al. [16]	RCT	42	38	Low risk of bias
Yoo et al. [2]	Retrospective	3085	2246	NOS score 7

Note: TIVA: total intravenous anesthesia; IA: inhalation anesthesia; NOS: Newcastle-Ottawa Scale.

drug administration and drug use [4]. The choice of general anesthesia may affect the postoperative rehabilitation and prognosis of patients.

A previous meta-analysis [5] illustrated that TIVA could reduce the recurrence rate of malignant tumours and prolong the OS and RFS of patients. Both in vivo and in vitro studies have confirmed that volatile anesthetic drugs promote the proliferation, invasion, and migration of malignant tumour cells [6–9]. At the same time, propofol used in TIVA can inhibit the proliferation and metastasis of malignant tumour cells [10]. In breast cancer, the influence of TIVA and IA on the prognosis of breast cancer patients has been controversial. Previous research results fail to show a consistent trend. Some studies [11] indicated that intravenous anesthesia could improve the immune function of patients with breast cancer. The postoperative recurrence-free

Study or subgroup	log [Hazard ratio]	SE	Weight	Hazard ratio IV, Fixed, 95% CI
Cho 2017	0.13	0.23	10.5%	1.14 [0.73, 1.79]
Hong 2019	−0.12	0.13	32.8%	0.89 [0.69, 1.14]
Huang 2019	0.33	0.25	8.9%	1.39 [0.85, 2.27]
Kim 2017	0.29	0.27	7.6%	1.34 [0.79, 2.27]
Yan 2018	0.25	0.16	21.6%	1.28 [0.94, 1.76]
Yan 2019	−0.18	0.23	10.5%	0.84 [0.53, 1.31]
Yoo 2019	−0.11	0.26	8.2%	0.90 [0.54, 1.49]
Total (95% CI)			100.0%	1.05 [0.91, 1.22]

Heterogenetiy: $\chi^2 = 6.82$, df = 6 ($P = 0.34$); $I^2 = 12\%$
Test for overall effect: $Z = 0.70$ ($P = 0.49$)

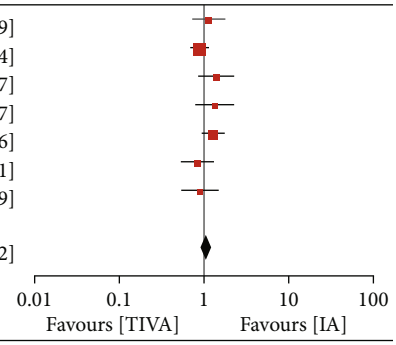

Figure 2: Forest map: comparison of postoperative OS between TIVA and IA breast cancer patients. TIVA: total intravenous anesthesia; IA: inhalation anesthesia; OS: overall survival.

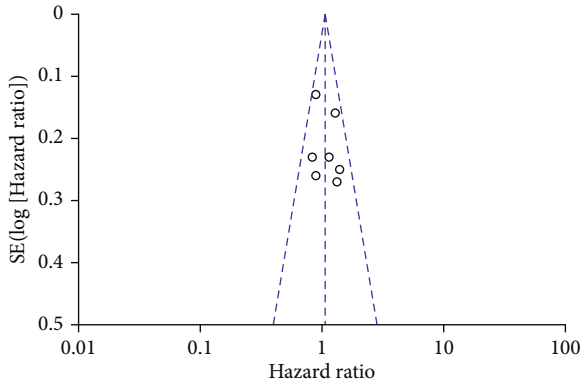

Figure 3: Funnel diagram: comparison of postoperative OS between TIVA and IA breast cancer patients. TIVA: total intravenous anesthesia; IA: inhalation anesthesia; OS: overall survival.

survival rate of patients with inhalation anesthesia was worse than that of patients with intravenous anesthesia. However, some studies [12] have shown no difference between the two anesthesia methods in the overall survival or relapse-free survival of breast cancer.

Based on the above controversy, this study is aimed at exploring the impact of TIVA and IA on the prognosis of breast cancer patients after resection through meta-analysis.

2. Materials and Methods

2.1. Bibliography Retrieval. The keywords included intravenous anesthesia, propofol, propofol-based intravenous anesthesia, inhalation anesthesia, breast cancer, breast surgery, mastectomy, and radical mastectomy. The literature was searched in PubMed, EMBASE, MEDLINE, Embase, CENTRAL database, and CNKI database according to the search terms. The documents were written in English and Chinese. The date of the literature search was March 5, 2022.

2.2. Literature Screening. Inclusion criteria are as follows: (1) The subjects were female patients with breast cancer; (2) the control group was set up in the study; (3) TIVA was implemented in the experimental group, and IA was implemented in the control group; (4) the observed indexes of the study included at least one of the recurrence-free survival (RFS) or overall survival of patients with breast cancer after operation; (5) research types included a randomized controlled trial (RCT) and observational study; and (6) the statistical data in the literature could calculate the value of hazard ratio (HR) and 95% confidence interval (CI).

Literature exclusion criteria are as follows: (1) other anesthesia methods were used to assist surgical treatment; (2) the subjects selected in the literature were complicated with other tumours; (3) no control group was set; (4) the baseline data of the control group and the experimental group were poorly balanced; (5) the literature data was incomplete and could not be supplemented by contacting the literature author.

2.3. Document Data Sorting. Lv and Xiao independently extracted the data and information from the literature. Two researchers used plot-digitizer software to extract graphic data information. The authors were contacted by email to request relevant data not shown in the literature. Two researchers cross-examined each other's data. If there were differences between the two authors, negotiation could reach an agreement.

2.4. Literature Quality Evaluation. Lv and Zhang evaluated the literature quality. According to the "bias risk assessment tool of randomized trials" in the Cochrane Manual, the bias risk assessment of RCTs was carried out. The evaluation contents included five aspects: the bias in the process of randomization, the bias from the established intervention measures, the bias from the lack of outcome data, the bias of outcome measurement, and the bias of selective reporting results. The literature was divided into "low risk of bias,", "some risks," and "high risk of bias." In the current study, the Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in observational studies. The contents included the selection of subjects (4 points), comparability between groups (2 points), and exposure factor measurement (3 points), a total of 9 points. In case of inconsistency in the judgment results of literature quality, two researchers

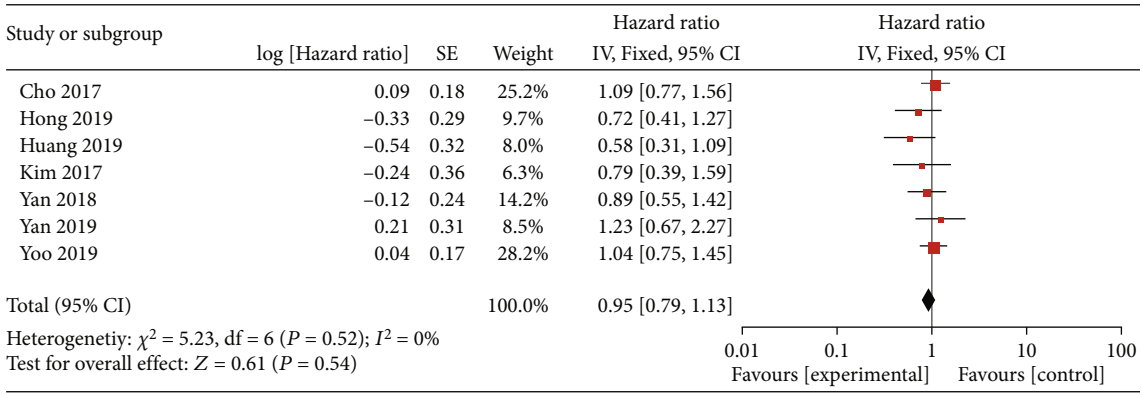

Figure 4: Forest map: comparison of postoperative OS between TIVA and IA breast cancer patients. TIVA: total intravenous anesthesia; IA: inhalation anesthesia; RFS: recurrence-free survival.

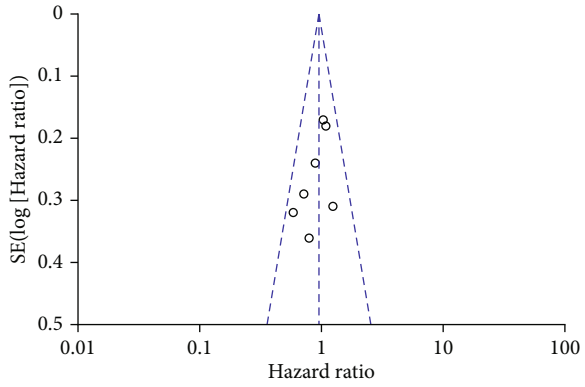

Figure 5: Funnel diagram: comparison of postoperative OS between TIVA and IA breast cancer patients. TIVA: total intravenous anesthesia; IA: inhalation anesthesia; RFS: recurrence-free survival.

reached an agreement after discussion. The two researchers compared the evaluation results after completing the literature quality evaluation. If there were differences, the two authors reached an agreement through discussion.

2.5. Heterogeneity Test and Publication Bias Test. The chi-square test was used for the heterogeneity test. When $I^2 > 50\%$ or $P < 0.1$, it was considered that there was heterogeneity among published literatures, and a random effect model was used. When $I^2 \leq 50\%$ or $P \geq 0.1$, there was no heterogeneity among published literatures, and the fixed-effect model was adopted. Funnel plots and Egger's test were used for the publication bias test.

2.6. Subgroup Analysis and Sensitivity Analysis. If there was heterogeneity between literature, subgroup analysis and sensitivity analysis were used to explore the source of heterogeneity. Sensitivity analysis was carried out by excluding low-quality and different effect models.

2.7. Statistical Method. This study used the Cochrane software RevMan 5.3 statistical analysis of the data. HR value and 95% CI were used for statistical description. Two-way $P < 0.05$ indicates statistically significant.

3. Results

3.1. Retrieval Results and Literature Quality Evaluation. According to the relevant subject words, this study retrieved 1846 articles about the impact of TIVA and IA on the prognosis of breast cancer patients after resection. According to the literature screening criteria, 7 literatures were further selected for meta-analysis. The flow chart of literature screening is shown in Figure 1. A total of 9781 breast cancer resection patients were included in the 7 articles, including 3736 (38.20%) patients receiving TIVA and 6045 (61.80%) patients receiving inhalation anesthesia. The risk assessment of literature bias is shown in Table 1.

3.2. Effects of TIVA and IA on Postoperative OS in Patients with Breast Cancer. Seven articles compared OS in patients with TIVA and IA breast cancer after the operation. There was no heterogeneity between the literatures ($\chi^2 = 6.82$, $P = 0.34$, $I^2 = 12\%$). The fixed-effect model was used to merge the effects (HR = 1.05; 95% CI (0.91, 1.22), test of overall effect $Z = 0.70$ ($P = 0.49$), see Figure 2). The analysis showed no significant difference in OS between TIVA and IA breast cancer patients. The funnel plot and Egger's test were showed that the scatter points were roughly symmetrical within the confidence interval, and there was no obvious publication bias ($P > 0.05$), as shown in Figure 3.

3.3. Effects of TIVA and IA on Postoperative RFS in Patients with Breast Cancer. Seven articles compared RFS in patients with TIVA and IA breast cancer. There was no heterogeneity between the literatures ($\chi^2 = 5.23$, $P = 0.52$, $I^2 = 0\%$). The fixed-effect model was used to merge the effects (HR = 0.95 ; 95% CI (0.79, 1.13), test of overall effect $Z = 0.61$ ($P = 0.54$), see Figure 4). The analysis showed no significant difference in RFS between TIVA and IA breast cancer patients. The funnel plot and Egger's test were indicated that the scatter points were roughly symmetrical within the confidence interval, and there was no obvious publication bias ($P > 0.05$), as shown in Figure 5.

4. Discussion

This meta-analysis recruited seven randomized controlled trials to compare the effects of TIVA and IA on the prognosis of patients with breast cancer after resection. We found no statistically significant difference in OS and RFS between TIVA and IA breast cancer patients. The results from previous studies are consistent with our analysis. Cho et al. [11] suggested that the analgesic effects of TIVA and IA were similar. TIVA could increase the proportion of NK cells in the blood of breast cancer patients after the operation and promote the immune function of breast cancer patients, thus reducing the recurrence rate of breast cancer. Hong et al. [13] showed that TIVA and IA had similar effects on OS in patients with malignant tumours through retrospective analysis. These tumours included breast cancer, liver cancer, lung cancer, gastric cancer, and colon cancer. Through retrospective analysis, Huang et al. [12] compared the prognosis of 632 breast cancer patients receiving IA and 334 breast cancer patients receiving TIVA. They pointed out no statistically significant difference in the 5-year survival and recurrence rate of breast cancer patients receiving the two anesthesia methods. Kim et al. [14] considered that TIVA and IA have similar effects on the prognosis of breast cancer patients. Yan et al. [15] showed that IA could increase VEGF expression in the serum of breast cancer patients, but there was no significant difference in the recurrence rate and survival rate of breast cancer. Yan et al. [16] showed no significant difference between TIVA and IA in myeloid-derived suppressor cells (MDSCs), overall survival rate, and recurrence rate after resection of breast cancer patients. Yoo et al. [2] considered that TIVA or IA had no significant effect on RFS and OS in patients undergoing breast cancer resection.

A meta-analysis pointed out that TIVA could reduce the recurrence of malignant tumours and prolong OS and RFS [5]. Meanwhile, various cancer types, such as breast cancer, non-small-cell lung cancer, colon cancer, rectal cancer, and gastric cancer, were included in that study. Furthermore, researchers observed a magnified effect in malignant surgery. With prolonged operation time, TIVA might increase the prognosis of patients. Yap et al. [5] also pointed out that TIVA could improve RFS in patients with breast cancer but had no effect on OS compared with IA. The possible reason for this phenomenon is that propofol used in TIVA can inhibit tumour metastasis. At the same time, volatile gas anesthetics may promote tumour cell metastasis and proliferation and inhibit cancer cell apoptosis [6–10].

A previous meta-analysis [17] has shown that the analgesic effect of intravenous anesthesia is inferior to inhalation anesthesia and can reduce the incidence of postoperative vomiting. Intravenous anesthesia is superior to inhalation anesthesia in maintaining anticancer immune status. Its potential mechanism is that propofol reduces IL-6 while retaining NKCC and NLR in the blood. In this current study, we speculate that propofol may potentially benefit the long-term prognosis of breast cancer after surgery. However, we did not find any difference in the prognosis of patients under intravenous anesthesia and inhalation anesthesia.

Studies have shown that propofol is associated with a higher relapse-free survival rate after breast surgery in malignant tumours with or without breast cancer. Still, it cannot reduce recurrence or prolong overall survival [18]. It is also pointed out that propofol-based intravenous anesthesia has advantages over inhalation anesthesia in reducing long-term recurrence and metastasis of tumours [19]. More multicenter, large sample size prospective randomized controlled trials are needed to explore the potential protective effect of propofol intravenous anesthesia on the long-term prognosis of breast cancer patients.

In conclusion, in breast cancer resection, there was no significant difference in OS and RFS between breast cancer resection patients who received TIVA versus IA. TIVA and IA have similar prognostic effects on patients.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Rui Lv and Chunli Zhang contributed equally to this work.

Acknowledgments

The project was supported by the Hainan Province Clinical Medical Center.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 5670303, 7 pages
https://doi.org/10.1155/2022/5670303

Research Article

Clinical Efficacy of Mechanical Traction as Physical Therapy for Lumbar Disc Herniation: A Meta-Analysis

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Received 19 May 2022; Revised 1 June 2022; Accepted 3 June 2022; Published 21 June 2022

Academic Editor: Xi Lou

Objective. This study is aimed at exploring the clinical effect of mechanical traction on lumbar disc herniation (LDH). *Methods*. Related literatures were retrieved from PubMed, Medline, Embase, CENTRAL, and CNKI databases. Inclusion of literature topic was comparison of mechanical traction and conventional physical therapy for lumbar disc herniation. Jadad scale was used to evaluate the quality of the included RCT studies. The Chi-square test was used for the heterogeneity test, and a random effect model was used with heterogeneity. Subgroup analysis and sensitivity analysis were used to explore the causes of heterogeneity. If there was no heterogeneity, the fixed effect model was used, and funnel plots were used to test publication bias. *Results*. Visual analog scale (VAS) in the mechanical traction group was lower than that in the conventional physical therapy group (MD = −1.39 (95% CI (-1.81, -0.98)), $Z = 6.56$, and $P < 0.00001$). There was no heterogeneity among studies ($\text{Chi}^2 = 6.62$, $P = 0.25$, and $I^2 = 24\%$) and no publication bias. Oswestry disability index (ODI) in the mechanical traction group was lower than that in the conventional physical therapy group (MD = −6.34 (95% CI (-10.28, -2.39)), $Z = 3.15$, and $P = 0.002$). There was no heterogeneity between studies ($\text{Chi}^2 = 6.27$, $P = 0.18$, and $I^2 = 36\%$) and no publication bias. There was no significant difference in Schober test scores between the mechanical traction group and the conventional physical therapy group (MD = −0.40 (95% CI (-1.07, 0.28)), $Z = 1.16$, and $P = 0.25$). There was no heterogeneity among studies ($\text{Chi}^2 = 1.61$, $P = 0.66$, and $I^2 = 0\%$) and no publication bias. *Conclusion*. Mechanical traction can effectively relieve lumbar and leg pain and improve ODI in patients with lumbar disc herniation but has no significant effect on spinal motion. The therapeutic effect of mechanical traction was significantly better than that of conventional physical therapy. Lumbar traction can be used in conjunction with other traditional physical therapy.

1. Introduction

Lumbar disc herniation (LDH), as the most common cause of low back and leg pain [1], was diagnosed in 60% to 80% of people at different ages [2]. The LDH is common in people aged 25 to 55 spending large percent of times sitting or standing with heavy workload. Current clinical treatment of LDH includes surgical treatment and nonsurgical treatment [3, 4]. Although the effect of surgical treatment is good, it faces the risk of nerve injury and adjacent vertebral bodies and recurrence [5]. Most patients with LDH are most likely treated conservatively [3, 6, 7]. Conservative treatment takes physical therapy as the primary treatment method, including hot compress, acupuncture, massage, bed rest, electrotherapy, and traction [8–10].

Lumbar traction has been widely used in the clinic; however, its clinical effect has been controversial. Lumbar traction is limited in eliminating the physical and mechanical compression of nerve roots in a short time [11] and will increase the risk of lumbar injury [12]. The known side effect of lumbar tract is pain [13]. In addition, lumbar traction does not improve spinal mobility. Some studies have reported that lumbar traction reduces the compression force on the intervertebral disc, reduces nerve root compression

by expanding the intervertebral foramen, and helps the intervertebral disc return to its original position in the spinal ligament by generating tension [14]. Previous meta-analyses have confirmed that mechanical traction in the supine position can relieve short-term pain in patients with radiculopathy. Radical lesions include lumbar disc degeneration or hernia, degenerative arthritis, lumbar spinal stenosis, space-occupying lesions, and inflammatory lesions, which are distinguished from lumbar disc herniation. Previous meta-analyses have pointed out that mechanical traction and other noninvasive treatments could only improve symptoms in the short term [2]. However, there was heterogeneity among the literatures included in the analysis, especially regarding long-term treatment effects, the source of heterogeneity was not elucidated, and the confidence of the results was low. The study was limited to the effects of mechanical traction on lumbar pain and function and did not identify changes in ODI and Schober's test. That being said, it is necessary to further conduct a meta-analysis to explore the clinical effect of mechanical traction on patients with LDH. This analysis contributed significantly in understanding the basis for clinical diagnosis and provided novel insights on the relationship between mechanical traction and LDH.

2. Materials and Methods

2.1. Literature Download. Literature search was conducted in PubMed, Medline, Embase, CENTRAL, and CNKI databases. The main search terms were low back and leg pain or lumbar disc or lumbar disc herniation and traction or mechanical traction or physiotherapy or decompression. There were no restrictions on the language and publication time of the literature. The cut-off timeline for the literature search was set at April 23, 2022.

2.2. Literature Screening. Inclusion criteria are as follows: (1) the subjects were patients with lumbar disc herniation; (2) the study design included an experimental group and control group; (3) the experimental group received traction therapy combined with routine physical therapy, and the control group received routine physical therapy without traction; (4) provide efficacy evaluation before and after treatment, including visual analog scale (VAS), Oswestry disability index (ODI), and Schober test; and (5) randomized controlled study.

Exclusion criteria are as follows: (1) repeated reports; (2) the baseline data of the experimental group and the control group were unbalanced, with a statistical difference; (3) the experimental group or control group tried to apply intervention measures other than physical therapy; (4) the literature data is missing and cannot be supplemented by contacting the literature author.

2.3. Data Extraction. Two researchers jointly extracted the author, title, publication time, the number of researchers, efficacy evaluation results before and after treatment, etc. For the data that cannot be obtained in the literatures, researchers were responsible reaching out to the author for personal retrieval. If two researchers disagree on the data, an agreement was reached through discussion.

2.4. Literature Quality Evaluation. In this paper, two researchers used the Jadad scale, including the generation method of random sequence, the method of randomized hiding, the use of the blind method, and withdrawal rules, to evaluate the quality of the included studies. On the Jadad scale, 1 to 3 points are low quality, and 4 to 7 points are high quality.

2.5. Heterogeneity Test and Publication Bias Test. The Chi-square test was used for the heterogeneity test. When I^2 corrected by degrees of freedom was more than 50% or $P < 0.1$, it was considered that there was heterogeneity among published literatures, and a random effect model was used. Subgroup analysis and sensitivity analysis were used to explore the causes of heterogeneity. When the I^2 corrected by degrees of freedom is ≤50% and $P \geq 0.1$, it was considered that there was no heterogeneity among the published literatures, and the fixed effect model was used. A funnel plot was used for the publication bias test.

2.6. Statistical Method. This study used Cochrane software RevMan5.3 to statistically analyze data. The variables included in this study are continuous variables. Mean difference (MD) and 95% confidence interval (CI) were used to describe the combined effect statistically. MD and 95% CI were calculated using the inverse variance statistical method. Bilateral $P < 0.05$ indicated statistically significant.

3. Results

3.1. Characteristics of Included Literature. A total of 1436 literatures were retrieved as described above. Screening through all literatures with defined criteria, there were 1430 literatures excluded and a total of 6 literatures included in this meta-analysis [15–20]. The working flow for screening is summarized in Figure 1. Further, the basic information of each literature and the in-detailed Jadad score are included in Table 1.

3.2. Comparison of VAS between Mechanical Traction and Conventional Physical Therapy. A total of 6 literatures involved the comparison of VAS of low back and leg pain after mechanical traction and conventional physical therapy. There were 239 patients in total with lumbar disc herniation, among whom, 123 cases in the mechanical traction group and 116 cases in conventional physical therapy. Heterogeneity test showed that there was no heterogeneity among the studies ($\text{Chi}^2 = 6.62$, $P = 0.25$, and $I^2 = 24\%$). The combined analysis suggested that the VAS of patients in the mechanical traction group was lower than that in a routine physical therapy group with MD $= -1.39$ (95% CI (-1.81, -0.98)), and the difference was statistically significant ($Z = 6.56$, $P < 0.00001$). On top of that, as shown in the funnel diagram (Figure 2), scattered points were distributed in the confidence interval and were generally symmetrical. No publication bias was indicated in the study as shown in Figure 3.

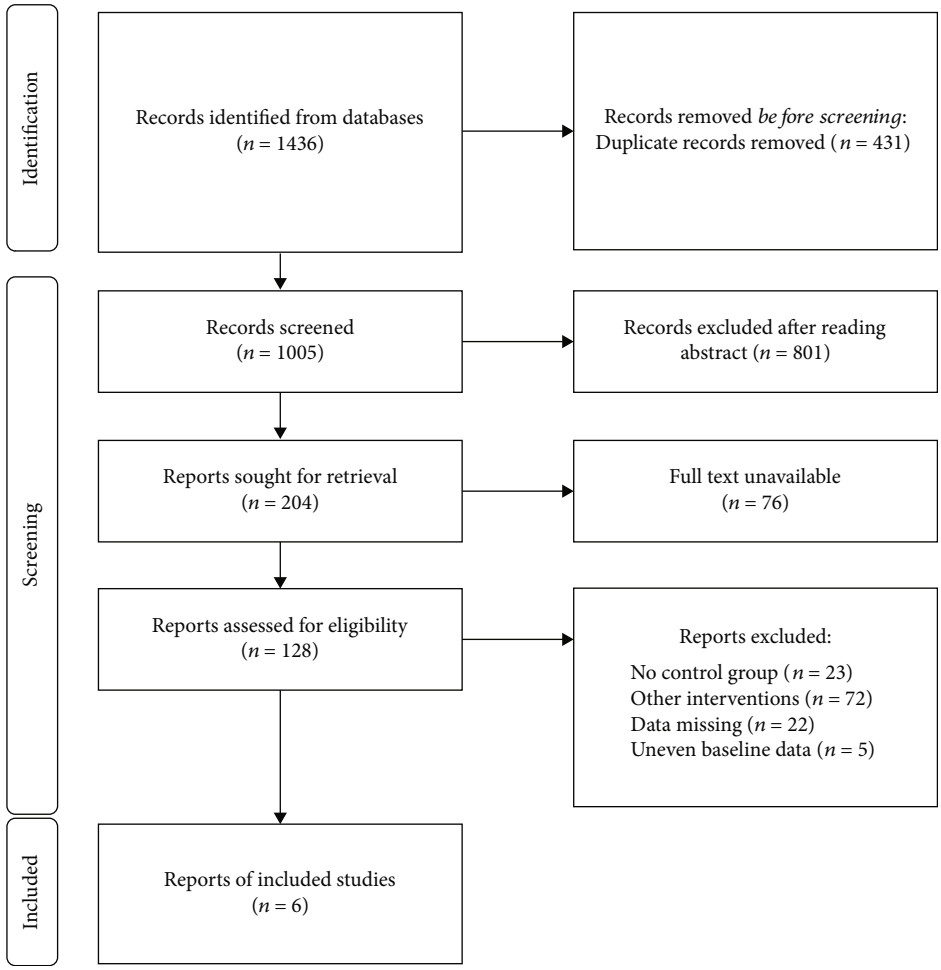

Figure 1: Document screening flow chart.

Table 1: Literature characteristics and Jadad score were included.

Author	Year	Study type	Study group	Control group	Frequency (times/week)	Traction	Jadad
Bilgilisoy et al. [15]	2018	RCT	$n = 39$ Age: 45.1 ± 11.2	$n = 40$ Age: 45.1 ± 11.2	Not mentioned	50%BW	4
Demirel et al. [18]	2017	RCT	$n = 10$ Age: 50.1 ± 11.8	$n = 10$ Age: 41.3 ± 12.8	Not mentioned	50%BW+5 pounds	5
Isner-Horobeti et al. [19]	2016	RCT	$n = 8$ Age: 33 ± 11	$n = 9$ Age: 33 ± 8	5	50%BW	4
Moustafa and Diab [16]	2013	RCT	$n = 30$ Age: 43.2 ± 2.4	$n = 28$ Age: 43.2 ± 1.7	3	Not mentioned	5
Ozturk et al. [20]	2006	RCT	$n = 24$ (14 men, 10 women) Age: 40.2 ± 11.4	$n = 22$ (8 men, 14 women) Age: 52.7 ± 8.8	5	50%BW	5
Prasad et al. [17]	2012	RCT	$n = 12$ Age: 36.55 ± 5.13	$n = 7$ Age: 34.46 ± 5.71	3	Not mentioned	5

RCT: randomized controlled trial.

3.3. Comparison of ODI between Mechanical Traction and Conventional Physical Therapy. Through screening, we identified 5 literatures which introduced a comparison of ODI after mechanical traction ad conventional physical therapy. Within the 5 literatures, there were total of 222 patients with lumbar disc herniation with 115 cases in the mechanical

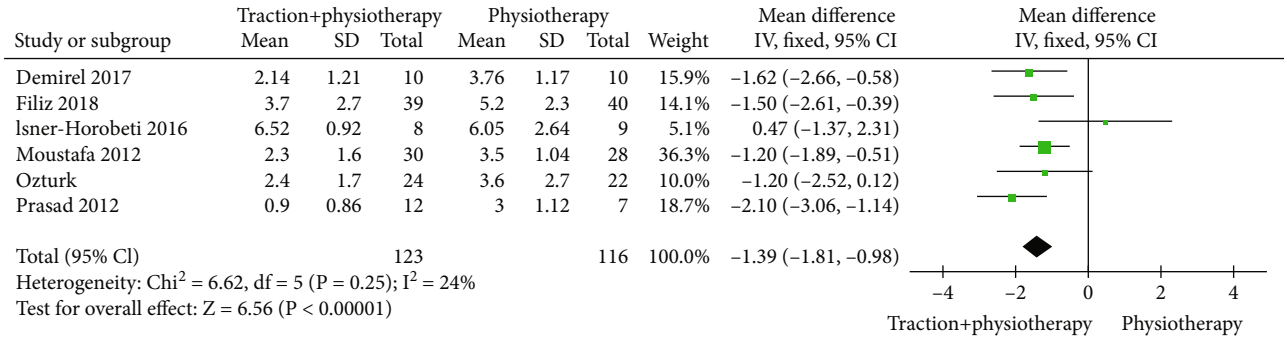

Figure 2: Forest diagram of VAS comparison between mechanical traction and conventional physical therapy groups.

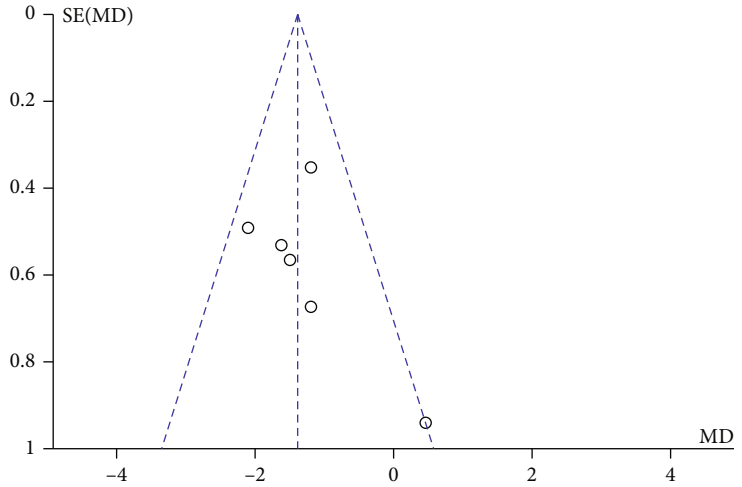

Figure 3: Funnel diagram of VAS comparison between mechanical traction and routine physical therapy groups. MD means mean difference; SE stands for standard error.

traction group and 107 cases in conventional physical therapy. The heterogeneity test showed that there was no heterogeneity among the studies ($Chi^2 = 6.27$, $P = 0.18$, and $I^2 = 36\%$). Further analysis showed that the ODI of patients in the mechanical traction group was lower than that in a routine physical therapy group (MD = −6.34 95%, CI (-10.28, -2.39)), and the difference was statistically significant ($Z = 3.15$, $P = 0.002$). The funnel chart showed a roughly symmetrical distribution of the scatter points within the confidence interval (Figure 4). No publication bias was observed while conducting analysis (Figure 5).

3.4. Comparison between Mechanical Traction and Conventional Physical Therapy Schober Test. During the investigation of Schober test after mechanical traction and conventional physical therapy, there were 200 patients with lumbar disc herniation with 101 cases in the mechanical traction group and 99 cases in conventional physical therapy investigated in 5 screen literatures. The heterogeneity test showed no heterogeneity among the studies ($Chi^2 = 1.61$, $P = 0.66$, and $I^2 = 0\%$). The combined analysis results showed that the Schober test score of patients in the mechanical traction group was lower than that in the conventional physical therapy group, MD = −0.40 (95% CI (-1.07, 0.28)), and the difference was not statistically significant ($Z = 1.16$, $P = 0.25$). Similar to other test, in Figure 6, the funnel chart showed that the scattered points were distributed semisymmetrical within the confidence interval. The publication bias screening showed no significant stand-out bias (Figure 7).

4. Discussion

The clinical efficacy of lumbar traction has been controversial, including in terms of long-term and short-term efficacy. We confirmed the short-term efficacy of limited lumbar traction through a meta-analysis. As published previously, mechanical traction could alleviate low back pain, reduce ODI, and improve symptoms in patients with lumbar disc herniation. Through our analysis, lumbar traction takes effects in two major ways. First of all, the vertebral bodies are separated through traction, which contributed to reduce the compressive force and further reduce the compression on the nerve root. The other way is to strengthen the role of the spinal ligaments and help the intervertebral disc reset. It has also been noted that lumbar traction is thought to alter disc size [2]. However, there is no evidence supporting such conclusion, and no theoretical basis was proposed.

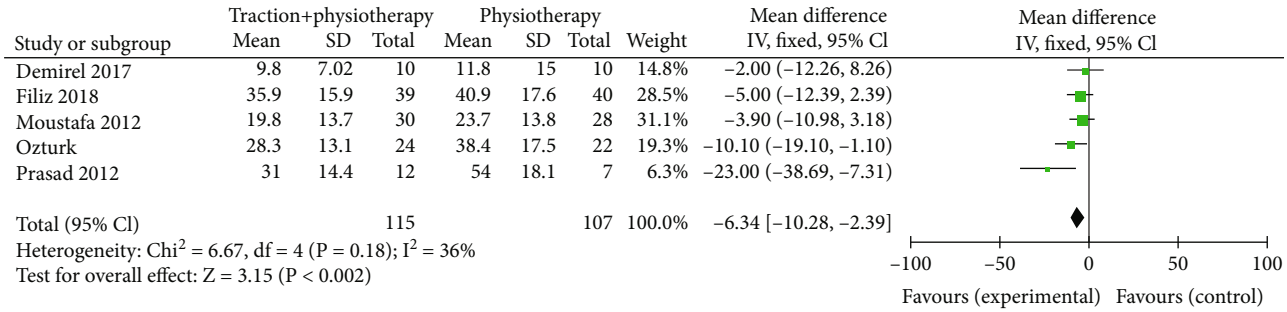

Figure 4: Forest diagram of ODI comparison between mechanical traction and conventional physical therapy.

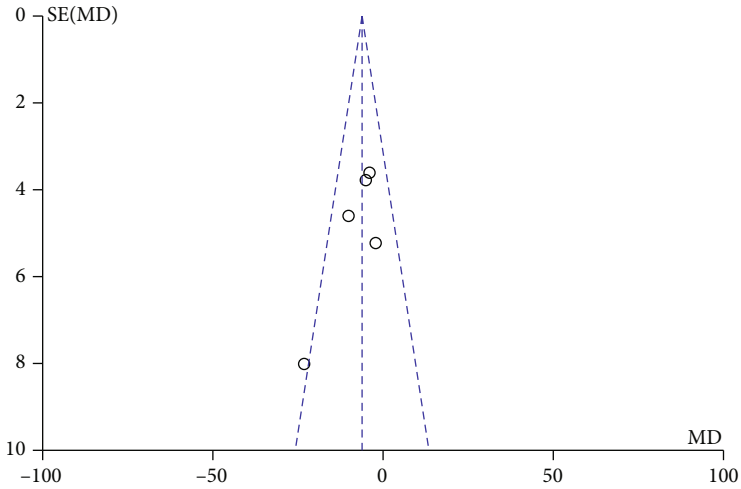

Figure 5: Funnel diagram of ODI comparison between mechanical traction and conventional physical therapy. MD means mean difference; SE stands for standard error.

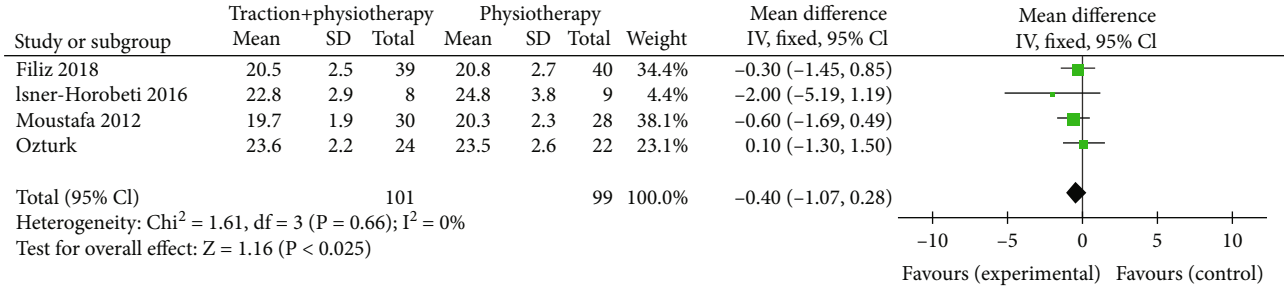

Figure 6: Forest diagram of comparison between mechanical traction and conventional physical therapy Schober test.

We reviewed the literature included in the analysis. Bilgilisoy et al. [15] compared the effects of supine traction, prone traction, and conventional physical therapy on ODI, pain, and activity in patients with a lumbar disc. They suggested that mechanical traction can improve ODI and reduce pain, but it has no significant effect on activity. The study [15] also pointed out that mechanical traction in a prone position was better than in a supine position. In other studies, such as Demirel et al. [18] compared the efficacy of traction decompression with conventional physical therapy. From which, both treatments could reduce the pain symptoms of patients with lumbar disc herniation and promote the functional recovery of patients. This study [18] suggested traction decompression as an auxiliary physical therapy method for lumbar disc herniation. Isner-Horobeti et al. [19] further compared the efficacy of high-intensity and low-intensity lumbar traction in treating acute sciatica secondary to intervertebral disc herniation. Both high-intensity and low-intensity traction could reduce nerve root pain and improve patients' dysfunction and psychological state. The curative effect of high-intensity traction was better than that of low-intensity traction. The impact of mechanical traction had

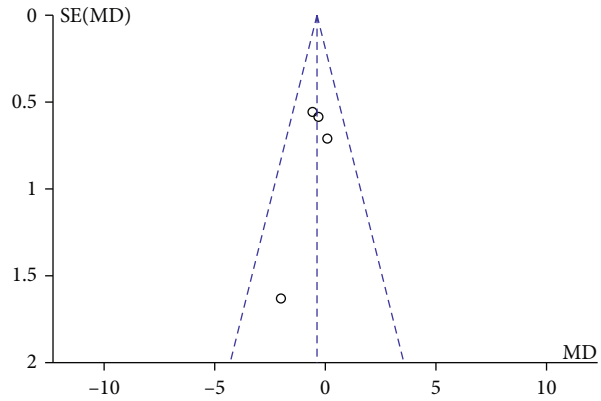

Figure 7: Funnel diagram of comparison between mechanical traction and conventional physical therapy Schober test. MD means mean difference; SE stands for standard error.

nothing to do with the initial amount of drug treatment, and the treatment effect could be maintained for at least 2 weeks. Moustafa and Diab [16] studied the effect of mechanical traction and physical therapy on unilateral lumbosacral radiculopathy caused by L5-S1 disc herniation. After 10 weeks of treatment, the traction group was better than the control group in ODI, low back and leg pain, modified Schober test, and intervertebral movement. At 6 months of follow-up, the difference between the traction group and the control group in the above variables was still statistically significant. However, the modified Schober test results of Moustafa and Diab [16] were inconsistent with our meta-analysis results. Other studies have also suggested that lumbar traction cannot improve spinal mobility [21, 22], which might be related to the strict restriction of the research object, meaning the inclusion of only patients with lumbar lordosis angle less than 39° might lead to more significant results. They also suggested a long-term effect was observed in 6-month follow-ups, which is controversial to other previous studies indicating that the curative effect of lumbar traction could only be reflected in the short term [2]. Ozturk et al. [20] studied the effect of continuous lumbar traction on the clinical and imaging manifestations of patients with lumbar disc herniation. The traction group was treated with physical therapy combined with continuous lumbar traction while the control group only received physical therapy. During Ozturk et al.'s study, patients with higher protrusion responded better to traction. Lumbar traction can not only effectively improve the clinical manifestations of patients with lumbar disc herniation but also reduce the degree of lumbar disc herniation. Prasad et al. [17] also concluded that intermittent traction combined with physical therapy could improve the clinical symptoms and function of lumbar disc herniation and improve the life treatment of patients. Intermittent traction could significantly reduce the need for surgery.

With all the strict analysis in this study, there are some limitations. The literature sizes and case sizes were limited by the strict criteria applied. In addition, sham traction controls and blank controls were included in the included studies, which may have had some impact on the results. Larger randomized controlled trials are still needed to confirm the therapeutic effect of mechanical traction on lumbar disc herniation.

Mechanical traction is a way of physical therapy which can effectively reduce the low back and leg pain and improve ODI in patients with lumbar disc herniation. Still, it has no significant effect on the spine's range of motion. The therapeutic effect of mechanical traction is significantly better than that of conventional physical therapy. Lumbar traction can be combined with other conventional physical therapy.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Wenxian Wang and Feibing Long contributed equally to this work.

Acknowledgments

This project was supported by Hainan Province Clinical Medical Center.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 6420738, 6 pages
https://doi.org/10.1155/2022/6420738

Research Article

Effect of Carbetocin on Postpartum Hemorrhage after Vaginal Delivery: A Meta-Analysis

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Received 8 May 2022; Revised 31 May 2022; Accepted 8 June 2022; Published 20 June 2022

Academic Editor: Xi Lou

Background. The efficacy of oxytocin and carbetocin in preventing postpartum hemorrhage (PPH) in women with vaginal delivery has been controversial. This study is aimed at conducting a meta-analysis that compares the efficacy of carbetocin and oxytocin in the prevention of PPH among women with vaginal delivery. *Methods*. Literature was retrieved from PubMed, Medline, Embase, CENTRAL, and CNKI databases. The randomized controlled trials (RCTs) that compare the efficacy of carbetocin and oxytocin to prevent PPH were searched. Data from the included literatures were extracted by two researchers, including author, title, publication date, study type, study number, the incidence of PPH, number of patients requiring additional uterotonics, and number of patients requiring blood transfusion. Jadad scale was used to evaluate the quality of the included RCTs. The Chi-square test was adopted for the heterogeneity test. A fixed-effect model was used for analysis if heterogeneity did not exist between literatures. If heterogeneity exists between literatures, a random-effect model was used for analysis. The source of heterogeneity was explored by subgroup analysis and sensitivity analysis. *Results*. The incidence of PPH in the carbetocin group was lower than that in the oxytocin group (OR = 0.62, 95% CI (0.46, 0.84), $Z = 3.14$, $P = 0.002$). There was no heterogeneity among studies ($\chi^2 = 7.29$, $P = 0.12$, $I^2 = 45\%$) and no significant publication bias ($P > 0.05$). The proportion of women requiring additional uterotonics in the carbetocin group was lower than that in the oxytocin group (OR = 0.41, 95% CI (0.29, 0.56), $Z = 5.34$, $P < 0.00001$). There was no heterogeneity among studies ($\chi^2 = 0.82$, $P = 0.84$, $I^2 = 0\%$) and no significant publication bias ($P > 0.05$). There was no significant difference in the proportion of women needing blood transfusion between the carbetocin group and the oxytocin group (OR = 0.92, 95% CI (0.66, 1.29), $Z = 0.46$, $P = 0.64$). There was no heterogeneity among studies ($\chi^2 = 3.06$, $P = 0.55$, $I^2 = 0\%$) and no significant publication bias ($P > 0.05$). *Conclusion*. Carbetocin is superior to oxytocin in preventing PPH among women with vaginal delivery and can be widely used in clinical practice.

1. Introduction

Postpartum hemorrhage (PPH), as one of the leading causes of maternal death worldwide [1, 2], accounts for 27.1% of all maternal deaths [3]. The proportion of deaths caused by PPH is positively related to the income levels across countries [3–6]. The main cause of PPH is uterine atony [7]. Any factor affecting the normal contraction and retraction function of postpartum uterine muscle fibers can increase the amount of postpartum hemorrhage [8]. Pregnant women with multiple pregnancies, giant fetuses, polyhydramnios, placenta previa, and other conditions are prone to uterine asthenia PPH [9].

The induction of uterine contractions using clinical treatment could reduce the risk of PPH [10]. For example, oxytocin, as a uterine contractile agent, is widely used to prevent PPH [11]. The disadvantages of oxytocin including poor thermal stability and low-temperature transportation

need cause the noneffective use in high temperature and humid environment [12]. Other conditions such as short half-life of oxytocin also lead to a frequent administration for patients. Overcoming the defects of oxytocin, another medical agent, carbetocin, showed better thermal stability and longer half-life [13, 14].

However, the efficacy of oxytocin and carbetocin in preventing postpartum hemorrhage in vaginal delivery has been controversial. Some studies [15] reported that application of carbetocin resulted in less PPH incident and lower amount of postpartum hemorrhage compared with oxytocin. In addition, the change of maternal systolic blood pressure after carbetocin administration was small. Other studies, however, noted that oxytocin and carbetocin showed similar therapeutic effects on PPH prevention [16]. To understand the similarity and differences, we conducted a meta-analysis to systematically evaluate the effects of oxytocin and carbetocin in PPH prevention in vaginal delivery.

2. Materials and Methods

2.1. Literature Extraction. Literature search was conducted in PubMed, Medline, Embase, CENTRAL, and CNKI databases. The searching criteria included (carbetocin) AND (postpartum haemorrhage OR PPH) AND (vaginal delivery OR vaginal birth). There were no restrictions on document language and publication time.

2.2. Literature Screening. Literature inclusion criteria: (1) the subjects were pregnant women with vaginal delivery; (2) the study included randomized control and experimental group; (3) the experimental group was given carbetocin, and the control group was given oxytocin; (4) the observed outcomes including at least one of the following: the incidence of PPH, the proportion of patients requiring additional uterotonics, and the proportion of patients receiving blood transfusion; (5) the type of study was randomized controlled study.

Literature exclusion criteria: (1) repeated reports and case reports; (2) the subjects included patients with cesarean section or undefined delivery method; (3) there was no control group in the study; (4) the balance of baseline data between the study group and the control group was poor; (5) the required data cannot be obtained, and the author of the literature cannot be contacted to supplement.

2.3. Data Extraction. In this paper, Huang and Xue jointly extracted the data information in the literature included in the analysis, including the author, title, publication time, research type, number of researchers, the incidence of PPH, number of patients requiring additional intrauterine tension, and the number of patients requiring blood transfusion. Data were unable to obtain in the literature can be obtained by contacting the author. When there were different opinions on literature data extraction, the two researchers discussed and reached an agreement.

2.4. Literature Quality Evaluation. The quality of included RCT studies was evaluated by Huang and Xue using the Jadad scale including the method of generating the random sequence, concealment of randomization, blinding, and the withdrawal rules.

2.5. Heterogeneity Test. The Chi-square test was used for the heterogeneity test. When I^2 corrected by degrees of freedom was more than 50% or $P < 0.1$, it was considered that there was heterogeneity among published literatures, and a random effect model was used. Subgroup analysis was used to explore the causes of heterogeneity and sensitivity. If the source of heterogeneity could not be identified, the literature results were discussed without merging. When the I^2 corrected by degrees of freedom was ≤50% and $P \geq 0.1$, it was considered that there was no heterogeneity among the published literatures, and the fixed effect model was used.

2.6. Publication Bias Assessment. Egger test was used to evaluate the publication bias. $P > 0.05$ suggested no significant publication bias, and $P < 0.05$ indicated that there was a certain publication bias.

2.7. Statistical Method. In this study, Cochrane software RevMan5.3 was used for statistical analysis of the data. Statistical descriptions of effect sizes were performed using odds ratio (OR) values and a 95% confidence interval (CI). Two-sided $P < 0.05$ indicated statistical significance.

3. Results

3.1. Characteristics of Included Literature. A total of 1349 literatures were retrieved according to method. Basing on screening criteria, 1344 literatures were excluded, and a total of 5 literatures were included in the study [15–19]. The flowchart of literature screening is shown in Figure 1. All 5 literatures were randomized controlled studies in English. This study included a total of 4631 pregnant women, among which, 2323 pregnant women used carbetocin and 2308 used oxytocin. The basic information of literature was summarized in Table 1, and Jadad score was listed in Table 2.

3.2. Comparison of PPH Incidence. Five studies were included to compare the incidence of maternal PPH in the carbetocin group and the oxytocin group in our meta-analysis. Heterogeneity test showed that there was no heterogeneity among the five studies ($\text{Chi}^2 = 7.29$, $P = 0.12$, $I^2 = 45\%$). Thus, the fixed-effect model was used for data consolidation. As shown in Figure 2, the incidence of PPH in carbetocin group was lower compared with that in oxytocin group (OR = 0.62, 95% CI (0.46, 0.84), $Z = 3.14$, $P = 0.002$). In addition, Egger test showed no significant publication bias among the studies ($P > 0.05$).

3.3. Comparison of the Proportion of Pregnant Women Using Extra Intrauterine Tension. In this meta-analysis, four studies compared the proportion of women in the carbetocin group and oxytocin group who needed additional intrauterine tension. Heterogeneity test showed that there was no heterogeneity among the four studies ($\text{Chi}^2 = 0.82$, $P = 0.84$, $I^2 = 0\%$). Following, the fixed-effect model was used for data consolidation. The results showed, in Figure 3, that the proportion of pregnant women who needed additional

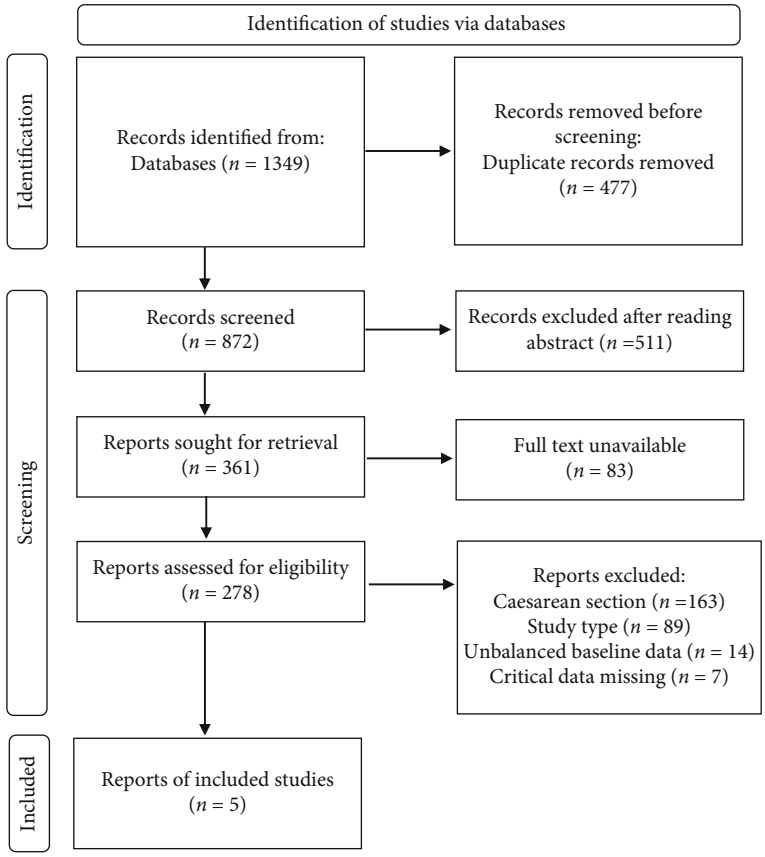

Figure 1: Flowchart of literature screening.

Table 1: Included literature characteristics.

Author and year	Study type	No. of patients Carbetocin	No. of patients Oxytocin	Outcomes	Drugs
Amornpetchakul et al. 2018 [17]	RCT	176	174	PPH, additional uterotonics, and blood transfusion	Oxytocin: 5 U; intravenous Carbetocin: 100 μg; intravenous
Elfayomy 2015 [19]	RCT	38	40	PPH, additional uterotonics, and blood transfusion	Oxytocin: 50 IU; intravenous Carbetocin: 100 μg; intravenous
Maged et al. 2016(A) [18]	RCT	100	100	PPH, additional uterotonics, and blood transfusion	Oxytocin: 5 IU Carbetocin: 100 μg
Maged et al. 2016(B) [15]	RCT	100	100	PPH, additional uterotonics, and blood transfusion	Oxytocin: 5 IU; per os Carbetocin: 100 μg; per os
Nelson et al. 2021 [16]	RCT	1909	1894	PPH, additional uterotonics, and blood transfusion	Oxytocin: 10 IU; intravenous Carbetocin: 100 μg; intravenous

intrauterine tension in the carbetocin group was lower than that in the oxytocin group (OR = 0.41, 95% CI (0.29, 0.56), $Z = 5.34$, $P < 0.00001$). Egger test showed no significant publication bias among the studies ($P > 0.05$).

3.4. Comparison of the Proportion of Parturient Receiving Blood Transfusion. Five studies selected for this meta-analysis compared the proportion of pregnant women requiring blood transfusion in the carbetocin group and oxytocin group. Heterogeneity test showed that there was no heterogeneity among the five studies ($\text{Chi}^2 = 3.06$, $P = 0.55$, $I^2 = 0\%$). The fixed-effect model was used for consolidation. There was no significant difference in the proportion of pregnant women requiring blood transfusion between carbetocin group and oxytocin group (OR = 0.92, 95% CI (0.66, 1.29), $Z = 0.46$, $P = 0.64$) as shown in Figure 4. Egger test

Table 2: Jadad score of included literatures.

Author and year	Randomization	Concealment of allocation	Double blinding	Withdrawals and dropouts
Amornpetchakul et al. 2018 [17]	1	1	2	1
Elfayomy 2015 [19]	2	1	2	1
Maged et al. 2016(A) [18]	2	2	2	1
Maged et al. 2016(B) [15]	1	2	1	1
Nelson et al. 2021 [16]	2	2	1	1

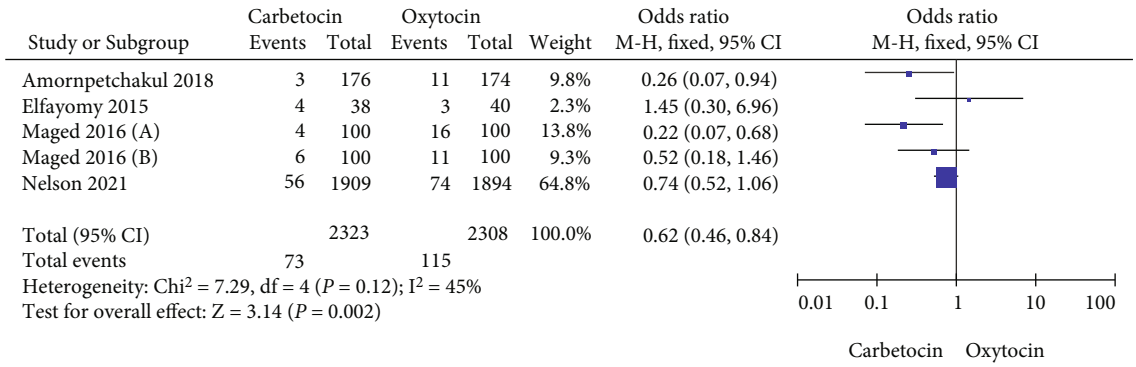

Figure 2: Forest chart compares the incidence of postpartum hemorrhage between the carbetocin and the oxytocin groups.

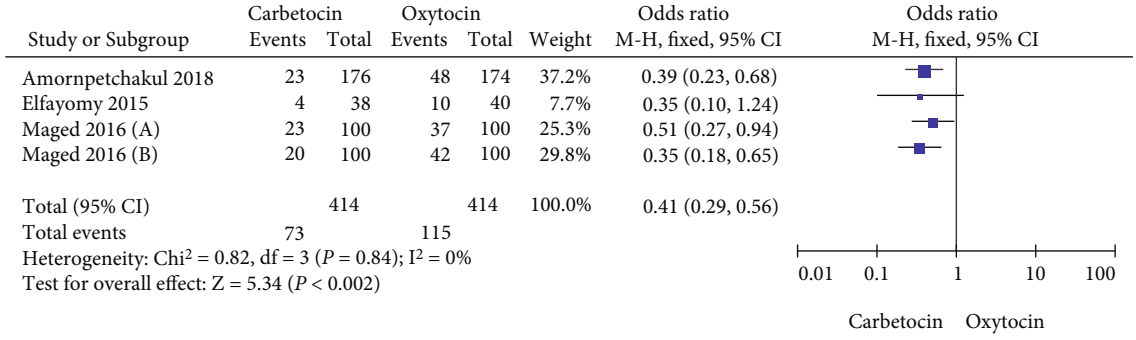

Figure 3: Comparison of the proportion of women in the carbetocin and oxytocin groups requiring additional uterine contractions.

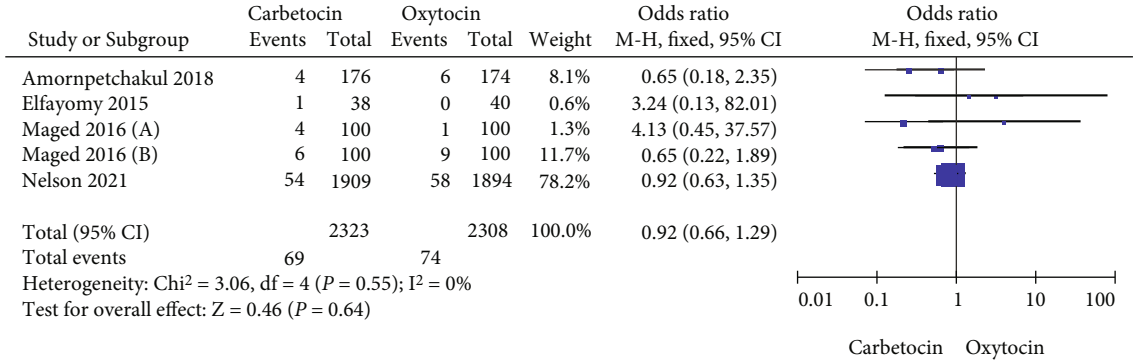

Figure 4: Forest map compares the proportion of pregnant women requiring blood transfusion in the carbetocin and oxytocin groups.

showed no significant publication bias among the studies ($P > 0.05$).

4. Discussion

Our meta-analysis showed that PPH incidence and the use of additional intrauterine tensors in the carbetocin group were lower than those in the oxytocin group. There was no significant difference between the two groups in the proportion of parturient receiving a blood transfusion. This conclusion is consistent with some of the research results included in our analysis. Furthermore, Amornpetchakul et al. [17] studied singleton pregnant women with at least one PPH risk factor. Their results showed that the carbetocin group had a lower incidence of prevention of dystonic PPH and less use of additional uterine tension drugs than the oxytocin group. It was also noted that, although the blood loss after delivery was lower than that in the oxytocin group, the incidence of anemia was lower in carbetocin treated group. However, other studies such as Elfayomy [19] found no significant difference between the carbetocin group and the oxytocin group in blood loss, decreased hemoglobin level, and the proportion of pregnant women injected with additional uterine tension. Additionally, the reduction of the placenta was similar in both carbetocin and oxytocin groups. However, carbetocin advantaged in hemodynamic safety and stable blood pressure postadministration. Taken together, this study suggested to use carbetocin instead of oxytocin for placental delivery management. Maged et al. [15] conducted a prospective and double-blind study and found that PPH and the amount of bleeding in the carbetocin group were lower than those in the oxytocin group. Only slight decrease in maternal hemoglobin and hemodynamic changes was observed in carbetocin group. There was no significant difference between carbetocin and oxytocin in the incidence of nausea, vomiting, and dyspnea. Carbetocin was suggested to be more likely to cause maternal tachycardia; however, further research is needed. Maged et al. [15] studied high-risk pregnant women with PPH, and in another study, Maged et al. [18] presented that carbetocin had significant advantages in preventing PPH incidence compared with oxytocin. Still, there is no significant difference between maternal hemodynamic changes and side effects. Nelson et al. [16] considered that the effect of carbetocin was not inferior to oxytocin in the prevention of PPH, and the incidence of side effects was similar.

Tareef et al. [20] found no significant difference in using additional intrauterine tensors between the carbetocin group and the oxytocin group in pregnant women with vaginal delivery and elective cesarean section. The incidence of PPH in the carbetocin group was higher than that in the oxytocin group. The need of blood transfusion was more commonly seen in carbetocin treated group. The final conclusion of this study is inconsistent with our meta-analysis study. This study was excluded from meta-analysis study due to the objects included women undergoing elective cesarean section. Also, this study was a retrospective study. Another retrospective analysis [14] concluded that carbetocin and oxytocin had similar effects on the prevention of PPH, but carbetocin increased the incidence of placental retention.

In addition, some studies [21] indicated that carbetocin has an overwhelming advantage in economic benefits and costs for preventing PPH in pregnant women undergoing elective cesarean section. However, the same principle does not apply to women undergoing vaginal delivery. Studies such as Briones et al. [22] suggested that carbetocin is not a cost-effective choice for either vaginal delivery or cesarean section. The use of carbetocin needs to consider the economic cost, especially in low or middle-income families. For that purpose, oxytocin application is more widely used in low or middle-income countries.

Regarding to the limitations in this study, there are few randomized controlled trials comparing the effects of carbetocin and oxytocin on postpartum hemorrhage. High-quality randomized controlled trials are needed to validate the conclusions. Second, the age and underlying disease on drug efficacy were not taken into consideration due to the limited information. The clinical significance could be further deepened if multilayer analysis could be conducted.

In conclusion, carbetocin is superior to oxytocin in preventing PPH in vaginal delivery and can be popularized in the clinic.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Xiaojuan Huang and Wanxing Xue contributed equally to this work.

Acknowledgments

The study was supported by Hainan Province Health and Family Planning Scientific Research (no.: 16A200015).

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 2851572, 9 pages
https://doi.org/10.1155/2022/2851572

Research Article

Effect of Different Glucose Monitoring Methods on Bold Glucose Control: A Systematic Review and Meta-Analysis

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Received 21 April 2022; Revised 16 May 2022; Accepted 1 June 2022; Published 18 June 2022

Academic Editor: Xi Lou

Objective. To evaluate the effectiveness of different glucose monitoring methods on blood glucose control and the incidence of adverse events among patients with type 1 diabetes mellitus. *Methods*. Using the method of literature review, the databases PubMed, Cochrane, and Embase were retrieved to obtain relevant research literature, and the selected studies were analyzed and evaluated. This study used Cochrane software RevMan5.4 to statistically analyze all the data. *Results*. A total of 15 studies were included in this study, including 10 randomized controlled trials and 5 crossover design trials, with a total of 2071 patients. Meta-analysis results showed that continuous blood glucose monitoring (CGM) could significantly reduce the HbA1c level of patients, weighted mean difference (WMD) = −2.69, 95% confidence interval (CI) (-4.25, -1.14), and $P < 0.001$ compared with self-monitoring of blood glucose (SMBG). Meanwhile, the incidence of severe hypoglycemia in the CGM group was significantly decreased, risk ratio (RR) = 0.52, 95% CI 0.35-0.77, and $P = 0.001$. However, there was no statistical difference in the probability of diabetic ketoacidosis between CGM and SMBG groups, RR = 1.34, 95% CI 0.57-3.15, and $P = 0.5$. *Conclusion*. Continuous blood glucose monitoring is associated with lower blood glucose levels than the traditional blood glucose self-test method.

1. Introduction

Diabetes, as a new global epidemic, has been increasing worldwide in recent years [1]. Diabetes is one of the most common chronic diseases in China, with a high prevalence rate of 12.8% [2]. Meanwhile, it also has a high incidence. Diabetes is divided into type 1 diabetes and type 2 diabetes. Type 1 diabetes is also known as insulin-dependent diabetes mellitus, which occurs primarily in children and adolescents and requires insulin to restore the blood glucose level. Although the incidence rate of type I diabetes is lower than type 2 diabetes, research suggested that type I diabetes has a higher economic cost to the national health care system than type II [3]. The increased financial burden may relate to the reliance on insulin therapy and the occurrence of serious complications [4]. Insulin treatment can effectively decrease blood sugar. Monitoring blood glucose levels is also very important to keep the blood glucose level at a normal level [5, 6].

The detection of blood glucose is helpful to early identify patients with hypoglycemia, evaluate the degree of glucose metabolism disorder, and reasonably formulate personalized blood glucose management plans for patients. However, the traditional self-monitoring of blood glucose (SMBG) method often cannot provide real-time blood glucose data and cannot give early warning of asymptomatic blood glucose abnormalities [7]. Continuous glucose monitoring (CGM) is a dynamic glucose monitoring method that includes an inserting subcutaneous sensor, which can automatically measure the individual interstitial glucose level all day and understand the patient's blood glucose fluctuation by providing an ambulatory glucose profile (AGP) [8]. At present, there are several main types of CGM systems: retrospective CGM (r-CGM), real-time blood glucose monitoring (rt-CGM), and intermittent scanning CGM (isCGM). Each system is slightly different in function [9]. However, the actual effect of CGM on blood glucose control in type 1

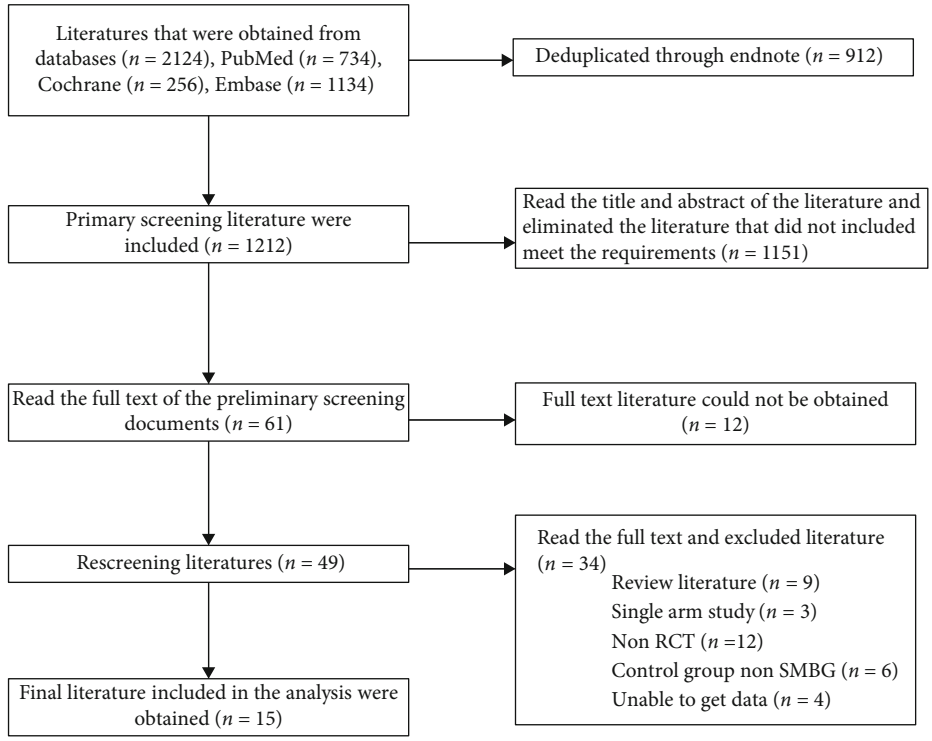

Figure 1: Document screening process and results.

diabetes mellitus is uncertain. To further evaluate the effectiveness of CGM and SMBG in maintaining glycemic control among patients with type 1 diabetes, this study will conduct a quantitative meta-analysis by retrieving the latest published clinical studies.

2. Method

2.1. Bibliography Retrieval. PubMed, Cochrane Library, and Embase were searched from January 2015 to April 2022. Search terms and keywords included "type 1 diabetes OR insulin dependent diabetes OR IDDM OR T1DM OR autoimmune diabetes OR" AND "continuous glucose monitor∗ OR CGM" AND "blood glucose self monitor∗ OR SMBG."

2.2. Literature Screening. Inclusion criteria: (1) the subjects were diagnosed with type 1 diabetes mellitus and were receiving intensive insulin therapy, with a study period of at least 8 weeks. (2) The study must be a two-arm study. The experimental group adopts continuous blood glucose monitoring, and the control group adopts traditional self-blood glucose monitoring; (3) the literature type was a randomized controlled study; (4) the study included at least one of the following outcomes: HbA1c level, severe hypoglycemia (SH), and diabetes mellitus (diabetic) ketoacidosis (DKI). The literature language, publication date, or impact factors were not limited.

Exclusion criteria: (1) news reports, expert opinions, critical literature, and abstracts; (2) republished literature; (3) unable to obtain enough literature to analyze the data.

2.3. Document Data Extraction. The literatures were screened and the data extraction was done by Wang and Li independently. The content includes: publication date, author's name, study type, patient inclusion criteria, number of patients, subject characteristics, data results and other information. If there were questions or differences in the literature screening and extraction process, a third researcher assisted in resolving and deciding through discussion at the meeting if necessary.

2.4. Literature Quality Evaluation. The quality of the included literature was evaluated according to the risk bias evaluation tool in the Cochrane manual. The evaluation contents include (1) whether the random allocation method is appropriate, (2) whether the random allocation scheme is hidden, (3) researchers and subjects were blinded, (4) blind evaluation of research results, (5) whether the result data is complete, (6) whether there are selective reports of results, and (7) whether there are other sources of bias. The evaluation results were divided into high, low, and uncertain risks. Two researchers independently evaluated the quality of the included literatures and then crosschecked. If there was any difference, both parties discussed it to reach an agreement or ruled by the third researcher.

2.5. Statistical Method. This study used Cochrane software RevMan5.4 to statistically analyze all the data. The counting data were statistically described by calculating risk ratio (RR) value and 95% confidence interval (CI), and the measurement data were statistically described by weighted mean difference (WMD) and 95% CI. It was considered statistically significant when $P < 0.05$ using a fixed-effect model or

Table 1: Basic characteristics of included literature.

ID	Research type	Country	Blood glucose monitoring mode	Sample size	Insulin regimen	Age	Baseline HbA1c (mmol/mol)	Baseline HbA1c (%)	Diabetes mellitus time	Study time	Outcome indicators
Ajjan et al. 2016[10]	RCT	Britain	RT-CGM	28	MDI	39 ± 11.5	77.06 ± 14.21	9.2 ± 1.3	15.8 ± 11.9	100 days	HbA1c
			SMBG	13	MDI	43.7 ± 9.9	74.87 ± 14.21	9.0 ± 1.3	19.6 ± 12.4		
Beck et al. 2017[11]	RCT	U.S.	RT-CGM	105	MDI	46 ± 14	70.5 ± 7.65	8.6 ± 0.7	19.0 ± 14.8	24 weeks	HbA1c, SH, DKA
			SMBG	53	MDI	51 ± 11	70.5 ± 6.56	8.6 ± 0.6	21.7 ± 17.8		
Bolinder et al. 2016[12]	RCT	Europe	isCGM	120	MDI/CSII	42 ± 13.3	50.7 ± 5.7	6.79 ± 0.52	20.0 ± 10.4	24 weeks	HbA1c, SH, DKA
			SMBG	121	MDI/CSII	45 ± 17.8	50.6 ± 6.7	6.78 ± 0.64	21.3 ± 14.8		
Bosi et al. 2019[13]	RCT	Britain	RT-CGM	76	CSII	49.0 ± 12.2	60.7 ± 9.9	7.7 ± 0.9	28.5 ± 11.1	24 weeks	HbA1c, SH, DKA
			SMBG	77	CSII	47.4 ± 12.5	59.7 ± 9.9	7.6 ± 0.9	29.7 ± 13.3		
Boucher et al. 2020[14]	RCT	New Zealand	isCGM	33	MDI/CSII	16.5 ± 1.9	94.55 ± 18.58	10.8 ± 1.7	7.0 ± 3.5	24 weeks	HbA1c, SH, DKA
			SMBG	31	MDI/CSII	16.7 ± 2.2	98.92 ± 17.49	11.2 ± 1.6	8.0 ± 4.0		
Dicembrini et al. 2020[15]	Cross design test	Europe	RT-CGM	14	CSII	45.7 ± 8.2	60.66 ± 4.37	7.7 ± 0.4	17.3 ± 18.5	16 weeks	HbA1c, SH, DKA
			SMBG	14	MDI	44.7 ± 8.7	61.75 ± 5.47	7.8 ± 0.5	19.0 ± 19.3		
Heinemann et al. 2018[16]	RCT	Europe	RT-CGM	74	MDI	45.8 ± 12.0	59.57 ± 10.93	7.6 ± 1.0	20.9 ± 14.0	26 weeks	HbA1c
			SMBG	74	MDI	47.3 ± 11.7	57.38 ± 10.93	7.4 ± 1.0	21.6 ± 13.9		
Jensen et al. 2022[17]	RCT	Europe/North America	P-CGM	117	MDI/CSII	49 ± 12	58.2 ± 5.7	NR	28 ± 12	16 weeks	HbA1c, SH
			SMBG	355	MDI/CSII	42 ± 15	58.4 ± 5.9	NR	23 ± 12		
Laffel et al. 2020[18]	RCT	U.S	RT-CGM	74	MDI/CSII	17 ± 3	73.78 ± 10.93	8.9 ± 1.0	9.0 ± 5.0	26 weeks	HbA1c, SH, DKA
			SMBG	79	MDI/CSII	18 ± 3	73.78 ± 10.93	8.9 ± 1.0	10.0 ± 5.0		
Lind et al. 2017[19]	Cross design test	Europe	RT-CGM	82	MDI	46.7 ± 13	69.3 ± 9.84	8.49 ± 0.9	23.4 ± 11.9	26 weeks	HbA1c, SH, DKA
			SMBG	79	MDI	42.6 ± 12.2	68.86 ± 9.84	8.45 ± 0.9	21.0 ± 11.7		
Pratley et al. 2020[20]	RCT	U.S	RT-CGM	103	MDI/CSII	68.3 ± 5.2	59.57 ± 9.84	7.6 ± 0.9	37.3 ± 18.5	24 weeks	HbA1c, SH, DKA
			SMBG	100	MDI/CSII	67.3 ± 5.2	58.48 ± 8.74	7.5 ± 0.8	36.0 ± 16.3		
Thabit et al. 2020[21]	Cross design test	Britain	RT-CGM	16	MDI/CSII	21 ± 2.28	NR	NR	NR	8 weeks	HbA1c, SH, DKA
			SMBG	15	MDI/CSII	21.4 ± 2.57	NR	NR	NR		

Table 1: Continued.

ID	Research type	Country	Blood glucose monitoring mode	Sample size	Insulin regimen	Age	Baseline HbA1c (mmol/mol)	Baseline HbA1c (%)	Diabetes mellitus time	Study time	Outcome indicators
Tumminia et al. 2015[22]	Cross design test	Europe	RT-CGM	10	MDI/CSII	NR	69.84 ± 4.37	8.54 ± 0.4	NR	24 weeks	HbA1c, SH, DKA
			SMBG	10	MDI/CSII	NR	NR	8.56 ± 0.5	NR		
van Beers et al. 2016[23]	Cross design test	Netherlands	RT-CGM	26	MDI/CSII	NR	NR	NR	NR	16 weeks	HbA1c, SH, DKA
			SMBG	26	MDI/CSII	NR	70.06 ± 5.47	NR	NR		
Zhang et al. 2021[24]	RCT	China	FGM	71	MDI/CSII	36.68 ± 19.71	NR	9.05 ± 1.43	4 ± 2.3	48 weeks	HbA1c
			SMBG	75	MDI/CSII	35.19 ± 18.91	NR	9.07 ± 1.18	5 ± 2.3		

Note: RT-CGM: real-time blood glucose monitoring; SMBG: self-blood glucose monitoring; isCGM: intermittent scanning CGM; P-CGM: individual continuous blood glucose monitoring; FGM: rapid blood glucose monitoring; SH: severe hypoglycemia; DKA: diabetes ketoacidosis; CSII: insulin pump; MDI: multiple subcutaneous injections per day; RCT: randomized control trials.

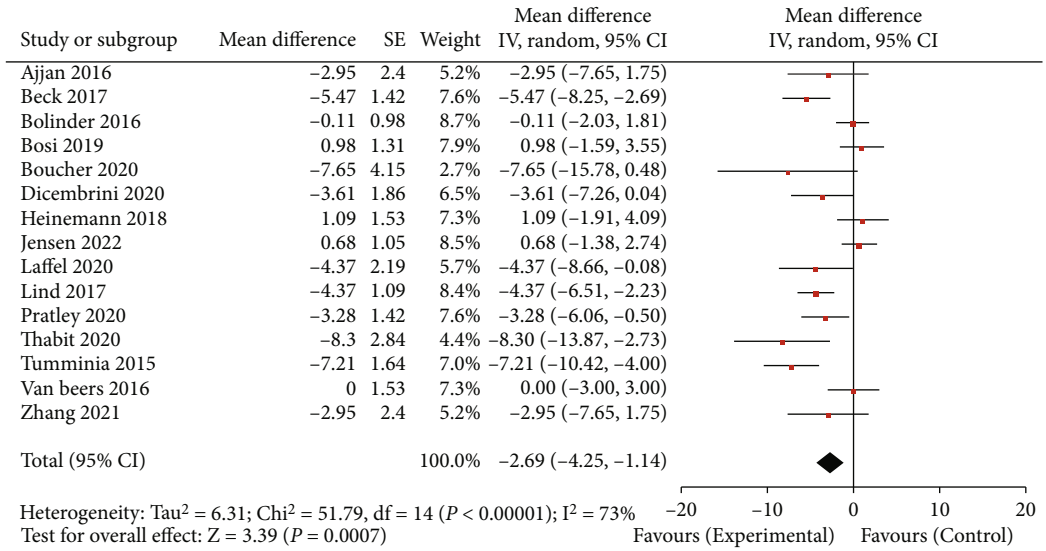

Figure 2: HbA1c horizontal forest map. CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose.

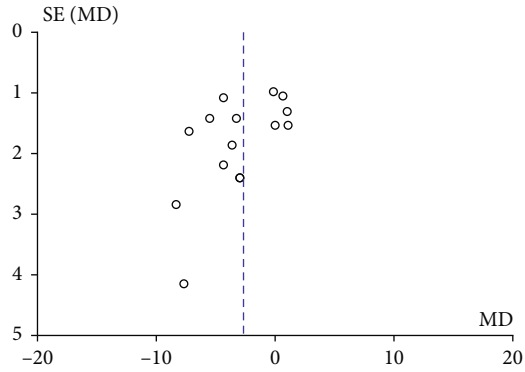

Figure 3: Horizontal funnel diagram of HbA1c. MD: mean difference.

random-effect model. The Chi-square test was used to test the heterogeneity between different studies. When the I^2 corrected by degrees of freedom was more than 50%, it was considered heterogeneous, and the random effect model was used. When I^2 corrected by degrees of freedom is ≤50%, it was considered that there was no heterogeneity, and the fixed effect model was adopted. The potential publication bias was estimated by funnel plot.

3. Results

3.1. Literature Search Results. In this study, 2124 relevant literatures were obtained through database retrieval. After the retirement, collected literatures were deduplicated by EndNote X9 management software. They were screened through reading topics and abstracts according to the predetermined inclusion and exclusion criteria and then further read the full text for rescreening. Finally, 15 literatures meeting the criteria were included. The specific screening process and results are shown in Figure 1.

3.2. Basic Characteristics and Quality Evaluation of Literature. According to the inclusion and exclusion criteria, a total of 15 studies were included. The basic information of the included literature is shown in Table 1. The published time was from 2015 to 2022. The included literature is relatively new. The literature types were prospective clinical trials, including 10 randomized controlled trials and 5 cross-design trials. The study population included people from the United States, the United Kingdom, Switzerland, the Netherlands, and China. The 15 studies included 2071 patients with type 1 diabetes. Most of the continuous blood glucose monitoring methods in the intervention group were real-time blood glucose monitoring, including 11 using RT-GCM, 2 using intermittent scanning CGM, 1 using personal continuous blood glucose monitoring, and 1 using rapid blood glucose monitoring. The insulin regimen included MDI, CSII, and MDI/CSII. The age of patients included adolescents, middle-aged, and elderly, but almost all were under the age of 50. The longest duration of diabetes was about 37 years. The course of each study was mainly 24/26 weeks. Cochrane risk bias assessment tool was used to evaluate the included literature. Only one literature was high-risk, three were uncertain, and the rest were low risk. It was considered that the quality of the included literature was high.

3.3. Meta-Analysis Results. All 15 studies reported the HbA1c level of patients after the intervention of CGM and SMBG. The heterogeneity test result I^2 was 73%, which had great heterogeneity. Therefore, the random effect model was used to merge the data. The results of the meta-analysis are shown in Figure 2. Compared with SMBG, CGM could significantly reduce the HbA1c level of patients. The combined result is WMD = −2.69, 95% CI (-4.25, -1.14), and $P < 0.001$. The publication bias of the included studies was detected. The results showed that the included literatures were symmetrically distributed around the combined effect of WMD value. The HbA1c

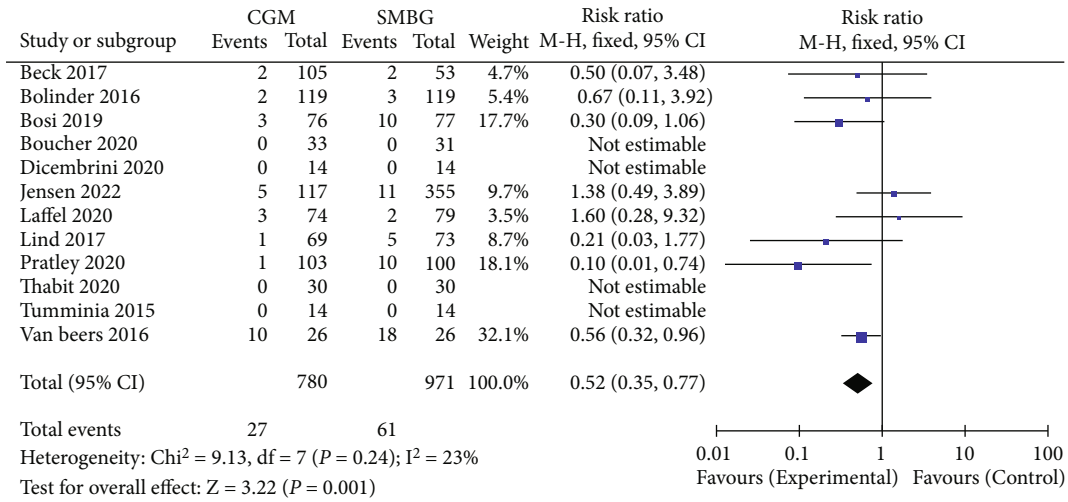

Figure 4: Forest map of severe hypoglycemia events. CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose.

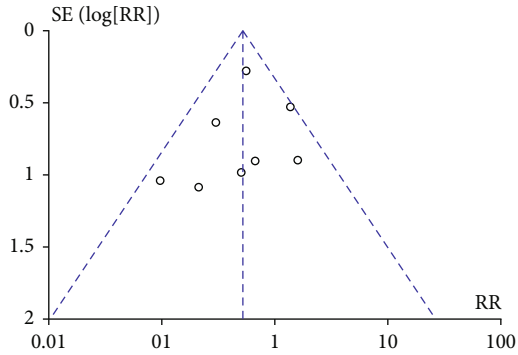

Figure 5: Funnel diagram of severe hypoglycemia events. RR: risk ratio.

level funnel is shown in Figure 3. It was considered that there was no publication bias.

12 studies reported severe hypoglycemic events among patients after the intervention of CGM and SMBG. The heterogeneity test result I^2 was 23%, and there was no heterogeneity. Therefore, the fixed-effect model was used to merge the data. The results of the meta-analysis are shown in Figure 4. Compared with SMBG group, the incidence of severe hypoglycemic events in CGM group was significantly lower, RR = 0.52, 95% CI 0.35-0.77, $P = 0.001$. The included studies were tested for publication bias. The results are shown in Figure 5. It was considered that there was no publication bias.

The 11 studies reported the risk of diabetic ketoacidosis after CGM and SMBG intervention. The heterogeneity test result I^2 was 0%, and there was no heterogeneity. Therefore, a fixed-effect model was used to merge data. Meta-analysis showed no statistical difference in the probability of occurrence of diabetes ketoacidosis between the CGM group and the SMBG group, RR = 1.34, 95% CI 0.57-3.15, and $P = 0.5$, respectively. The meta-analysis results showed no significant difference in the probability of occurrence of diabetic ketoacidosis. The results are shown in Figure 6. The included studies were tested for publication bias. The results are shown in Figure 7. It was considered that there was no publication bias.

4. Discussion

Diabetes, as one of the most common chronic diseases in the country, brings severe illness and financial burden to patients and families. Type 1 diabetes mellitus is dependent on insulin therapy, but this treatment may cause severe hypoglycemia. Therefore, it is essential to maintain the blood glucose level at an average level through real-time monitoring. HbA1c is the gold standard for assessing glycemic control and an alternative indicator [25] for evaluating the risk of long-term diabetes complications. CGM can play an early warning role among patients' blood glucose values as a dynamic blood glucose monitoring method. However, there is still some controversy about the actual effect of CGM on variables such as HbA1c. This study was conducted to analyze and discuss the three indicators of HbA1c level reduction, the incidence of severe hypoglycemia, and diabetes ketoacidosis before and after the intervention.

The results showed that the CGM group decreased by 2.69 mmol/mol at the HbA1c level compared with the SMBG group. Although the reduction was up to 5 mmol/mol, the decrease in HbA1c level is enough to reduce the risk of diabetes complications to a certain extent [13]. In addition, patients with high HbA1c levels often have macrovascular risks. Reducing HbA1c levels can effectively reduce the incidence of cardiovascular disease and death [26]. Compared with the SMBG group, the risk of severe hypoglycemic events in the CGM group was reduced by 48%, which is inconsistent with the results of other meta-analyses [6, 27]. This difference may be related to inconsistent criteria for determining adverse events. Still, the latest published clinical trial [15] showed that CGM could effectively reduce the occurrence of severe hypoglycemic events. There is no difference between the two methods in the incidence of diabetic ketoacidosis. This study indicated that the probability of

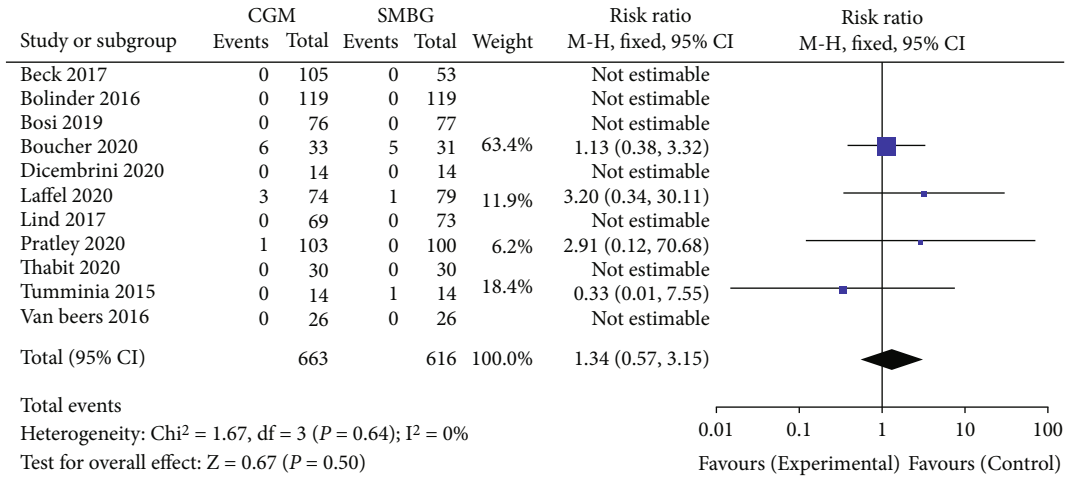

Figure 6: Forest chart of diabetes ketoacidosis. CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose.

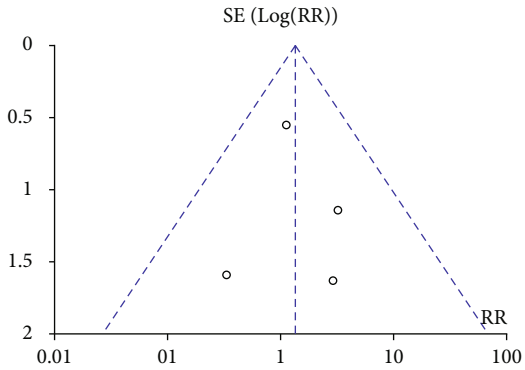

Figure 7: Funnel plot of diabetes ketoacidosis event. RR: risk ratio.

occurrence of diabetic ketoacidosis was about 1.3%. The incidence of diabetic ketoacidosis was rare. The results of this study are for reference only. Further studies on the effects of CGM on diabetic ketoacidosis are needed.

Some previous studies are consistent with our research direction. Maiorino et al. [28] noted that CGM could benefit patients with diabetes. In particular, this study highlights the advantages of CGM in controlling HbA1c control over time frames. Langendam et al. [29] pointed out that the evidence for the effectiveness of CGM is limited. Previous studies overstated his effectiveness. CGM did improve outcomes compared to patients who had never used a monitor. The control of HbA1c is largely influenced by compliance. The research objects included in this meta-analysis were biased. CGM was not popular at that time, and patients were more concerned about the cost of CGM. Our study incorporates recent high-quality randomized controlled trials that provide strong evidence for the results 22258980.

There are some limitations to our study. First, there was heterogeneity at the HbA1c level in the literature we included in the analysis. We have not been able to identify the source of heterogeneity. Second, the metrics we use to evaluate efficacy are inadequate, and more clinical indicators are needed to evaluate the efficacy of the two methods.

In conclusion, the results of this study suggested that continuous blood glucose monitoring is associated with lower blood glucose levels than the traditional blood glucose self-test method. Therefore, for patients with type 1 diabetes, CGM is a better method for monitoring blood glucose. It is suggested that type 1 diabetes patients, especially those with poor diabetes control, should use CGM instead of SMBG in blood glucose monitoring. This study promotes the management of patients with type 1 diabetes by evaluating the effectiveness of CGM and providing a reference for current and future related research.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Yeling Wang and Congcong Zou contributed equally to this work.

Acknowledgments

This study was supported by the First Affiliated Hospital of Hainan Medical University.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 6962654, 6 pages
https://doi.org/10.1155/2022/6962654

Research Article

ACEI and ARB Lower the Incidence of End-Stage Renal Disease among Patients with Diabetic Nephropathy: A Meta-analysis

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Received 10 April 2022; Accepted 11 May 2022; Published 31 May 2022

Academic Editor: Xi Lou

Objective. This study explores the effects of Angiotensin-Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB) on the incidence of end-stage renal disease (ESRD) in diabetic nephropathy (DN) patients. *Methods*. Literatures were searched in PubMed, Embase, Medline, CENTRAL, and CNKI databases. These literatures included a randomized controlled trial to evaluate the efficacy of ACEI and ARB among patients with DN. The endpoint event included the occurrence of ERSD. Risk ratio (RR) and 95% confidence interval (CI) were used to represent the combined effect size. A fixed-effect model was used to analyze if heterogeneity did not exist between literatures. If heterogeneity exists between literatures, a random-effect model was used to analyze. The source of heterogeneity was explored by subgroup analysis and sensitivity analysis. *Results*. A total of 11 literatures were included in the study. The RR of ESRD was 0.79 (95% CI (0.79, 0.90), $Z = 3.58$, $P = 0.0003$) in the patients treated with RAS blockers compared with placebo, and there was no heterogeneity between studies ($\text{Chi}^2 = 5.09$, $P = 0.88$, $I^2 = 0\%$). The funnel plot showed that the scatter point was biased to the left with publication bias. The RR of ESRD was 0.63 (95% CI (0.41, 0.95), $Z = 2.18$, $P = 0.03$) in the patients treated with ACEI compared with placebo. There was no heterogeneity between studies ($\text{Chi}^2 = 2.23$, $P = 0.95$, $I^2 = 0\%$). Compared with placebo, RR of ESRD among patients with ARB intervention was 0.81 (95% CI (0.71, 0.93), $Z = 3.00$, $P = 0.003$). There was no heterogeneity between studies ($\text{Chi}^2 = 1.49$, $P = 0.48$, $I^2 = 0\%$). *Conclusion*. ACEI and ARB can reduce the risk of ESRD among diabetic nephropathy patients.

1. Introduction

In recent years, the incidence of diabetes mellitus, primarily type 2 diabetes, gradually increased [1–3]. Diabetic nephropathy (DN) is one of the most common complications of diabetes [4, 5]. The end-stage renal disease (ESRD) is irreversible, which often diagnosed in the advanced stage [4]. DN is the most common single cause of ESRD [5]. The proportion of ESRD caused by diabetic nephropathy is increasing, which may be related to the increase in the diabetes incidence rate and the prolongation of the life span of diabetic patients [5]. Patients with diabetic nephropathy need to maintain dialysis or receive kidney transplantation [6, 7]. These treatment methods bring heavy economic and psychological burdens and occupy a lot of medical resources [7]. Delaying the progression of DN has important clinical significance [7].

For diabetic patients, the role of renin-angiotensin system (RAS) blockers, including Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB), has been controversial in improving clinical prognosis and reducing clinical events. According to a meta-analysis, ACEI and ARB have the advantage of [8] in treating diabetic nephropathy compared with other antihypertensive drugs. However, meta-analysis studies indicated that ACEI and ARB in reducing the risk of kidney events

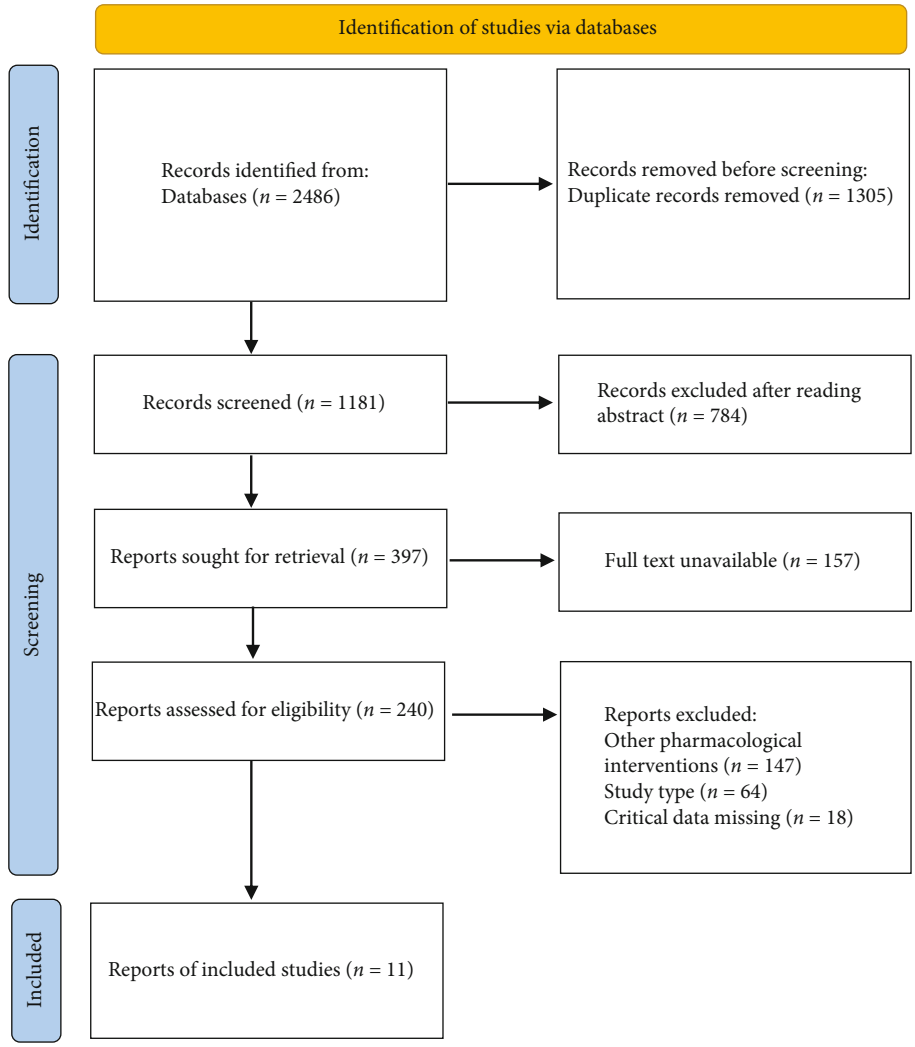

Figure 1: Document screening flow chart.

in diabetic patients are not superior to other antihypertensive drugs [9]. In diabetic nephropathy, a randomized controlled study showed that although ACEI could reduce the risk of serum creatinine double the baseline, it did not affect the incidence of ESRD ([10]). Therefore, a meta-analysis helps explore whether ACEI and ARB drugs can reduce the incidence of ESRD among patients with DN.

2. Materials and Methods

2.1. Literature Retrieve. Literature search was performed in MEDLINE, PubMed, Embase, CENTRAL, and CNKI databases. The search terms were ((“ACEI” OR “ARB” OR “RAS” OR “Angiotensin-Converting Enzyme Inhibitors” OR “Angiotensin Receptor Blockers” OR “Renin angiotensin system”) AND (“diabetes” OR “diabetic nephropathy”). There are no restrictions on literature language, publication time, and follow-up duration.

2.2. Literature Screening. Literature included the following criteria: (1) subjects were diabetic nephropathy patients; (2) the experimental group and control group were set up. The experimental group was treated with ACEI drugs or ARB drugs. The control group was treated with placebo; (3) endpoint events included the occurrence of terminal nephropathy; and (4) randomized controlled study.

Exclusion criteria are as follows: (1) repeated reports, (2) the balance of baseline data was poor, (3) the experimental group was treated with other drugs besides ACEI drugs, and (4) the literature data was missing and cannot be supplemented.

2.3. Data Extraction. In this paper, two researchers jointly extracted the author, title, publication time, number of researchers in the control and experimental groups, number of patients with ESRD, etc. For the data that could not be obtained in the literature, the researchers contacted the author to obtain it. If two researchers disagree on the data, an agreement was achieved through discussion.

2.4. Literature Quality Evaluation. In this paper, two researchers applied the Jadad scale to evaluate the quality of the included RCT research, including the generation

Table 1: Literature characteristics and Jadad score.

Study and year	No. of ESRD	No. of patients	Diabetes type	Jadad
Bauer [11], 1992	3	33	Mixed	3
Brenner [16], 2001	341	1513	2	4
Imai [15], 2011	153	586	2	5
Katayama [14], 2002	6	79	1	5
Lewis [18], 1993	36	409	1	5
Lewis [17], 2001	183	1149	2	4
Marre [10], 2004	14	3627	2	3
Maschio [19], 1996	7	21	2	5
Parving [20], 1989	5	32	1	3
Ravid [12], 1993	9	108	2	5
Tong [13], 2006	3	38	2	4

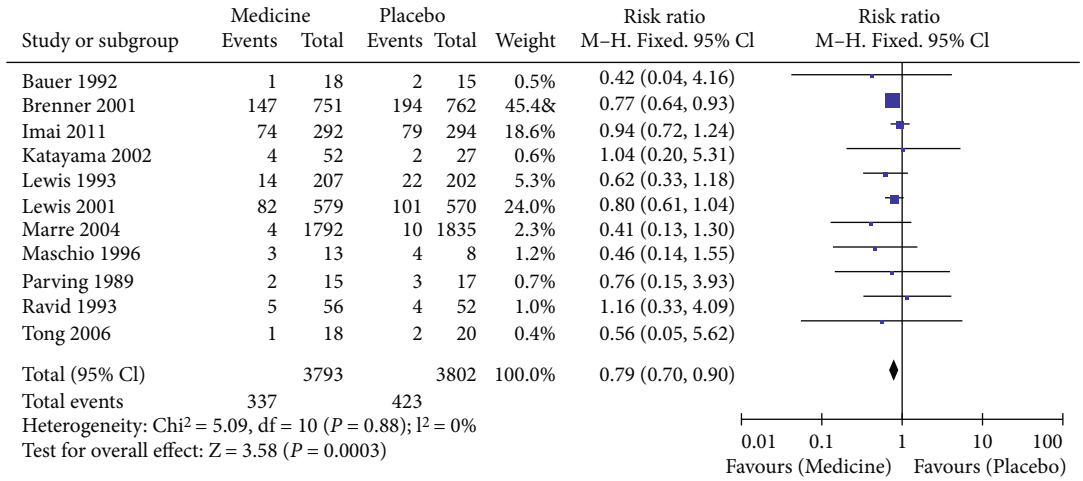

Figure 2: Forest diagram of the effect of RAS blocker and placebo on the incidence of end-stage renal disease.

method of random sequence, randomized hiding, the use of blind method, withdrawal, and withdrawal rules.

2.5. Heterogeneity Test and Publication Bias Test. Chi-square test was applied for the heterogeneity test. If $I^2 > 50\%$ or $P < 0.1$, it was considered that there was heterogeneity among published literatures, and a random effect model was used. In order to show the causes of heterogeneity, subgroup analysis and sensitivity analysis were conducted. If $I^2 \leq 50\%$ and $P \geq 0.1$, it was considered that no heterogeneity was among the published literatures, and the fixed effect model was used. Publication bias test was conducted by funnel plot.

2.6. Statistical Method. This study used the Cochrane software RevMan5.3 statistical analysis of the data. Risk ratio (RR) value and 95% confidence interval (CI) were calculated using Mantel-Haenszel statistical method. Bilateral $P < 0.05$ indicated statistically significant.

3. Results

3.1. Characteristics of Included Literature. A total of 2486 literatures were retrieved in the above database. A total of 2475 literatures were excluded, with 11 literatures included in the study [10–20]. The flow chart of literature screening is shown in Figure 1. The basic information of literature and the Jadad score are shown in Table 1.

3.2. RAS Blockers Reduce the Incidence of ESRD. A total of 11 articles were included, including 7595 diabetic nephropathy patients. 337 of 3793 patients in the RAS blocker drug intervention group had ESRD. As shown in Figure 2, 423 of the 3802 people in the placebo control group developed the ESRD. The heterogeneity test showed that no heterogeneity was among the studies ($\text{Chi}^2 = 5.09$, $P = 0.88$, $I^2 = 0\%$). The combined analysis showed that the RR of patients with ESRD treated with RAS blocker was 0.79 compared with placebo (95% CI (0.79, 0.90), $Z = 3.58$, $P = 0.0003$). As shown in Figure 3, the funnel plot demonstrated that the scatter points were biased to the left, and there was publication bias.

3.3. ACEI and ARB Reduce the Incidence of ESRD. Subgroup analysis was carried out according to different drugs, divided into ACEI and ARB subgroups. Eight literatures were included in the ACEI subgroup. The heterogeneity test showed that no heterogeneity was among the studies ($\text{Chi}^2 = 2.23$, $P = 0.95$, $I^2 = 0\%$). The combined analysis showed that compared with

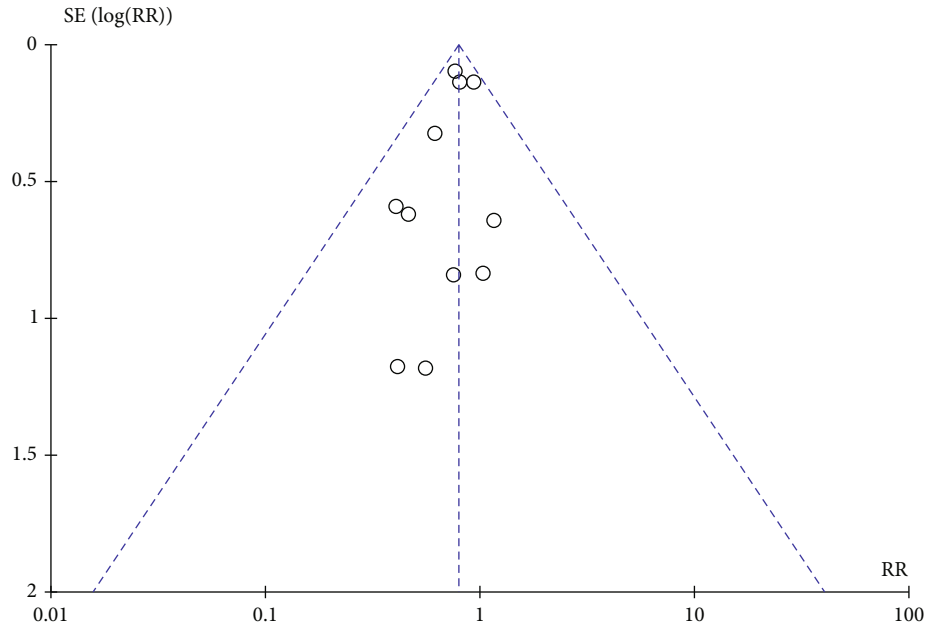

Figure 3: Funnel plot of the effect of RAS blocker and placebo on the incidence of end-stage renal disease. OR stands for odd ratio; SE stands for standard error.

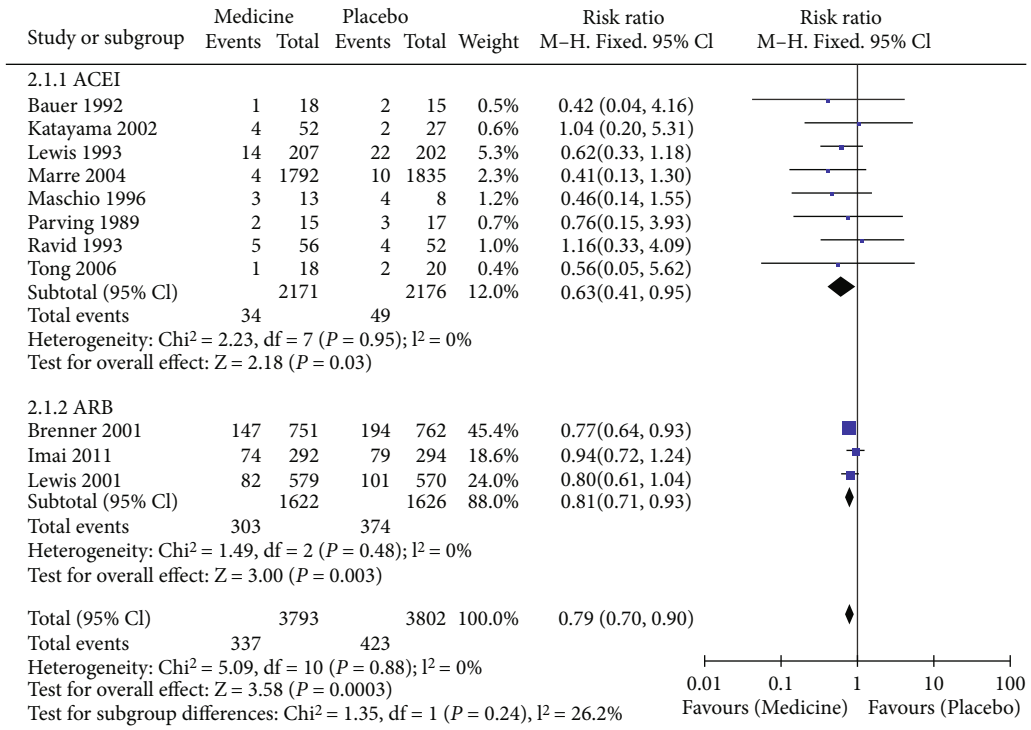

Figure 4: Forest map of the effects of ACEI and ARB versus placebo on the incidence of end-stage renal disease.

placebo, the RR of patients with end-stage renal disease after ACEI intervention was 0.63 (95% CI [0.41, 0.95], $Z = 2.18$, $P = 0.03$) as shown in Figure 4. Three articles were included in the ARB subgroup. Heterogeneity test showed that no heterogeneity was among the studies ($\text{Chi}^2 = 1.49$, $P = 0.48$, $I^2 = 0\%$). The combined analysis showed that compared with placebo, the RR of patients with end-stage renal disease after ARB intervention was 0.81 (95% CI (0.71, 0.93), $Z = 3.00$, $P = 0.003$) as shown in Figure 4.

4. Discussion

A total of 11 literatures were included in this study for meta-analysis with no heterogeneity among the literatures.

Meta-analysis showed that renin-angiotensin system blocker could reduce the incidence of ESRD among patients with DN. The angiotensin and ACEI subtypes were divided into two groups. NO heterogeneity was among studies in ACEI subgroups, such as ARB subgroups. Meta-analysis of the ACEI and ARB subgroups showed that ACEI and ARB drugs could reduce the risk of ESRD among patients with DN. The results of the subgroup analysis were consistent with the overall analysis. A previous meta-analysis [21] showed that ACEI treatment did not affect the renal outcome, while ARB treatment significantly reduced the risk of ESRD. We believe that the conclusions of this study are controversial. The study conducted a sensitivity analysis, excluding the study of Patel [22], and concluded that ACEI drugs could reduce the incidence of ESRD. Unfortunately, they did not conclude with the results of the sensitivity analysis. We also looked at Patel et al.'s findings for diabetes patients, not diabetic nephropathy patients, and combined ACEI and diuretics. Therefore, it was not included in our study. In addition, we also noted a randomized controlled study [23], showing that ACEI drugs could reduce the risk of DN and the risk of cardiovascular adverse events. Class ACEI drugs can protect cardiovascular and kidneys in diabetic patients. However, we cannot get the full text because the study was aimed at diabetic patients, not diabetic nephropathy patients. The information in the summary section could not provide the data information needed in this study because this randomized study had not been included in our analysis.

At present, meta-analysis of ACEI and ARB has little effect on renal protection among patients with DN. Some meta-analyses explored the effects of the two drugs on the kidney of diabetic patients [8, 9, 24]. A meta-analysis [8], which included 28 RCT trials, found that ACEI and ARB drugs had protective effects on the kidney among patients with type 2 diabetes compared with other antihypertensive drugs and placebo. Another meta-analysis of [24] included 63 RCT trials, including 36917 diabetic patients. The results showed that ACEI drugs had renal protective effects on diabetic patients, while ARB drugs did not show their protective effects on the kidneys. Another meta-analysis of 19 RCT studies [9] showed that ACEI and ARB were not superior to other antihypertensive drugs in reducing all-cause death, cardiovascular time, and renal events. These meta-analyses obtained inconsistent conclusions, which may be related to the differences in research objects, the differences in intervention schemes in the control group, and the different definitions of endpoint events. There was heterogeneity in clinical manifestations of diabetes, including prognosis.

There are also some limitations in our research. First of all, we did not distinguish between type 1 diabetes and type 2 diabetes. There are differences in the pathogenesis of type 1 diabetes and type 2 diabetes and differences in the course of the disease, clinical manifestations, prognosis, and sensitivity to drugs, which may impact our results. Further studies are needed to confirm whether there is a difference in efficacy between RAS inhibitors in type 1 and type 2 diabetes. Secondly, our study did not distinguish the effects of different doses of ACEI and ARB on diabetic nephropathy. Previous studies have shown that these two drugs slow down the decline of albuminuria and glomerular filtration rate in a dose-dependent manner [20]. Thirdly, we did not explore the efficacy of RAS inhibitors in diabetes patients of different ages, genders, and diets. All of these clinical variables may influence outcomes. Finally, most of the research data we obtained came from developed countries, which may also bias our results.

In particular, some studies have pointed out that the combination of ARB and ACEI drugs may lead to hyperkalemia and increase the risk of acute renal injury [25]. However, this study concluded that ACEI and ARB drugs have protective effects on the kidney among patients with diabetic nephropathy. However, it is still necessary to conduct a large-scale RCT study with multiple centers to observe the effectiveness and safety of different doses and drug regimens.

In summary, this study suggests that ACEI and ARB drugs can reduce the risk of ESRD among patients with DN.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Xiaojuan Deng and Dayun Li contributed equally to this work.

Acknowledgments

This project was supported by the Hainan Province Clinical Medical Center.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 9281661, 8 pages
https://doi.org/10.1155/2022/9281661

Research Article

Meta-Analysis of the Effect of Aerobic Training on Blood Pressure in Hypertensive Patients

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Received 4 April 2022; Revised 5 May 2022; Accepted 10 May 2022; Published 25 May 2022

Academic Editor: Xi Lou

Background. We aimed to evaluate the effect of different aerobic training methods and exercise duration on blood pressure in hypertensive patients, including systolic blood pressure (SBP) and diastolic blood pressure (DBP). *Methods.* Using the literature review method, the English database PubMed was retrieved to obtain relevant research literature, and the selected studies were analyzed and evaluated. *Results.* 14 clinical studies were included in this study, with a total of 1027 patients, including 681 in the aerobic training group and 409 in the control group. Based on heterogeneity test results, the differences of SBP and DBP before and after the physical intervention were combined using a random effect model. The results indicated that the aerobic training group could significantly reduce SBP compared with the control group, WMD = −9.91, 95% CI (-14.21, -5.61), $P < 0.0001$. The DBP was reduced significantly in the aerobic training group, WMD = −4.32, 95% CI (- 7.02, -1.62), $P < 0.001$. The results of subgroup analysis showed that both progressive training and nonprogressive training could reduce blood pressure in patients, and training time less than 12 weeks and more than 12 weeks could reduce blood pressure in patients. *Conclusion.* Implementing aerobic training can effectively reduce blood pressure in hypertensive patients. Progressive training, nonprogressive training, and different training cycles can all benefit hypertensive patients.

1. Introduction

Hypertension, a multifactorial chronic disease, is one of the major health concerns which affects more than 1 billion adults worldwide [1]. The current percentages of people suffering from hypertension in China is 25.2% and increasing by years [2, 3]. As known, hypertension is closely related to several cardiovascular incidence and mortality rates. Thus, hypertension is identified as an important risk factor for vascular diseases [4, 5] and could bring severe diseases and financial burdens to families and society. Other than drug treatments, active lifestyle could significantly ameliorate hypertension syndrome as well [6].

In physical therapy, moderate-intensity aerobic exercise often supplemented with dynamic resistance training, as the first-class recommendation of the guide, is the main way to decrease blood pressure. A meta-analysis showed that moderate-intensity training had the best blood pressure improvement effect in hypertensive patients, while high-volume high-intensity interval training was more effective in reducing body weight and resting heart rate [6]. Off notes, aerobic exercise was considered a great starting point for hypertensive patients compared with moderate-intensity training and high-intensity training per antihypertensive physical therapy guidelines. Several review articles have concluded that aerobic exercise appeared to be beneficial in blood pressure control in patients with hypertension [7]. Different training variables, such as prior progressive training for patient adaptation, could affect the antihypertensive effect of aerobic training. Progressive training is defined as

gradually or systematically increasing the training intensity, such as increasing the frequency and intensity of training with health improvement to promote continuous training adaptability [8]. In addition, the length of training also contributed to the training effects. With the significance in clinic, this study adopted the method of meta-analysis, including the latest research on the treatment of hypertension with aerobic training, to conduct a quantitative study on the antihypertensive effect of aerobic training. In brief, this study performed a subgroup analysis to analyze the impact of progressive training and the length of exercise on the antihypertensive effect.

2. Materials and Methods

2.1. Literature Retrieval Strategy. PubMed, an English database, was searched for published clinical trials on the effect of aerobic training on blood pressure in patients with hypertension from January 2010 to March 2022. The retrieval method was medical subject words combined with free words. The English retrieval subject words were "hypertension OR blood pressure high OR high blood pressure" AND "exercise OR physical exercise OR exercise aerobic OR aerobic exercise OR exercise training" AND "blood pressure OR diastolic pressure OR systolic pressure". At the same time, the references were manually retrieved in the relevant literature.

2.2. Literature Screening. Inclusion criteria are as follows: (1) The subjects were adults with hypertension (≥ 18 years old) who participated in at least four weeks of supervision and structured aerobic exercise intervention. (2) The study should at least be a two-arm study, including at least the experimental group receiving aerobic training and the control group not receiving aerobic training. (3) The outcome index includes at least one of diastolic blood pressure (DBP) and systolic blood pressure (SBP), and the value of diastolic/systolic blood pressure before and after intervention or the difference before and after intervention can be obtained.

Exclusion criteria are as follows: (1) some or all patients in the study received other types of physical training in addition to aerobic training; (2) hypertensive patients with cardiovascular diseases such as heart failure, coronary artery disease, and peripheral artery disease; (3) news reports, expert opinions, critical literature, and abstracts; (4) duplicate published literature; (5) unbalanced baseline data between the experimental and control groups; and (6) unable to obtain enough literature to analyze the data.

2.3. Document Data Extraction. According to the above inclusion and exclusion criteria, two professional researchers independently screened the literature, determined the final included literature, and extracted the data according to the predetermined data extraction table. The main extraction contents include (1) basic information, including title, publication date, and author's name; (2) data included in the literature, including research type, research population, intervention measures, and outcome indicators; and (3) characteristics of included literature, including research methods, object characteristics, and data results. Suppose there are questions or differences in the process of literature screening and extraction. In that case, a third researcher will assist in resolving the differences and decide through discussion at the meeting if necessary.

2.4. Literature Quality Evaluation. The quality of the included literature was evaluated according to the risk bias evaluation tool in the Cochrane manual. The evaluation contents include (1) whether the random allocation method is appropriate, (2) whether the random allocation scheme is hidden, (3) whether the blind method is adopted, (4) whether the result data is complete, (5) whether there are selective reports of results, and (6) whether there are other sources of bias. The evaluation results were divided into high risk, low risk, and uncertain risk. Two researchers independently evaluated the quality of the included literature and then cross-checked it. If there is any difference, both researchers will discuss it to reach an agreement or rule by the third researcher.

2.5. Statistical Method. This study used Cochrane software RevMan5.4 statistical analysis of all data. Taking the weighted mean difference (WMD) and 95% CI as the effect quantity, the effects of aerobic training and no aerobic training on diastolic and systolic blood pressure in patients with hypertension were statistically described by combining with the mean value, standard deviation, and sample size of the difference between SBP and DBP at baseline and after the intervention. After using the fixed-effect model or random effect model, it was considered statistically significant when $P < 0.05$. The Chi-square test was used to test the heterogeneity between different studies. When the I^2 corrected by degrees of freedom was more than 50%, it was considered to be heterogeneous, and the random effect model was used. When I^2 corrected by degrees of freedom is ≤50%, it was considered no heterogeneity, and the fixed effect model was adopted. The potential publication bias was estimated by funnel plot.

3. Results

3.1. Literature Search Results. In this study, 4558 relevant literatures were obtained through database retrieval. After retrieval, all literature were duplicated by EndNote X9 and manually screened based on topics and abstracts topics and abstracts using preestablished inclusion and exclusion criteria. The prescreened literatures were then fully assessed basing on full text for final selection. In this study, there were 14 literatures fitted into all designed criteria and were included for final meta-analysis. The specific screening process and results are shown in Figure 1.

3.2. Basic Characteristics and Quality Evaluation of Literature. All 14 included studies were published as English literature. The summary of basic information for 14 included studies was shown in Table 1. As indicated earlier, the publication time ranged from 2010 to 2021. Thus, the included literatures were up to most possible current date.

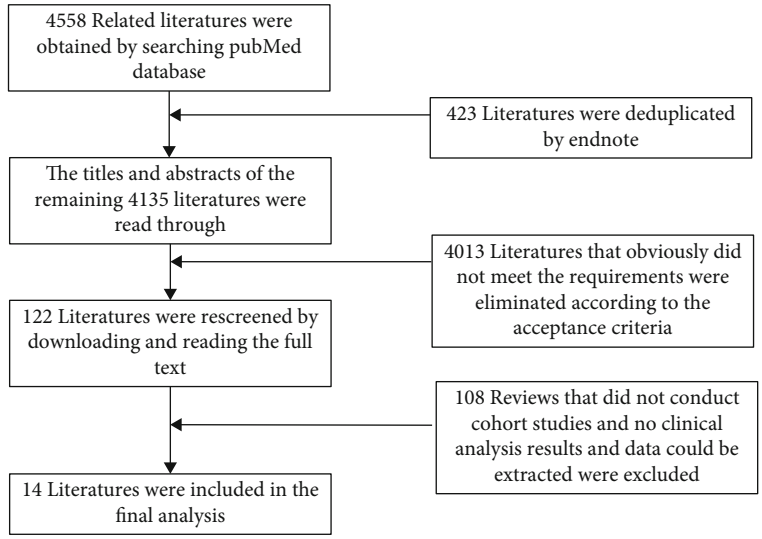

Figure 1: Document screening process and results.

Table 1: Basic characteristics of included literature.

ID	Progressive training	Age	Training time	Training mode	Duration	Weekly frequency
Abdelaal and Mohamad 2015 [9]	Yes	52.5	12 weeks	Treadmill	Start:20-35 min end:40-50 min	3
Baghaiee et al. 2018 [10]	Yes	38.1	12 weeks	NR	Start:25 min end:45 min	3
Farahan et al. 2010 [11]	Yes	47.7	10 weeks	Aquatic sports	35 min	3
Lamina 2010 [12]	Yes	58.4	8 weeks	Cyclic dynamometer	Start:45 min end:60 min	3
Latosik et al. 2014 [13]	Yes	NR	8 weeks	Cross country walking	45 min	NR
Soltani et al. 2020 [14]	Yes	47.9	8 weeks	Walking/running	27 min	3
Wong et al. 2018 [15]	Yes	73.5	20 weeks	Swimming	Start:25-30 min end:40-45 min	3-4
Arca et al. 2014 [16]	No	64	12 weeks	Cyclic dynamometer aquatic sports	20 min	3
Blumenthal et al. 2021 [17]	No	63	4 weeks	NR	30-40 min	3
He et al. 2018 [18]	No	57.5	12 weeks	Walking	60 min	3
Khalid et al. 2013 [19]	No	52.8	8 weeks	Walking	20 min	3
Izadi et al. 2018 [20]	No	61.6	6 weeks	Cyclic dynamometer	35 min	3
Maruf et al. 2014 [21]	No	52.0	12 weeks	Dancing	35 min	3
Ramos et al. 2018 [22]	No	60.6	12 weeks	Athletics	50 min	3

Overall, for this meta-analysis, both randomized controlled trials and observational studies were included. There were 1027 patients with hypertension in total, including 681 in the aerobic training group and 409 in the control group with no sexual bias, whose ages were all over 35 years old. In general, the durations of aerobic training were all over 4 weeks including 4 weeks for one study, 6 weeks for one study, 8 weeks for four studies, 12 weeks for six studies, and 20 weeks for one study. Aerobic exercise mainly included walking, running, swimming, cross-country, track and field, and cyclic dynamometer. In the aspect of progressive training, progressive training prior to aerobic training was adapted in 7 literatures while the others did not include progressive training period. The exercise duration was between 20 and 60 minutes, averaged at 40 min, which fell into the recommended exercise time frame by professional. The exercise frequency was three times a week. The difference of SBP and DBP between the aerobic training group and the control group after training were shown in Table 2. Taken from this table, the aerobic training showed some degree of beneficial effects in reducing blood pressure in patients with hypertension.

Cochrane risk bias evaluation tool was used to evaluate the included literature. Only three literatures fully adopted the principles of randomization, distributive concealment, and blind method, and the evaluation quality was low risk. Most of the other literatures did not describe randomization, distributive concealment, and blind method, and the quality of risk was uncertain.

Table 2: Results of blood pressure difference between SBP and DBP included in the literature.

ID	Sample		SBP				DBP			
			Aerobic training group		Control		Aerobic training group		Control	
	Experimental group	Control group	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Abdelaal et al. 2015 [9]	20	19	-4.95	2.50	0.68	3.20	-4.20	1.30	0.58	1.71
Baghaiee et al. 2018 [10]	20	20	-0.56	0.26	0.04	0.25	-0.01	0.49	0.02	0.05
Farahani et al. 2010 [11]	12	28	-16.67	12.16	-1.78	11.35	-4.17	90.54	0.18	6.49
Lamina 2010 [12]	252	105	-14.99	16.64	2.60	16.18	-4.25	7.98	-1.07	2.62
Latosik et al. 2014 [13]	15	10	-10.20	13.18	-6.60	6.00	-2.00	8.33	-0.60	4.01
Soltani et al. 2020 [14]	20	10	-8.00	13.69	2.00	11.27	-6.50	11.75	1.00	5.92
Wong et al. 2018 [15]	52	48	-11.00	1.18	1.00	1.18	-9.00	1.18	0.00	1.18
Arca et al. 2014 [16]	33	14	-12.00	16.73	-1.00	2.37	-8.00	1.31	-4.00	1.18
Blumenthal et al. 2021 [17]	90	50	-12.20	11.83	-7.20	11.83	-5.80	10.65	-4.40	9.47
He et al. 2018 [18]	20	22	-8.30	6.28	2.20	5.48	-1.10	5.11	0.80	3.83
Khalid et al. 2013 [19]	12	13	-24.00	6.63	-9.00	7.93	-9.00	5.72	0.00	4.69
Izadi et al. 2018 [20]	15	15	-3.43	7.73	0.67	7.40	-2.13	4.33	0.93	4.90
Maruf et al. 2014 [21]	45	43	-18.77	15.65	-8.81	18.84	-8.98	11.78	-5.60	12.72
Ramos et al. 2018 [22]	12	12	−4.4	5.20	6.10	3.50	-10.10	3.30	1.30	3.40

3.3. Meta-Analysis Results

3.3.1. Meta-Analysis Results. 14 literatures have reported the effects of aerobic training on SBP and DBP in patients with hypertension. The heterogeneity test results I^2 of the two outcome indicators were 99%, indicating high heterogeneity. Therefore, the random effect model was used to merge the data. The meta-analysis results showed that the decline values of SBP and DBP in the aerobic training group before and after physical intervention were significantly higher than those in the control group. The difference of SBP in the aerobic training group was 8.90 mmHg lower than that in the control group. The combined result was WMD = −8.90, 95% CI (- 13.19, - 4.61), $P < 0.0001$, as shown in Figure 2. The difference of SBP was 4.59 mmHg lower than that in the control group. The combined result was WMD = −4.59, 95% CI (-7.38, -1.79), $P = 0.001$, as shown in Figure 3.

The publication bias was also taken into consideration as there were more than 10 literatures included in this study. The results showed that the included literatures were not symmetrically distributed around the combined effect WMD value. The funnel of SBP difference results was shown in Figure 4, distributed in the upper right corner, and the funnel of DBP difference results was shown in Figure 5, distributed in the upper part of the set. Taken from the funnel evaluation, there was obvious publication bias introduced. To overcome the publication bias, further subgroup analysis of the results was conducted.

3.3.2. Subgroup Analysis Results. The meta-analysis results suggested that there were apparent heterogeneity and publication bias. Therefore, subgroup analysis was conducted based on whether or not progressive training was performed and on the duration of training. We applied a 12-week cutoff based on the median training duration in the included literature. The subgroup analysis results indicated that the differences of SBP and DBP in the experimental group without progressive training and the training cycle ≤ 12 weeks after intervention were lower than those in the control group ($P < 0.05$). The differences were statistically significant (see Tables 3 and 4).

4. Discussion

This study reviewed the literature and meta-analysis of the effects of aerobic training on systolic and diastolic blood pressure in adult patients with hypertension. The main methods of aerobic training included in the literature were walking, running, swimming, cross-country, track and field, and cyclic dynamometer. The training intensity and frequency were gradually increased according to the adaptability of patients. This type of progressive training was approved to be beneficial on training effect to patients; however, it is uncertain whether progressive training has any impacts on SBP and DBP compared with conventional training. In addition, extended training duration did not cause further effects on blood pressure. Taken combined results and subgroup analysis together, in this study, aerobic training significantly reduced SBP and DBP compared with the control group.

The conclusion of this study is consistent with the published conclusion on the effect of aerobic training on blood pressure in patients with hypertension. The meta-analysis results of Cao et al. [7], Igarashi et al. [23], and de Barcelos et al. [24] illustrated the reduction of SBP and DBP in the aerobic training group were about 8-12 mmHg and 5-6 mmHg, respectively. In this study, the WMD of the

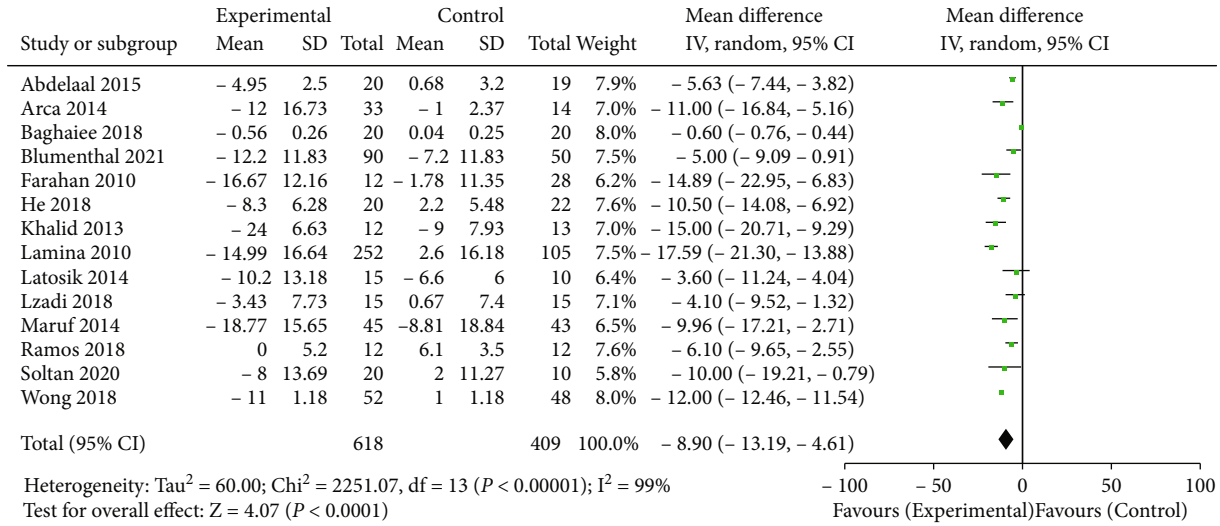

Figure 2: SBP difference between the aerobic training group and control group before and after intervention.

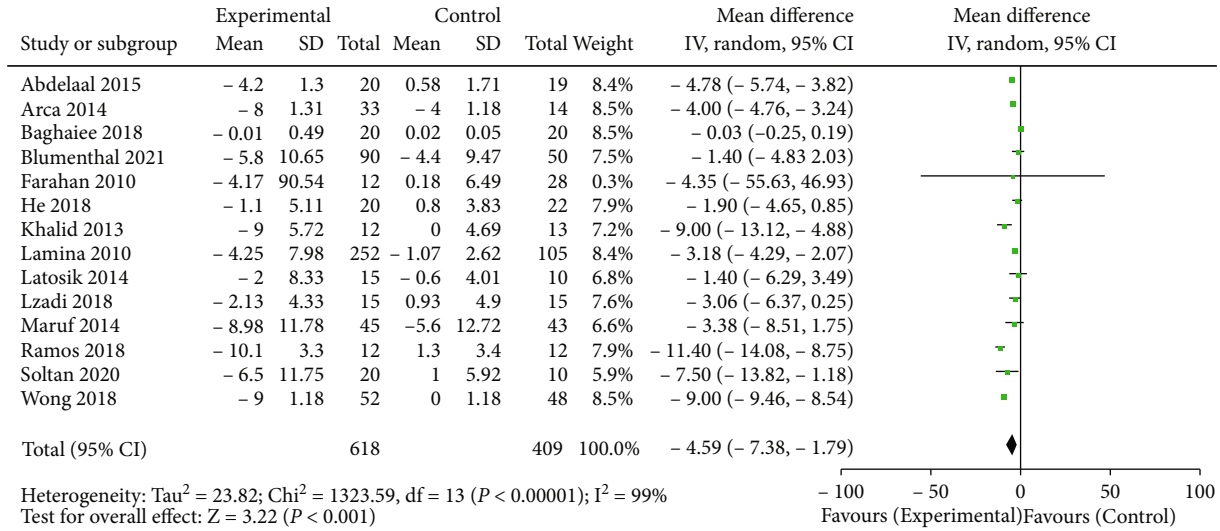

Figure 3: Forest diagram of DBP difference between the aerobic training group and control group before and after intervention.

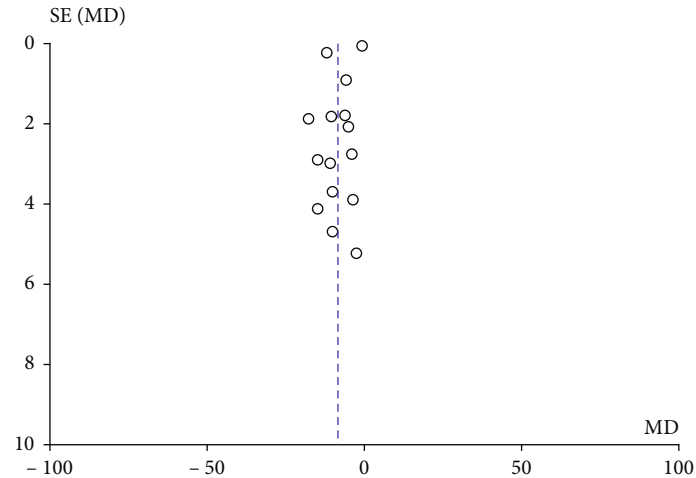

Figure 4: Funnel chart of SBP difference between the aerobic training group and control group before.

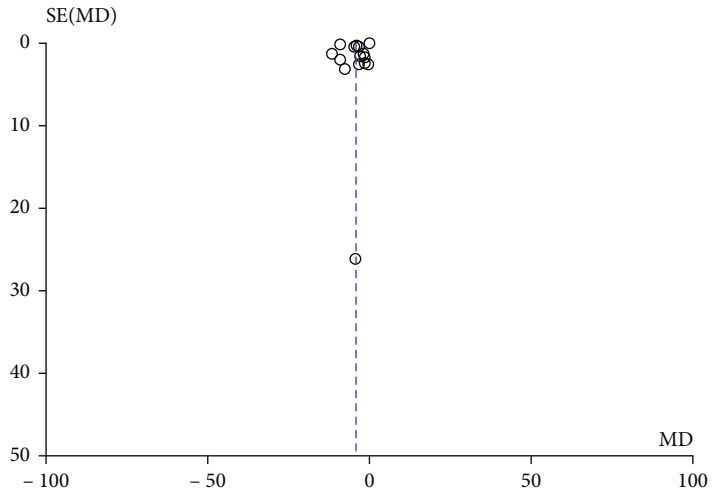

Figure 5: Funnel chart of DBP difference between the aerobic training group and control group before and after intervention.

Table 3: Subgroup analysis of the effect of aerobic training on SBP.

Variables	Number of literatures (articles)	Heterogeneity test		Effect magnitude		
		I^2 value	P value	WMD value	95% CI value	P value
Progressive training						
Yes	7	100	<0.001	-9.07	(-15.25, -2.89)	<0.001
No	7	54	0.03	-8.18	(-10.87, -5.5)	<0.001
Training cycle						
<12 weeks	7	82	<0.001	-10.08	(-15.14, -5.02)	<0.001
≥12 weeks	7	100	<0.001	-7.35	(-12.98, -1.71)	0.01

Table 4: Subgroup analysis of the effect of aerobic training on DBP.

Variables	Number of literatures (articles)	Heterogeneity test		Effect magnitude		
		I^2 value	P value	WMD	I^2 value	P value
Progressive training						
Yes	7	100	<0.001	-4.26	(-8.75, 0.24)	0.06
No	7	83	<0.001	-4.45	(-6.86, -2.04)	<0.001
Training cycle						
<12 weeks	7	45	0.09	-3.37	(-4.32, -2.43)	<0.001
≥12 weeks	7	99	<0.001	-4.44	(-8.16, -0.73)	0.02

difference before and after the intervention was used as the effect quantity. The difference before and after the intervention in the aerobic training group was 9.91 mmHg lower than that in the control group, and the DBP was 4.32 mmHg lower, which further confirmed the antihypertensive effect of aerobic training. A previous study has shown that blood pressure decrease in patients with hypertension has significant clinical significance. A 10 mmHg reduction in SBP could reduce the risk of cardiovascular disease by 20%, stroke by 27%, and death by 13% [25].

Exercise intensity, duration, and frequency of each exercise played roles in regulating exercise effects. Relevant guidelines recommend moderate-intensity aerobic exercise, 30 to 60 minutes a day or 150 minutes a week, with a frequency of 4 to 7 times a week for training patients with hypertension [26]. In addition, it is generally recommended to gradually increase the exercise intensity, duration, and frequency using a progressive training to improve the effect of aerobic exercise. This study conducted a subgroup analysis on the use of progressive training. The results showed that the SBP with progressive training decreased more than those without progressive training, and there was no difference found in DBP. Subgroup analysis of training duration showed that when the training time was less than 12 weeks, the decline of SBP in the aerobic training group was higher, but the decrease of DBP was lower.

In one word, this study further confirmed that aerobic training has a significant effect on reducing diastolic and systolic blood pressure in patients with hypertension. Whether to use progressive training or whether the training time is

longer than 12 weeks played little role. Therefore, it is suggested to select appropriate exercise methods and duration according to the guideline's recommendations for regular training in patients with hypertension.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Yanping Fu and Qiongfang Feng contributed equally to this work.

Acknowledgments

This study was supported by the Haikou Hospital of Traditional Chinese Medicine.

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Hindawi
Computational and Mathematical Methods in Medicine
Volume 2022, Article ID 2968044, 5 pages
https://doi.org/10.1155/2022/2968044

Research Article

Risk Factors and Risk Model Construction of Stroke in Patients with Vertigo in Emergency Department

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Received 15 April 2022; Revised 30 April 2022; Accepted 4 May 2022; Published 20 May 2022

Academic Editor: Xi Lou

Objective. We aimed to explore the risk factors of stroke in patients with vertigo in the emergency department and establish a risk prediction model for stroke patients. *Methods*. A total of 301 patients experiencing vertigo in our hospital from January 2020 to January 2021 were retrospectively included. Patients were divided into the stroke group ($n = 56$) and the nonstroke group ($n = 245$). The clinical characteristics of patients in both groups were collected and compared, followed by binary logistic regression that was employed to determine the risk factors that affect stroke diagnosis. The receiver operating characteristic (ROC) curve was used to clarify the effectiveness of the constructed model. *Results*. Patients in the stroke group were older and had higher systolic and diastolic blood pressure on admission than the nonstroke group. Meanwhile, they demonstrated a higher proportion of diabetes and atrial fibrillation and focal muscle weakness, dysarthria, dysphagia, or ataxia in neurological examinations compared to the nonstroke group (all $P < 0.05$). The proportion of patients in the nonstroke group who had a history of vertigo or inner ear disease was significantly higher than that in the stroke group ($P < 0.05$). The patient's age ≥ 60 years old (OR = 3.57), diabetes (OR = 4.57), atrial fibrillation (OR = 4.26), previous history of vertigo or inner ear disease (OR = 0.16), focal muscle weakness (OR = 4.34), and dysphagia or ataxia (OR = 4.08) were associated with a higher risk of stroke. The area under the curve for stroke was 0.87, and the sensitivity and specificity were 98.2% and 57.6%, respectively, as the sum of the assigned scores was greater than 3. *Conclusions*. Age ≥ 60 years old, diabetes, atrial fibrillation, previous history of vertigo or inner ear disease, focal muscle weakness, dysphagia, or ataxia were associated with a higher risk of stroke. The risk model constructed based on our findings may help to assess the risk of stroke in patients with vertigo in the emergency department.

1. Introduction

Vertigo is common complaints seen in the emergency department. Studies have found that the primary cause of up to 4% of emergency department visits is vertigo [1]. The causes of vertigo are diverse, including otolith, Meniere's syndrome, vertebrobasilar insufficiency, and moderate stroke, thus making the diagnosis of vertigo very difficult [2]. Meanwhile, vertigo caused by stroke often progresses rapidly. Early detection and intervention can significantly improve the prognosis of patients. Therefore, distinguishing between stroke and nonstroke in the emergency room is of great clinical significance. At present, the ABCD2 score is widely used to determine whether vertigo patients have stroke preliminarily. The standard for evaluation mainly includes five aspects: age, blood pressure, clinical presentation, duration of symptoms, and diabetes [3]. However, the score comes from the population with a transient ischemic attack, and the prediction efficiency of stroke caused by macrovascular disease is poor [4]. This study retrospectively analyzed the clinical data of vertigo patients in the emergency department of our hospital, identified the risk factors related to the diagnosis of stroke, and constructed a risk model.

2. Materials and Methods

2.1. Research Object. This study retrospectively included 301 patients in the emergency department of our hospital with "vertigo" as the first symptom from January 2020 to January 2021. Inclusion criteria: (1) the first medical record was "vertigo"; (2) the cause was finally diagnosed. Exclusion criteria: (1) the patient had an apparent history of trauma and bleeding before seeing a doctor; (2) incomplete records of medical history and vital signs and lack of admission blood pressure and other records; (3) patients with final vertigo without definite diagnosis; (4) the patient had no cranial imaging results and could not determine whether there was a stroke.

2.2. Research Methods. The clinical and imaging data of patients presenting to the emergency department were collected through the electronic medical record system, including patient age, gender, systolic blood pressure, diastolic blood pressure complications (hypertension, diabetes, hyperlipidemia, coronary atherosclerotic heart disease, and atrial fibrillation), smoking, past stroke/transient ischemic attack, past vertigo and inner ear history, current use of antiplatelet and anticoagulant drugs, combined symptoms (headache, shoulder pain, ear distention, or hearing loss), and neurological findings (focal hyperdynamic, dysarthria, nystagmus, dysphagia, and ataxia) according to the final diagnosis. The patients were divided into stroke group and nonstroke group.

2.3. Statistical Analysis. SPSS 24.0 Chinese version software was used for statistical analysis. The measurement data of nonnormal distribution were expressed by the median and interquartile range (IQR). The groups were compared using the Mann–Whitney U nonparametric test. The counting data were expressed in frequency and percentage, and the groups were compared by the chi-square test. Bring the statistically significant variables in the univariate comparison into the binary logistic regression analysis and take whether the patient has a stroke as the dependent variable to clarify the variables affecting the patient's stroke. Each meaningful variable was assigned according to the obtained risk ratio. The assigned variables were identified by the subject's working characteristic curve to determine whether the patient was the best cut value, the area under the curve (AUC), sensitivity, and specificity of stroke. Bilateral test, test level $\alpha = 0.05$.

3. Results

3.1. Comparison of General Characteristics of Patients. Of the 301 patients included in this study, 56 were diagnosed with a stroke, and 245 were nonstroke. Compared with the nonstroke group, the stroke group had higher age, a higher systolic and diastolic blood pressure, a higher proportion of diabetes and atrial fibrillation, and focal muscle weakness and dysarthria in the neurological examination. The positive rate of dysphagia or ataxia was higher (all $P < 0.05$). The proportion of patients with a previous history of vertigo or inner ear in the nonstroke group was significantly higher than that in the stroke group ($P < 0.05$), see Table 1.

3.2. Multivariate Logistic Regression Analysis. All statistically significant variables in Table 1 were brought into binary logistic regression for analysis. It was found that patients aged over 60 years (OR = 3.57), diabetes mellitus (OR = 4.57), atrial fibrillation (OR = 4.26), past vertigo or inner ear history (OR = 0.16), focal muscular weakness (OR = 4.34), and dysphagia or ataxia (OR = 4.08) were associated with a higher risk of stroke, as shown in Table 2.

3.3. Assignment of Relevant Factors. According to the results in Table 2, the corresponding statistically significant indicators were assigned, and the results were shown in Table 3. The previous history of vertigo or inner ear was the protective factor of stroke, with a value of -6 (1/0.16), and the other factors were harmful factors, with a positive value.

3.4. ROC Curve. The results of the ROC curve showed that when the total score of patients was >3, the AUC of stroke in vertigo patients was 0.87 (95% CI, 0.82-0.90), and the sensitivity and specificity were 98.2% and 57.6%, respectively, as shown in Figure 1. When the total score of patients was >13, the specificity of stroke in vertigo patients was as high as 100%.

4. Discussion

Vertigo is one of the main complaints often encountered by medical staff in the emergency department in clinical work. There are various causes of vertigo, and some patients have benign outcomes. In this study, we identified stroke risk factors in 301 patients with "vertigo" and constructed the related risk model.

This study found that age ≥ 60 was associated with the risk of being diagnosed with "stroke" in patients with vertigo, which was consistent with previous reports. A previous [5] stroke-related epidemiologic study suggested that the incidence rate of stroke in adults aged 35-44 years was 30-120/100000 per year, while the incidence rate in 65-74 years olds increased significantly to 670-970/100000 per year. Kerber and his colleagues' study of 1666 patients with vertigo in the emergency department showed that the average age of patients finally diagnosed with stroke was significantly higher than patients without stroke [6]. It suggests that medical staff should pay special attention to excluding the possibility of stroke when receiving elderly patients with vertigo.

Similar to previous studies, this study also found that diabetes in stroke patients was significantly higher than that in nondiabetic patients. Diabetes and other metabolic abnormalities have been recognized as risk factors for stroke [7, 8]. Lee et al. found that diabetes mellitus can significantly increase the risk of stroke in hospitalized vertigo patients [9].

This study found that atrial fibrillation was associated with a higher risk of stroke in patients with vertigo diagnosed with stroke. Long-term atrial fibrillation will produce mural thrombus, which will enter the brain with blood flow after falling off, resulting in ischemic stroke [10, 11]. After analyzing the data of Denmark, Christiansen et al. [12] found that the incidence of stroke with atrial fibrillation in the 50-year-old population was 1.1%. If the patient had a

Table 1: Comparison of general characteristics between stroke group and nonstroke group.

	Stroke group ($n = 56$)	Nonstroke group ($n = 245$)	χ^2/Z value	P value
Age (years) (IQR)	70 (59, 78)	54 (44, 66)	-5.44	<0.001
Age ≥ 60 years (cases, %)	39 (69.64)	93 (37.96)	18.58	<0.001
Gender (male) (cases, %)	27 (48.21)	91 (37.14)	2.34	0.13
Systolic blood pressure (mmHg) (IQR)	157 (140.25, 175)	137 (124, 154.50)	-5.45	<0.001
Diastolic blood pressure (mmHg) (IQR)	90.5 (76.5, 98.0)	79 (71, 89.5)	-3.69	<0.001
Systolic blood pressure ≥ 140/diastolic blood pressure ≥ 90 mmHg (cases, %)	44 (78.57)	115 (46.94)	18.30	<0.001
Complication				
Hypertension (cases, %)	37 (66.07)	132 (53.88)	2.75	0.10
Diabetes mellitus (case, %)	35 (57.14)	67 (27.35)	25.14	<0.001
Hyperlipidemia (cases, %)	25 (44.64)	106 (43.27)	0.04	0.85
Coronary atherosclerotic heart disease (cases, %)	8 (14.29)	36 (14.69)	2.63	0.11
Atrial fibrillation (cases, %)	12 (21.43)	13 (5.31)	15.56	<0.001
Smoking (cases, %)	26 (46.43)	105 (42.86)	0.24	0.63
Previous history of stroke/transient ischemic attack (cases, %)	7 (12.50)	17 (6.94)	1.92	0.17
Previous history of vertigo or inner ear (cases, %)	5 (8.93)	92 (37.55)	17.10	<0.001
Currently used drugs				
Antiplatelet drugs (cases, %)	13 (23.21)	62 (25.31)	0.11	0.74
Anticoagulant drugs (cases, %)	4 (7.14)	21 (8.57)	0.12	0.73
Combined symptoms				
Headache or shoulder pain (cases, %)	5 (8.93)	23 (9.39)	0.01	0.92
Ear distention or hearing loss (cases, %)	7 (12.50)	29 (11.84)	0.02	0.89
Nervous system examination				
Focal hypodynamia (cases, %)	25 (44.64)	34 (13.88)	27.38	<0.001
Dysarthria (cases, %)	14 (25.00)	24 (9.80)	9.55	0.002
Nystagmus (cases, %)	6 (10.71)	23 (9.39)	0.09	0.76
Dysphagia or ataxia (cases, %)	17 (30.36)	28 (11.43)	12.84	<0.001

IQR: interquartile range.

Table 2: Results of multivariate binary logistic regression analysis for predicting stroke in patients with vertigo.

Factors	β	SE	Wald	P value	OR value (95% CI)
Age (≥60 years = 1; <60 years = 0)	1.27	0.41	9.61	0.002	3.57 (1.60, 7.97)
Systolic blood pressure (≥140 mmHg = 1; <140 mmHg = 0)	0.88	0.49	3.25	0.07	2.41 (0.93, 6.27)
Diastolic blood pressure (≥90 mmHg = 1; <90 mmHg = 0)	0.34	0.45	0.58	0.45	1.41 (0.58, 3.41)
Diabetes mellitus (with = 1; no = 0)	1.52	0.40	14.75	<0.001	4.57 (2.10, 9.91)
Atrial fibrillation (yes = 1; no = 0)	1.45	0.57	6.59	0.01	4.26 (1.41, 12.89)
Previous history of vertigo or inner ear (yes = 1; no = 0)	-1.83	0.57	10.36	0.001	0.16 (0.05, 0.49)
Focal hypodynamia (yes = 1; no = 0)	1.47	0.41	12.72	<0.001	4.34 (1.94, 9.74)
Dysarthria (yes = 1; no = 0)	0.95	0.50	3.54	0.06	2.58 (0.96, 6.91)
Dysphagia or ataxia (yes = 1; no = 0)	1.41	0.47	8.94	0.003	4.08 (1.62, 10.25)

CI: confidence interval; OR: odds ratio; SE: standard error.

history of stroke before, the risk of stroke recurrence within 5 years was 10.2%.

The previous history of vertigo or inner ear is a protective factor in diagnosing stroke in patients with vertigo. In other words, if the patient has recurrent vertigo or has a clear history of the inner ear, the possibility of vertigo caused by stroke will be reduced. A single-center retrospective study conducted by Kuroda et al. [13] found that no previous history of vertigo or inner ear can significantly increase the risk of stroke in vertigo patients. It suggests that it is crucial for medical staff in the emergency department to inquire about the history of vertigo or inner ear in detail.

Table 3: Evaluation of risk factors for stroke in patients with vertigo.

Variable	Assignment
Age ≥ 60 years	4
Diabetes mellitus	5
Atrial fibrillation	4
Previous history of vertigo or inner ear	-6
Focal hypodynamia	4
Dysphagia or ataxia	4

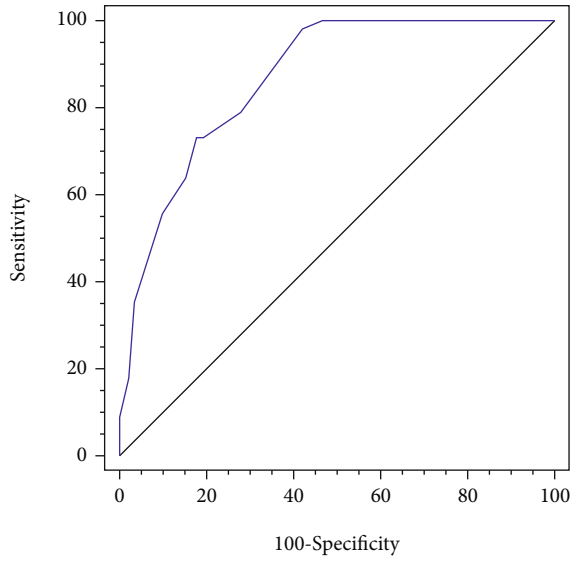

Figure 1: Working characteristic curve of subjects with the total score assigned to identify whether vertigo patients are stroke.

Positive neurological signs, including focal hypodynamia, dysphagia, and ataxia, are crucial for diagnosing stroke. In the classic ABCD2 scoring system, the clinical manifestation (c) is unilateral weakness and language disorder, with 2 and 1 points, respectively [4]. Navi et al. found that the ABCD2 scoring system is helpful to assist in identifying vertigo patients in the emergency department as stroke [14].

This study has some limitations. First, this study is a retrospective analysis, so the possible bias will affect the results and conclusions of the study. Second, this study is designed as a single-center, and the models and findings need to be confirmed by prospective and multicenter studies. Finally, due to the differences in the characteristics of the population included in different research institutes, this study may not apply to other characteristic populations.

To sum up, this study explored stroke risk factors in patients with vertigo in the emergency department and established a risk prediction model. It was found that age over 60 years old, diabetes mellitus, atrial fibrillation, history of vertigo or inner ear disease, focal muscle strength reduction, dysphagia, or ataxia were associated with a higher risk of stroke. The model constructed in this study may be helpful for medical staff in the emergency department to identify patients with vertigo caused by stroke in clinical work.

Data Availability

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

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The study was supported by Peking Union Medical College Foundation "Rui E" Emergency Medicine Research Special Fund (R2020002).

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