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Gualou Xiebai Guizhi Decoction in the Treatment of Angina Pectoris in Coronary Heart Disease: A Systematic Review and Meta-analysis

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Abstract: The effectiveness of the Gualou Xiebai Guizhi Decoction (GLXBGZD) in treating angina pectoris associated with coronary heart disease (CHD), a prevalent cardiovascular condition, remains a topic of inquiry. Hence, this meta-analysis systematically evaluated its efficacy in this context. A comprehensive search spanning PubMed, Web of Science, Embase, SinoMed, WanFang Database, China National Knowledge Infrastructure, and Chinese Scientific Journal Database, from inception to November 2022, was conducted to identify studies investigating GLXBGZD combined with conventional antianginal drugs for CHD-related angina pectoris. Outcome measures encompassed clinical effectiveness rate, left ventricular ejection fraction, blood lipid levels, and angina pectoris duration and frequency. Meta-analysis was performed utilizing Stata17 and Review Manager 5.4 software. The study was registered in PROSPERO under the number CRD42022375760. Seven eligible studies involving 688 patients were included. Compared to conventional treatments, GLXBGZD combined with conventional treatments exhibited a significant improvement in the clinical efficacy rate (odds ratio, 3.90; 95% confidence interval, 2.21–6.86; P <0.001). Furthermore, GLXBGZD combined with conventional treatments showed promising trends in enhancing heart function and blood lipid profiles (including reductions in total cholesterol, triglyceride, and low-density lipoprotein levels, along with an increase in high-density lipoprotein levels), as well as in reducing the duration and frequency of angina. However, we did not reach statistical significance for these outcomes (all P >0.05). In conclusion, the combination of GLXBGZD with conventional treatment demonstrated an enhanced clinical efficacy in the management of CHD-related angina pectoris. Nevertheless, there remains insufficient evidence to conclusively establish the benefits of GLXBGZD combined with conventional treatment in improving blood lipid levels and cardiac function, as well as in reducing the duration and frequency of angina pectoris.

1. Introduction

Coronary heart disease (CHD), a common cardiovascular disease with annually increasing clinical incidence and mortality, is a clinical syndrome caused by acute myocardial ischemia and hypoxia due to stenosis or occlusion of the coronary artery lumen [1, 2]. Patients with CHD angina pectoris often manifest with paroxysmal chest pain, which can extend to the neck, pharynx, shoulder, back, medial left finger, and other parts. Generally, symptoms can be relieved by rest or sublingual glyceryl trinitrate within approximately 5?minutes [3]. Clinically, antianginal drugs such as nitrate ester preparations, β-receptor blockers, and calcium channel blockers are the first line for symptomatic management of angina pectoris in CHD [4]. There are certain limitations to the complicated disease of CHD angina pectoris, despite these drugs effectively relieving clinical symptoms [5]. In addition, a significant number of patients remain symptomatic despite the use of antianginal drugs [6].

Traditional Chinese medicine (TCM) has been widely used in China for thousands of years, and its clinical efficacy has been demonstrated. As per TCM, angina pectoris in CHD belongs to the "obstruction of qi in the chest" category. The primary pathogenesis is "heart vessel blockage stasis" [7]. The Gualou Xiebai Guizhi decoction (GLXBGZD) is a traditional Chinese herbal formula composed of Gualou (Trichosanthis Fructus), Xiebai (Allii Macrostemonis Bulbus), Guizhi (Cmnamomi Mmulus), Zhishi (Fructus aurantii immaturus), Houpo (Magnoliae Officmalis Cortex), Fuling (Poria), Baizhu (Macrocephalae Rhizoma), Honghua (Carthami Flos), Banxia (Pinelliae Rhizoma), Chuanxiong (Chuanxiong Rhizoma), Yanhusuo (Corydalis Rhizoma), Yujin (Curcumae Radix), Gancao (Radix Rhizoma Glycyrrhizae), and other traditional Chinese medicines. GLXBGZD has the effects of warming yang and invigorating qi, eliminating phlegm and blood stasis, dredging yang, and resolving stagnation; its effectiveness in the treatment of CHD has been demonstrated in modern pharmacological studies [8-10].

Clinical application of GLXBGZD combined with Western medicine has shown more clinical benefits in relieving the clinical symptoms of patients with CHD angina pectoris than Western medicine alone [11]. Recently, several randomized controlled experiments have shown that the advantages of GLXBGZD with Western medicine are reflected in improved clinical efficacy, relief of angina pectoris symptoms, regulation of blood lipid levels, and safety [12, 13]. However, owing to the small sample size and different evaluation and research protocols, the research results are uneven, which affects their reliability of research results and guidance for clinical treatment to a certain extent. This article is based on a meta-analysis of GLXBGZD in treating angina pectoris of CHD to provide reliable medical evidence for clinical application and scientific research on GLXBGZD.

2. Methods

2.1. Literature Search Strategy

Electronic databases, including Web of Science, PubMed, Embase, SinoMed, WanFang database, China National Knowledge Infrastructure (CNKI), and Chinese Scientific Journal Database (VIP) were searched to retrieve relevant literature using a combination of subject words and free words. Search terms included "coronary disesae," "angina pectoris," "ischemic heart disease," "gualou xiebai baijiu tang," and "guizhi decoction." The retrieval time from the inception of these databases to November 2022 was limited.

2.2. Inclusion Criteria

Inclusion criteria included: 1) population: patients having CHD-related angina pectoris confirmed

based on the diagnostic criteria of CHD in the Chinese Coronary Heart Disease Diagnosis and Treatment Guidelines (2019 edition); 2) intervention: the conventional treatments of the control group and the observation group were identical, and patients in observation group were additionally treated with GLXBGZD on the basis of the conventional treatment; 3) study types: prospective and retrospective cohort studies and randomized clinical trials (RCTs) regardless of whether blinding and allocation concealment are used; and 4) outcomes: the outcomes included clinical effective rate, and the improvement on total serum cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), duration of angina pectoris, frequency of angina pectoris, and left ventricular ejection fraction (LVEF). Clinical efficacy can be assigned into three categories including "significantly effective," "effective," and "ineffective." The clinical efficacy rate was defined as the sum of the significantly effective and effective rates.

2.3. Exclusion Criteria

The exclusion criteria were: 1) studies that were repeatedly published, studies with incomplete data, nonclinical trials such as animal experiments, reviews, or meta-analyses, and 2) studies involving any other traditional Chinese medicine interventions, such as moxibustion and acupuncture.

2.4. Data Extraction

Studies that met the inclusion criteria were independently selected by two investigators. Subsequently, the available data were independently extracted from the eligible studies by two investigators according to a predesigned table, including the first author, publication year, sample size, age of the involved participants, conventional therapeutic drugs, courses of treatment, and outcome-evaluation measures. Any disagreements were addressed through consultations with experts and arbitrators.

2.5. Quality Assessment

RCTs were assessed using the Cochrane Risk of Bias Evaluation Scale in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The methodological quality of non-RCT studies was assessed from the three aspects (selection, comparability, and exposure) in the Newcastle–Ottawa Scale (NOS).

2.6. Statistical Analysis

Stata (version 17.0; StataCorp, College Station, TX, USA) and Review Manager (RevMan, Version 5.4; https://revman.cochrane.org/) software were used for the meta-analysis. Odds ratios (ORs) or standardized mean differences (SMDs), together with the corresponding 95% confidence intervals (CIs), were used as statistical effects for dichotomous and continuous variables, respectively. The I2 and Cochran's Q tests were used to analyze heterogeneity. When I2 was 0–50% and P-value was ≥0.1, there was no statistical difference in heterogeneity among studies, and a fixed-effect model could be employed. Heterogeneity among studies was considered significant when I2 >50% and P <0.1, and a random-effects model was used. Begg's rank correlation and Egger regression were used to quantitatively evaluate publication bias. Sensitivity analysis was performed by eliminating single studies and recalculating the pooled estimates. Subgroup analysis was performed based on the male–female ratio or the duration of treatment to explore the possible factors affecting outcomes.

3. Results

3.1. Literature Search and Screening Results

Based on the search strategy, 152 items of Chinese literature and 6 items of English literature were initially retrieved, including 49 articles from CNKI, 10 from VIP, 50 from WanFang, 43 from SinoMed, 1 from Web of Science, and 4 from PubMed. Of the 158 studies, 59 were duplicates and were initially removed (Figure 1). Subsequently, 72 irrelevant studies (such as case reports and master's theses not involving GLXBGZD) were removed after reading the title and abstract. Among the remaining 27 studies, 19 with incomplete data and 1 having inconformity with the inclusion criteria were excluded after reading the full text. Ultimately, seven studies [12-18] were included.

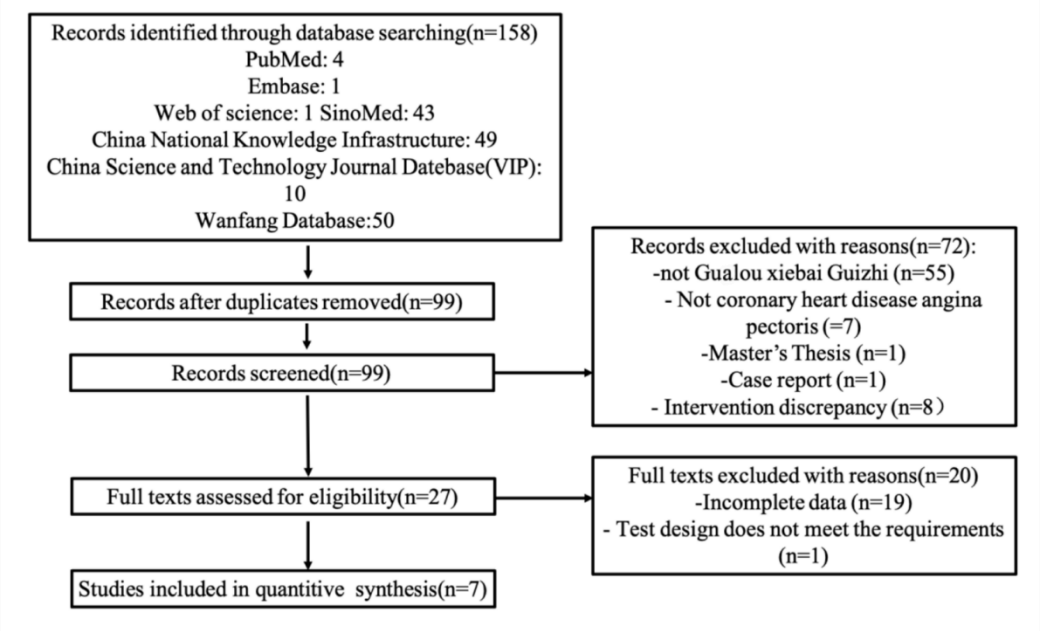


Figure 1: Literature screening flow chart

3.2. Characteristics of the Included Studies

Detailed characteristics of the included studies are listed in Table 1. These studies were conducted in China from 2015 to 2021, and 688 participants were included: 344 each in the observation group and control groups. Comparisons between routine treatment with GLXBGZD (observation group) and routine treatment alone (control group) were performed in all studies, and the treatment course ranged from 3 weeks to 3 months. Modified GLXBGZD was used in two studies [12, 13]. Five studies [12-14, 16, 17] reported the clinical efficacy rate. Five studies [14-18] reported the LVEF outcomes, and three studies [12, 15, 16] reported the duration of angina attacks and frequency of angina pectoris. Additionally, TC, TG, LDL-C, and HDL-C levels were reported in four studies [12, 13, 17, 18].

Table 1: Characteristics of the included studies

Study	Sample size O/C	Study type	Age (years)	Intervention Observation group	Intervention Control group	Course of treatment	Outcome indicators
Yang, Y 2019	(52/52)	RCT	O:70.03±4.32 C:69.78±4.27	Control (Routine treatment) + Gualou Xiebai Guizhi Decoction Modified	Metoprolol Tartrate Tablets Isosorbide Mononitrate Tablets Simvastatin Tablets	2 months	①②③⑥⑦
Hou, S 2020	(70/70)	Case-control study	O:62.75±2.40 C:63.34±2.30	Control (Routine treatment) + Gualou Xiebai Guizhi Decoction	Aspirin clopidogrel bisulfate Atorvastatin	3 weeks	②③⑥⑦⑧
Liu, AJ 2021	(30/30)	RCT	O:57.50±5.82 C:58.26±6.03	Control (Routine treatment) + Gualou Xiebai Guizhi Decoction Modified	Isosorbide Mononitrate Tablets Aspirin Enteric-coated Tablets Atorvastatin Calcium Tablets	4 weeks	①②③④⑤⑥⑦
Wu, Y 2020	(46/46)	RCT	O:69.83±6.35 C:69.70±6.73	Control (Routine treatment) + Gualou Xiebai Guizhi Decoction	Aspirin Metoprolol Tartrate Isosorbide Mononitrate	3 months	①⑧
Zhang, HX 2020	(39/39)	RCT	O:63.55±4.64 C:63.53±4.62	Control (Routine treatment) + Gualou Xiebai Guizhi Decoction	Aspirin clopidogrel bisulfate atorvastatin	4 weeks	①②③⑥⑦⑧
Cao, Y 2016	(39/39)	RCT	O and C: 62.3±5.70	Control (Routine treatment) + Gualou Xiebai Guizhi Decoction	Oxygen inhalation Analgesia elimination of heartache nitrophospholipid drugs β-blockers	40 days	①④⑤⑧
Li, WD 2015	(68/68)	RCT	O:63.60±6.20 C:61.70±7.30	Control (Routine treatment) + Gualou Xiebai Guizhi Decoction	Oxygen inhalation Analgesia elimination of heartache nitrophospholipid drugs β-blockers	40 days	④⑤⑧

O, observation group; C, control group; ①, clinical efficacy; ②, serum total cholesterol; ③, triglyceride; ④, duration of angina attack; ⑤, frequency of angina pectoris; ⑥, high-density lipoprotein cholesterol; ⑦, low density lipoprotein cholesterol; ⑧, left ventricular ejection fraction.

3.3. Quality Assessment of the Included Studies

Among the seven included studies, one was a case-control study [18] and was assessed using NOS; it received a NOS score of 6 points, including 2 points regarding selection (S), 1 points regarding comparability (C) and 3 points regarding Exposure/Outcome (E/O), indicating a moderate methodological quality. The other six studies [12-17] were RCTs and were evaluated using the Cochrane Risk of Bias Evaluation Scale (Figure 2). All these studies provided sufficient information regarding selective reporting and incomplete outcome data and thus were evaluated as having low attrition bias and reporting bias. However, none of these studies provided sufficient information on allocation concealment, blindness, and other biases, and were evaluated as having "unclear risk." Moreover, two studies [13, 17] were found to have high selection bias owing to the lack of information on random sequence generation.

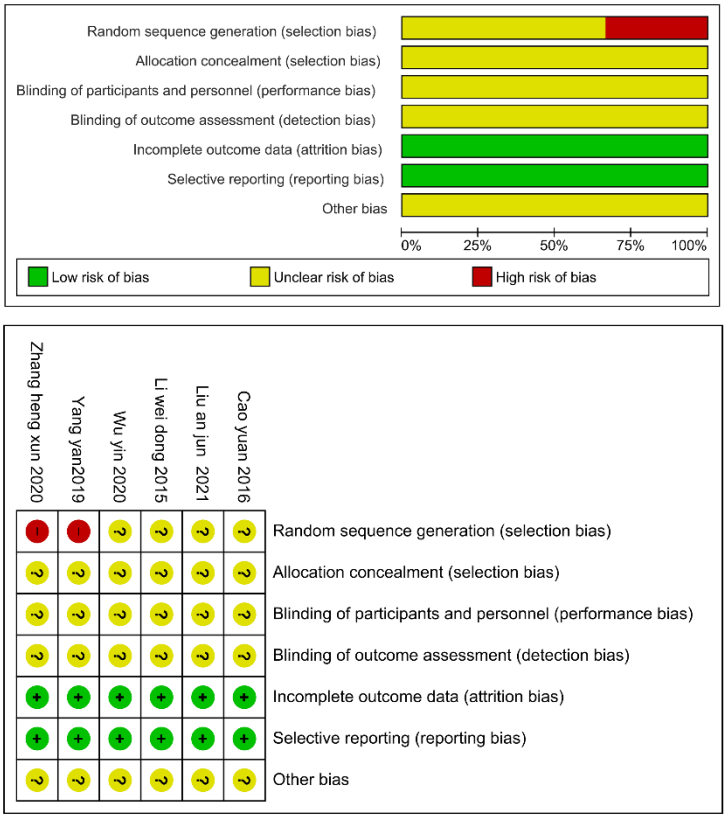


Figure 2: Quality evaluation of randomized clinical trial using Cochrane risk bias evaluation scale

3.4. Clinical effective rate

Five studies [12-14, 16, 17] involving 548 participants reported the clinical effective rate, and there was no significant heterogeneity among studies (I2 = 0%; P = 0.895). Merged results under a fixed-effects model indicated that the clinical efficacy rate of the observation group was 3.9 times higher than that of the control group (OR, 3.90; 95% CI, 2.21–6.86; P <0.001; Figure 3A).

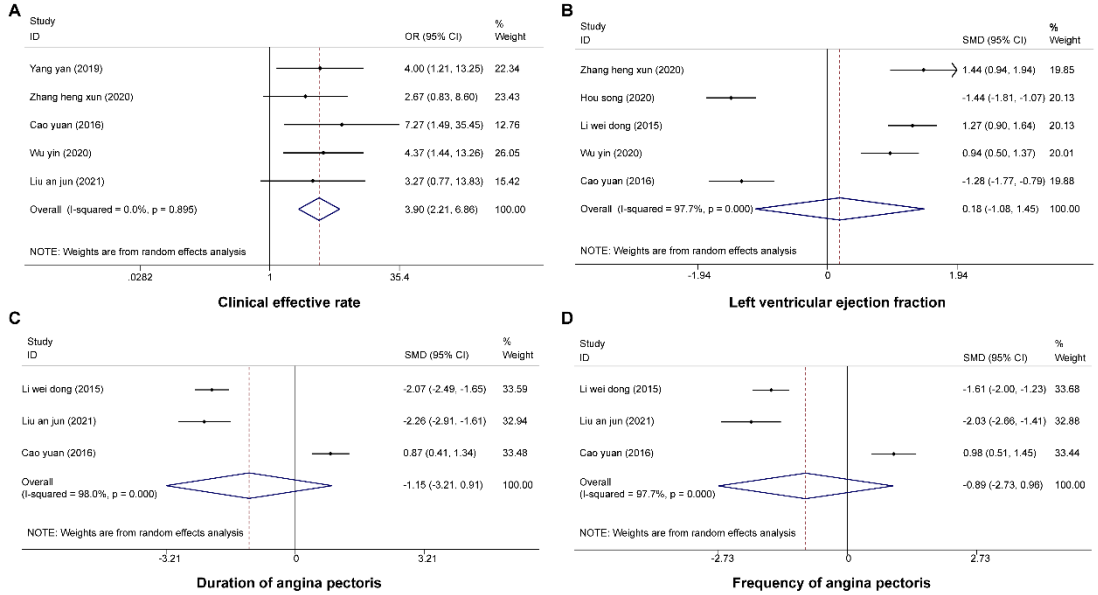
3.5. LVEF

LVEF was mentioned in five studies [14-18] involving 524 patients, and significant heterogeneity was observed among the studies (I2 = 97.7%; P <0.001). The merged results under a random-effects model indicated that these two groups had similar effects on LVEF (SMD, 0.18; 95% CI –1.08 to

1.45); P = 0.776; Figure 3B).

3.6. Angina Attack Duration and Frequency

Three studies [12, 15, 16] involving 274 participants reported angina attack duration and frequency. There was significant heterogeneity among the studies regarding both angina attack duration (I2 = 98.0%; P <0.001) and frequency of angina pectoris (I2 = 97.7%; P <0.001). The duration of angina attacks in the observation group appeared to be shorter than that in the control group; however, the difference was not statistically significant (SMD, –1.15; 95% CI –3.21 to 0.91; P = 0.275; Figure 3C). In addition, frequency of angina pectoris in the observation group also showed reduced tendency compared to control group, however no statistical difference was observed (SMD, –0.89, 95% CI –2.73 to 0.96;, P = 0.347; Figure 3D).

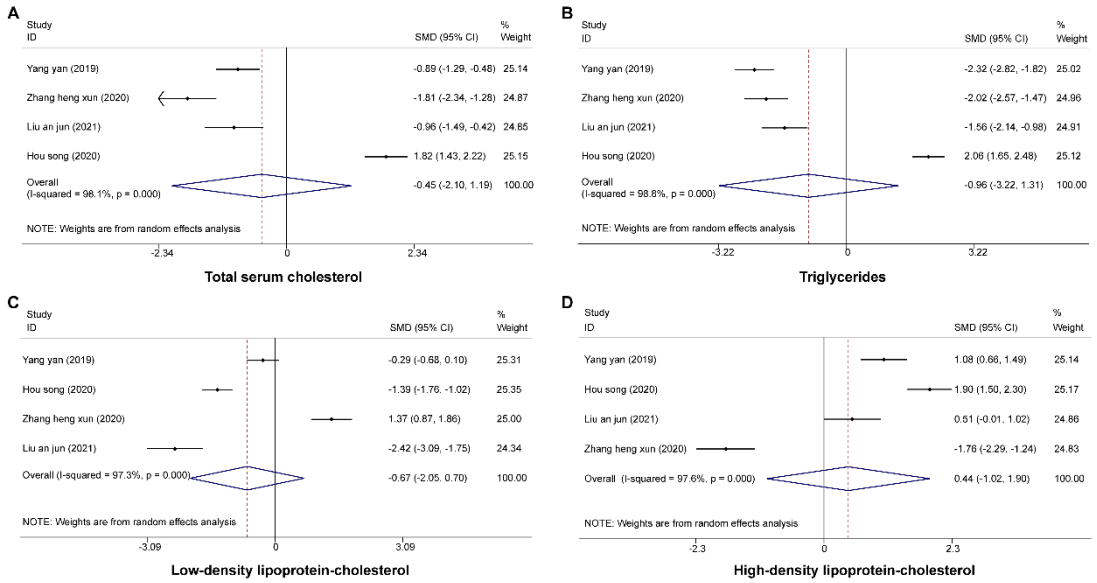


Forest plots showing the merged results of the total clinical effective rate (A), left ventricular ejection fraction (B), angina pectoris duration (C), and frequency (D).

Figure 3: Meta-analysis of angina pectoris symptoms and cardiac function

3.7. Blood Lipids

Four studies [12, 13, 17, 18] involving 274 participants reported TC, TG, LDL-C and HDL-C levels. There was significant heterogeneity among the studies for each of the four blood lipids indicators (I2 = 50.0%; P <0.001), and a random-effects model was used. Compared to the control group, the observed group seemed to have decreased levels of TC (SMD, –0.45, 95% CI – 2.10 to 1.19; P = 0.591), TG (SMD, –0.96, 95% CI – 3.22 to 1.31); P = 0.408), and LDL-C (SMD, –0.67, 95% CI – 2.05 to 0.70; P = 0.338), but there was no statistical difference (Figure 4A–C). Additionally, the observed group seemed to have increased HDL-C levels compared to the control group (SMD, 0.44, 95% CI – 1.02 to 1.90; P = 0.558), but the difference was not statistically significant (Figure 4D).

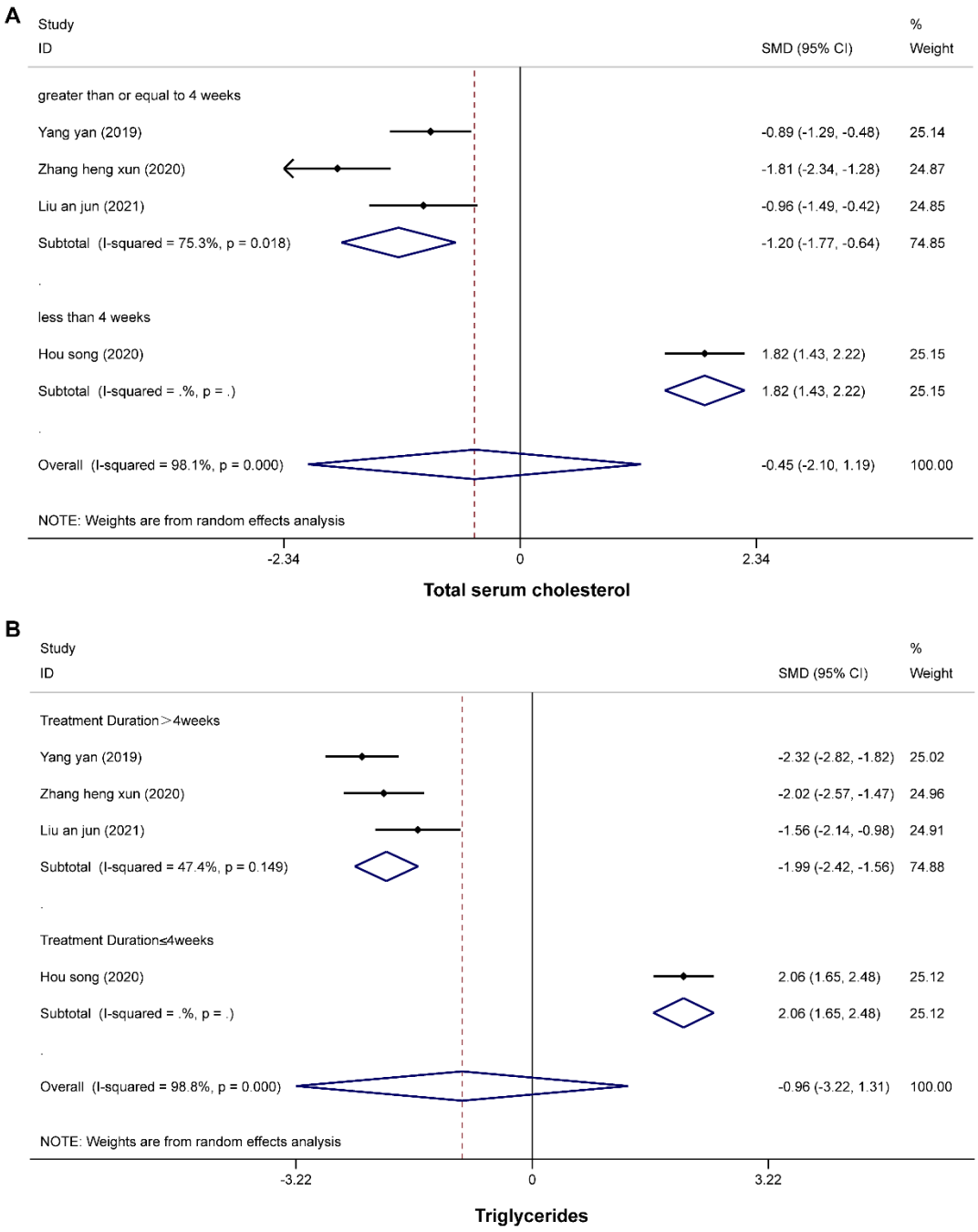


Forest plots showing the merged results of total serum cholesterol (A), triglyceride (B), low-density lipoprotein cholesterol (C), and high-density lipoprotein cholesterol (D) levels.

Figure 4: Meta-analysis of blood lipids

3.8. Sensitivity and subgroup analysis

The robustness of the pooled results was evaluated using sensitivity analysis. There was little difference in the clinical efficacy rate, left ventricular ejection fraction, HDL-C, and LDL-C levels between the original combined effect size and reevaluation, indicating relatively low sensitivity and stable results. Nevertheless, regarding TC, TG, angina pectoris duration, and the frequency of these outcome indicators, the combined effect size changed from insignificant to significant when potentially anomalous studies were eliminated. Specifically, after eliminating the study by Hou et al. [18] in the sensitivity analysis, the observation group showed a significant decrease in TC levels (SMD, –1.20, 95% CI – 1.77 to –0.64; P <0.001) and TG (SMD, –1.99, 95% CI – 2.42 to –1.56), P <0.001) compared to the control group, which was insignificant between groups before excluding this study. In the study by Hou et al., the course of treatment was less than four weeks, whereas it was greater than four weeks in the other three studies. Heterogeneity among the studies on TC (I2 = 98.1%, P<0.001 changed to I2 = 75.3%, P = 0.018) and TG (I2 = 98.8%, P<0.001 changed to I2 = 47.4%, P = 0.149) decreased after eliminating the study by Hou et al., indicating that the course of treatment might be a source of heterogeneity (Figure 5A, B).

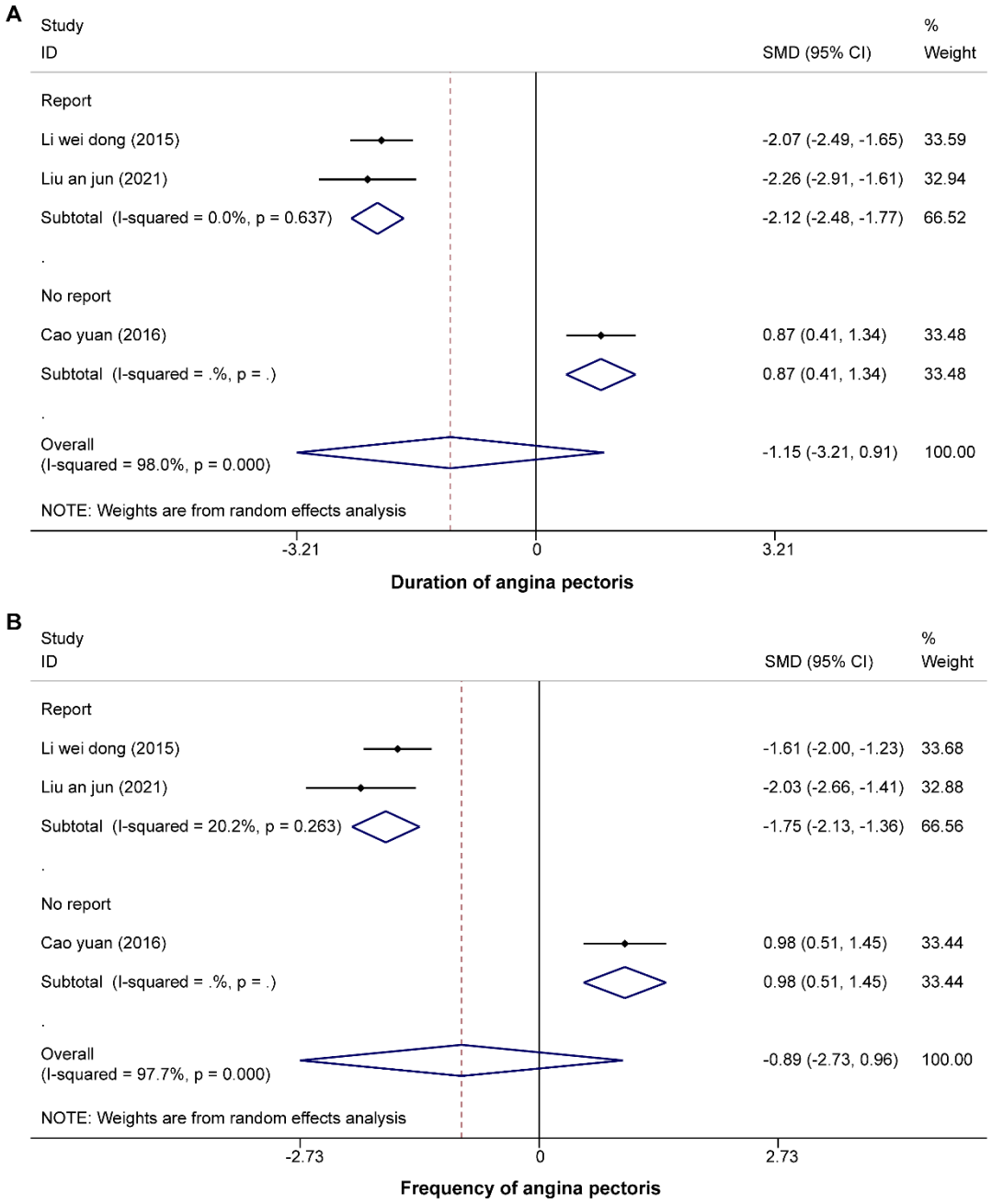


Forest plots showing the outcomes of total serum cholesterol (A) and triglycerides (B) in the two subgroups divided by treatment course (less than 4 weeks or not).

Figure 5: Subgroup analysis based on treatment course

When the study by Cao et al. [16] was excluded from the sensitivity analysis, the observation group showed a significant decrease in angina pectoris duration (SMD, –2.12, 95% CI – 2.48 to –1.77; P <0.001) and frequency (SMD, –1.75, 95% CI – 2.13 to –1.36), P <0.001) compared with the control group, which was insignificant between the groups before excluding this study. Subgroup analysis was performed based on the male/female ratio to explore the possible factors affecting these two outcomes. The male/female ratio was mentioned in all studies except for the study by Cao et al. Heterogeneity among studies on angina pectoris duration (I2 = 97.7%, P <0.001 changed to I2 = 0%,

P = 0.637) and angina pectoris frequency (I2 = 98.0%, P <0.001 changed to I2 = 20.2%, P = 0.263) significantly decreased after eliminating the study by Cao et al., indicating that the male/female ratio might be a source of heterogeneity (Figure 6A, B).



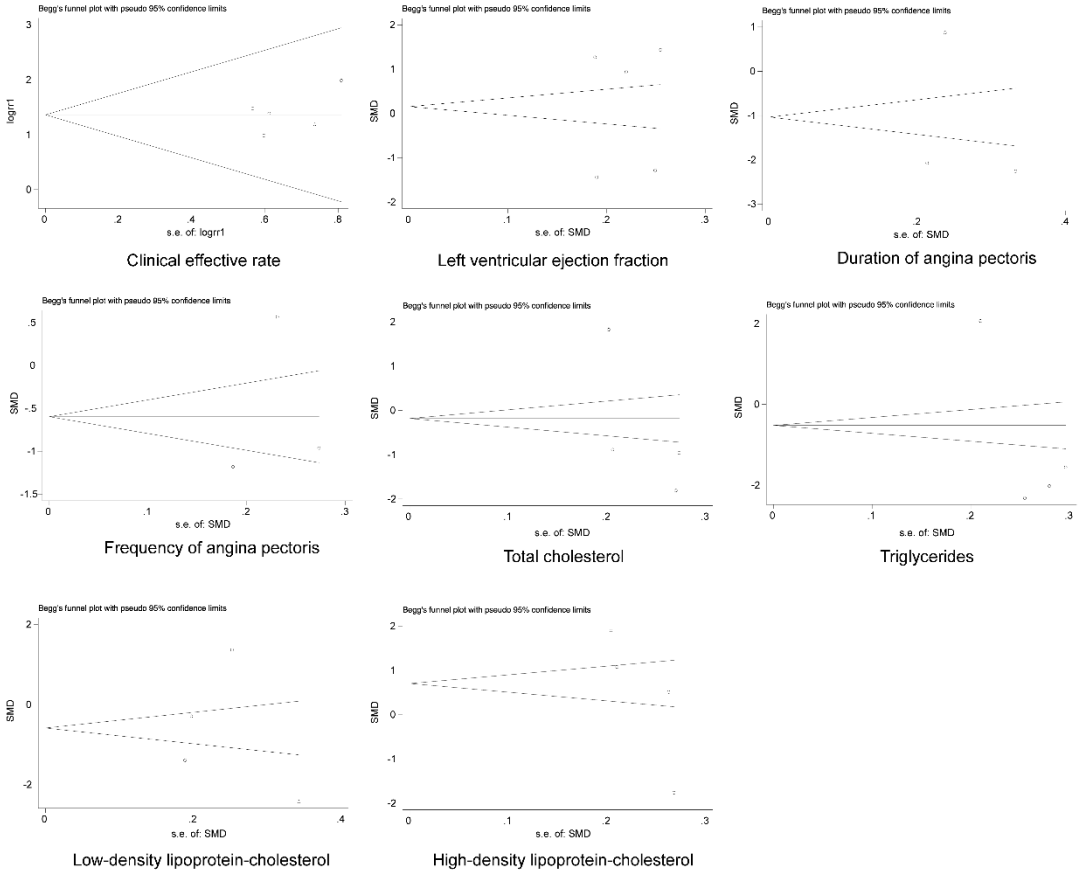
Forest plots showing the outcomes of angina pectoris duration (A) and frequency (B) in the two subgroups divided according to whether the male/female ratio was reported.

Figure 6: Subgroup analysis based on male/female ratio

3.9. Publication Bias

Egger's test and Begg's funnel plots were used to assess whether there was a significant publication bias among the studies for each outcome. Although asymmetry in the scatter distribution was observed in several funnel plots, Egger's test indicated no significant publication bias among the

studies for all outcomes (all P >0.05; Figure 7).



Funnel plots showing the publication bias among studies for all outcomes.

Figure 7: Publication bias assessment

4. Discussion

Angina pectoris of CHD belongs to the category of "obstruction of qi in the chest" in theories of TCM [19]. The onset of CHD and angina pectoris is mainly characterized by precordial pain, insomnia, anxiety, and other symptoms that seriously affect the physiological state and quality of life [20]. Current clinical use of β-blockers, nitrate esters, calcium channel blockers, antiplatelet aggregation drugs, statins, and other Western medicine in the treatment of CHD angina pectoris, but long-term use of adverse reactions increases the risk [21]. Therefore, fewer side effects and better efficacy are needed in the treatment of CHD-angina pectoris.

TCM believes that the core pathogenesis of “obstruction of qi in the chest” mainly includes qi deficiency, blood stasis, and phlegm turbidity [22]. The impassability of blood stasis and phlegm turbidity obstruction meridians is painful, and chest obstruction for a long time leads to a deficiency of qi, blood, yin, and yang. Therefore, the main therapeutic goal is the regulation of qi and promotion of blood circulation. GLXBGZD has the effects of warming yang, invigorating qi, eliminating phlegm and blood stasis, dredging yang, and resolving stagnation, and has been used in the treatment of CHD angina pectoris. However, their effectiveness has not yet been fully investigated. Therefore, this meta-analysis aimed to provide objective evidence to explore the effectiveness of GLXBGZD on CHD angina pectoris from the aspects of the clinical efficacy rate and improvements in blood lipids, cardiac function, and angina pectoris duration and frequency. The merged results of five studies [12-14, 16, 17] demonstrated that GLXBGZD plus conventional treatment could markedly improve the total

clinical efficacy rate for CHD-angina pectoris compared to conventional treatment alone. Additionally, although there was no statistical difference, our meta-analysis revealed the potential clinical benefits of GLXBGZD in improving blood lipid levels (including TC, TG, HDL-C, and LDL-C) [12, 13, 17, 18] and cardiac function (LVEF) [14-18], and reducing the duration and frequency of angina pectoris [12, 15, 16]. These findings indicate that the use of GLXBGZD could improve the clinical efficacy rate, blood lipid levels, and angina pectoris duration and frequency. This is consistent with the findings of Feng et al. [23]. However, only six RCTs and one case control study were included, and the methodological quality of these RCTs was relatively low. In particular, a single study led to large heterogeneity and unstable results regarding the outcomes of TC, TG, and the duration and frequency of angina pectoris. Hence, the conclusions should be interpreted with caution and further confirmed based on high-quality RCTs.

Modern clinical studies have demonstrated that the main mechanism of CHD is atherosclerosis and that the essence of atherosclerosis is inflammation. Inflammatory factors produce toxic substances such as peroxides and oxygen free radicals, which damage the vascular endothelium and trigger atherosclerosis. The activation and concentration of inflammatory factors can strengthen the inflammatory response, oxidative stress, cytoplasmic–endoplasmic reticulum activation, immune response, and other mechanisms that damage the structure and function of endothelial cells, leading to platelet aggregation, smooth muscle cell proliferation, and luminal stenosis/occlusion [22, 24]. GLXBGZD significantly improved blood lipid levels, inhibited inflammatory reactions, dilated coronary blood flow, and improved cardiac function [23]. The underlying mechanism of action of GLXBGZD in the treatment of CHD-angina pectoris appears to be multifactorial. The extracts of Gualou (Trichosanthis Fructus) and Xiebai (Allii Macrostemonis Bulbus) contain active ingredients, such as phytosterols, saponins, flavonoids, and triterpenoids, which have beneficial effects on the cardiovascular system, including dilation of coronary arteries, anti-platelet aggregation, increasing coronary blood flow, reducing blood viscosity, and modulating blood lipids [10, 25-27]. The active ingredients of Guizhi (Cmnamomi Mmulus) include cinnamaldehyde and cinnamic alcohol, and these two components have been proven to inhibit myocardial inflammation, relieve coronary vasospasm, contribute to vasodilation, and protect myocardial cell [28-31].

The limitations of this study: First, the methodological quality of the included RCTs was relatively poor. None of these RCTs provided sufficient information on allocation concealment, blindness and other bias, and were evaluated as “unclear risk.” Moreover, the random method was not mentioned in two studies [13, 17], and was found to have a high selection bias. A lack of such information may affect the accuracy of the research results. Next, all included studies were conducted in Chinese, which limited the extrapolation of the results. Finally, heterogeneity should also be considered. Owing to the particularity of the traditional Chinese medicine decoction, there are specific differences in the composition and dosage of GLXBGZD used in each study. The modified GLXBGZD was used in two studies [12, 13]. Moreover, the treatment duration, clinical effectiveness standards, and traditional therapeutic regimens differed across studies. These differences may have led to heterogeneity in research results. For example, treatment duration was identified as a source of heterogeneity in the subgroup analysis based on treatment duration.

In summary, this meta-analysis indicated that GLXBGZD plus conventional treatment could improve the total clinically effective rate of CHD angina pectoris compared with conventional treatment alone. However, evidence is insufficient to demonstrate the advantages of GLXBGZD plus conventional treatment in improving blood lipid levels, cardiac function, and the duration and frequency of angina pectoris. Larger-scale, high-quality, multicenter RCTs with long-term follow-ups are needed to further elucidate the effectiveness and safety of GLXBGZD in the treatment of CHD-angina pectoris.

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