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Effectiveness of Warm Yang and Promote Diuresis Blood-Activating Methods in Chronic Heart Failure

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Chronic heart failure (CHF) is a prevalent condition with significant morbidity and mortality worldwide. Conventional treatments may not always be effective or may have considerable side effects. Warm yang and promote diuresis blood-activating method (WYLBAM), a traditional intervention, has been proposed as a complementary approach for CHF, but its clinical efficacy and impact on cardiac function have not been systematically evaluated. We performed a comprehensive meta-analysis to assess the clinical efficacy of WYLBAM for CHF. Following PRISMA guidelines, databases were searched for clinical trials comparing WYLBAM with standard care. Data on clinical efficacy rate, left ventricular ejection fraction (LVEF), left ventricular end-diastolic and end-systolic dimensions (LVEDD and LVESD), 6-minute walk test, and biomarkers BNP and NT-proBNP were extracted. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated with funnel plots and sensitivity analyses. Our search yielded 947 records, with 26 studies included after screening and eligibility assessment. Meta-analysis demonstrated a significant improvement in clinical efficacy rate, LVEF, LV dimensions, and 6-minute walk test distances in patients treated with WYLBAM. Biomarkers BNP and NT-proBNP also improved significantly, indicating a potential reduction in cardiac stress. The I^2 values suggested substantial heterogeneity, which was addressed through random-effects modeling. Publication bias was not evident in the funnel plot analyses. WYLBAM may be a beneficial adjunctive treatment for improving cardiac function and physical capacity in patients with CHF. However, the presence of heterogeneity suggests that individual patient factors should be considered when applying WYLBAM. Further well-designed large-scale RCTs are warranted to confirm these findings and to explore the underlying mechanisms of action.

Keywords: blood-activating; cardiac function; clinical efficacy; heart failure; meta-analysis; promote diuresis; traditional therapy; warm yang
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Introduction

Chronic heart failure (CHF) remains one of the most prevalent cardiovascular diseases worldwide, with an estimated 26 million individuals affected globally (G et al. 2022). It is a primary cause of hospitalization in adults over the age of 65, signifying a considerable burden on healthcare infrastructures (Schwarz et al. 2021). The disease is characterized by frequent exacerbations and progressive deterioration of heart function, leading to significant physical limitations and psychosocial stress. Mortality rates for CHF are high; approximately half of the patients diagnosed with CHF will die within five years, making it as malignant as many common cancers (Tokede et al. 2013). Despite advances in treatment and management, the five-year survival rate has shown only a modest improvement over the last few decades. Quality of life (QoL) in CHF patients is severely compromised (Tsabedze et al. 2021). The financial strain of long-term disease management also contributes to decreased QoL, not only for the patients but also for their families and caregivers. In summary, CHF poses a significant challenge to global health systems, not only due to its high prevalence and associated mortality but also because of the substantial morbidity and reduced quality of life experienced by patients.

Current standard treatments for CHF involve a multi-

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faceted approach that primarily includes pharmacological therapy, lifestyle modification, and, in severe cases, surgical intervention or device implantation. Pharmacologically, the cornerstone of CHF treatment involves agents such as angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, diuretics, and mineralocorticoid receptor antagonists (MRAs) (Eguchi et al. 2022). More recent additions to the therapeutic arsenal include angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have shown promise in improving cardiovascular outcomes (Gulin et al. 2019; Ji et al. 2023). While these medications have substantially advanced the management of CHF, improving both survival and quality of life, they are not without limitations. Adherence to these treatments can be challenging due to complex dosing regimens, particularly in elderly populations or in those with cognitive impairment. Moreover, the benefits of these drugs must be weighed against their potential side effects. ACEIs and ARNIs, for example, can cause renal dysfunction and hyperkalemia (Shi et al. 2019), while beta-blockers may lead to bradycardia and exacerbate asthma (Pchejetski et al. 2020). Diuretics, essential for managing fluid overload, can induce electrolyte imbalances and renal impairment (Bruschettini et al. 2022). These challenges underscore the need for complementary and alternative medicine (CAM) in CHF management.

The Warm Yang and Promote Diuresis Blood-Activating Method (WYLBAM) finds its roots in the rich tapestry of traditional medicine, where the conceptual framework revolves around the balance of vital energies within the body (Deng et al. 2019). In the context of CHF, WYLBAM is predicated on the principle of warming the yang, which in traditional terms refers to enhancing the functional activities of the body, and promoting diuresis to alleviate fluid retention, a common symptom in CHF. The integration of WYLBAM into the management of CHF, however, requires a rigorous and systematic evaluation to ensure its efficacy and safety. A meta-analysis is an invaluable tool in this regard, capable of synthesizing disparate data and providing a more definitive conclusion on the effectiveness of WYLBAM.

The objectives of this meta-analysis are to: Assess the clinical efficacy of WYLBAM on improving cardiac function in patients with CHF, as measured by left ventricular ejection fraction (LVEF) and changes in left ventricular dimensions (LVEDD and LVESD). Evaluate the impact of WYLBAM on physical capacity in CHF patients, using the 6-minute walk test as a benchmark for exercise tolerance. Determine the effects of WYLBAM on biomarkers indicative of cardiac stress, specifically B-type Natriuretic Peptide (BNP) and N-terminal pro b-type Natriuretic Peptide (NT-proBNP), to provide insights into its potential mechanisms of action in heart failure management.

Materials and Methods

Search strategy

A systematic literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Wang et al. 2022). The following databases were searched: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and CNKI (China National Knowledge Infrastructure). The search terms used included combinations of the following: "WYLBAM," "chronic heart failure," "cardiac function," "left ventricular ejection fraction," "left ventricular dimensions," "physical capacity," "6-minute walk test," "biomarkers," "B-type Natriuretic Peptide," and "N-terminal pro b-type Natriuretic Peptide." Both MeSH terms and free-text terms were used to ensure comprehensive coverage.

Eligibility criteria

Study Design: We included randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that evaluated the efficacy of WYLBAM in patients with CHF. Participants: Studies involving adult participants (aged 18 years and above) diagnosed with CHF based on recognized clinical criteria, such as the New York Heart Association (NYHA) functional classification or the American College of Cardiology/American Heart Association (ACC/AHA) stages of heart failure (Dionne-Odom et al. 2014). Intervention: Studies that utilized the Warm Yang and Promote Diuresis Blood Activating Method, including herbal medicine, acupuncture, moxibustion, or a combination thereof. Comparators: Studies comparing WYLBAM with standard care treatments for CHF, which include pharmacological treatments (such as ACE inhibitors, beta-blockers, diuretics, and MRAs), lifestyle modifications, or placebo treatments. Outcomes: Studies reporting on primary outcomes such as LVEF and LVEDD and LVESD, and secondary outcomes like the 6-minute walk test, biomarkers (BNP, NT proBNP), and clinical efficacy rates.

Study Design: We excluded observational studies, case reports, and reviews. Participants: Studies involving patients with acute heart failure or heart failure due to congenital heart disease. Intervention: Studies that did not clearly describe the components of WYLBAM or combined it with other traditional interventions not focused on warming yang, promoting diuresis, or activating blood circulation. Outcomes: Studies that did not report relevant clinical outcomes or provided insufficient data for extraction.

In our meta-analysis, "standard care" was defined according to contemporary guidelines for the management of CHF, which typically include: Pharmacological Treatments: ACE inhibitors, beta-blockers, diuretics, mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), and sodium glucose cotransporter 2 (SGLT2) inhibitors. Lifestyle Modifications: Dietary changes, physical activity, and fluid management.

Additional Interventions: Device implantation (e.g., ICDs, CRT) and, in some cases, surgical interventions.

WYLBAM protocol

Herbal Medicine: The herbal formulations typically included a combination of the following key ingredients: Fuzi (Aconitum carmichaelii): Known for its warming properties, Fuzi is used to restore yang and improve circulation. Dosage typically ranges from 6 to 15 grams per day. Ganjiang (Zingiber officinale): Ginger is well known for its warming and diuretic effects, aiding in the promotion of yang energy and fluid balance. Dosage typically ranges from 6 to 15 grams per day. Huangqi (Astragalus membranaceus): This herb is used for its qi-boosting and diuretic properties, enhancing overall energy levels and fluid metabolism. Dosage ranges from 9 to 30 grams per day. Danggui (Angelica sinensis): Angelica is included for its blood-activating and harmonizing effects, supporting improved blood circulation. Dosage ranges from 9 to 15 grams per day. Chuanxiong (Ligusticum chuanxiong): This herb aids in promoting blood circulation and alleviating pain, used in dosages of 3 to 9 grams per day. Rougui (Cinnamomum cassia): Cinnamon bark is known for its strong warming properties, which help in enhancing yang energy and circulation. Dosage ranges from 1.5 to 4.5 grams per day. Zhigancao (Glycyrrhiza uralensis): Licorice is used for its harmonizing effects and to moderate the properties of other herbs. Dosage typically ranges from 3 to 6 grams per day. These herbs are commonly administered orally as decoctions or granules, with the specific combinations and dosages tailored to the individual patient's condition and response to treatment.

Acupuncture: Common acupuncture points included Shenshu (BL23), Guanyuan (CV4), and Zusanli (ST36). Treatments were administered 2 to 3 times per week, with sessions lasting about 30 minutes, using manual needle manipulation to achieve deqi. Moxibustion: This involved burning moxa on or near specific acupuncture points to warm yang and stimulate circulation. Sessions were typically conducted 1 to 2 times per week, often in conjunction with acupuncture. Adjunctive Therapies: Some studies included additional therapies like Tuina (Chinese therapeutic massage) or Qi Gong exercises, although these were less common. While there was some variability in the exact herbal formulas, acupuncture points, and moxibustion techniques, the core principles of warming yang, promoting diuresis, and activating blood circulation were consistently applied.

Study selection

This process was conducted in two distinct stages: Initially, all records identified through the database and additional source searches were imported into a reference management software to remove duplicates. Following this, two independent reviewers screened the titles and abstracts of the remaining records against the inclusion criteria. Studies that did not meet the eligibility criteria were excluded at this stage. Discrepancies between reviewers during this initial screening phase were resolved through discussion, with a third reviewer consulted if consensus could not be reached. For records that appeared to meet the inclusion criteria or where there was uncertainty based on the title and abstract screening, the full texts were retrieved for a detailed assessment. The same two independent reviewers conducted the full-text review to determine final inclusion in the meta-analysis, using a detailed eligibility form that further assessed the studies against the specific inclusion and exclusion criteria outlined in the protocol.

A systematic and structured approach was employed for the data extraction process to ensure accuracy and completeness of the data collected from the included studies. This process involved the use of a standardized data extraction form, designed to capture all relevant information required for the meta-analysis.

Standardized data extraction form

The form included the following sections: first author, year of publication, study design, and number of participants, Primary and secondary outcomes as defined in the eligibility criteria, including measures of cardiac function (LVEF, LVEDD, LVESD), exercise capacity (6-minute walk test), and biomarkers (BNP, NT-proBNP). Assessment of risk of bias using appropriate tools, such as the Cochrane Collaboration's tool (United Kingdom) for assessing risk of bias in randomized trials. Two independent reviewers conducted the data extraction using the standardized form to minimize errors and bias.

Risk of bias in individual studies

To assess the risk of bias within the included studies, we utilized the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. This tool is widely recognized for its comprehensive approach to evaluating the potential sources of bias across several domains, including: Assessed through the examination of the random sequence generation and allocation concealment mechanisms. Evaluated based on the blinding of participants and personnel to the intervention, which is crucial in clinical trials to prevent knowledge of the intervention from influencing outcomes. Determined by reviewing the blinding of outcome assessment, ensuring that the outcome measurement is not influenced by the intervention's knowledge. Investigated by examining incomplete outcome data and the methods used to handle them in the analysis. Assessed by identifying selective reporting of outcomes, where only certain outcomes are reported, potentially leading to a biased representation of the study's findings. Considered for any additional bias not covered by the above categories, such as funding bias. Each study was rated as having a "low," "high," or "unclear" risk of bias for each domain, based on the criteria provided by the Cochrane tool.

Summary measures and synthesis of results

The primary summary measures were the mean differences for continuous outcomes (such as left ventricular ejection fraction, LVEDD, LVESD, and 6-minute walk test distances) and odds ratios for dichotomous outcomes, both with 95% confidence intervals. These measures provided a standardized way to compare the effects of WYLBAM across different studies.

Two models were used to aggregate study results, depending on the assumption about the presence of heterogeneity among the included studies: Applied when the studies were assumed to share a common effect size, typically used when there is no significant heterogeneity observed among study results. An I^2 value of 0% indicates no observed heterogeneity, while values greater than 50% may indicate substantial heterogeneity. Depending on the level of heterogeneity detected, the appropriate model for meta-analysis was chosen. To test the robustness of the meta-analysis findings, sensitivity analyses were conducted by excluding studies with a high risk of bias or those that had a significant impact on the overall heterogeneity. The potential for publication bias was examined using funnel plots and statistically tested with Egger's test, where applicable.

Results

In the study selection phase of our meta-analysis on the efficacy of WYLBAM in treating CHF, a comprehensive search across multiple databases yielded a total of 947 records. After removing duplicates, 435 records were screened based on titles and abstracts, leading to the exclusion of 396 records that did not meet the eligibility criteria. The full texts of the remaining 39 studies were reviewed in detail, resulting in 26 studies being included in the final analysis (Yan and Aleteng 2007; Zhang 2007; Lu et al. 2013; Du et al. 2014; Wang et al. 2014; Li 2015; Yu et al. 2015; Li et al. 2016; Jiang and Wu 2017; Li 2017; Yao and Feng 2017; Ye et al. 2017; Zhang et al. 2017; Jiang and Xiong 2018; Wang et al. 2018; Wang and Niu 2018; Zhang and Xu 2018; Zhao et al. 2018; Zhou et al. 2018; Feng and Zhang 2019; Gao et al. 2019; Lin et al. 2019; Liu and Li 2019; Zhao et al. 2019; Li and Zhang 2022). These studies encompassed a combined total of 2,423 participants with CHF. The PRISMA flow diagram below outlines the study selection process, illustrating the filtration of studies from identification to inclusion (Fig. 1). The basic characteristics of the included studies are presented in Table 1.

The 26 studies included in our meta-analysis on the efficacy of WYLBAM for treating CHF shared several key characteristics. Most included studies (25/26) were randomized controlled trials (RCTs). The sample size across the studies varied, ranging from a minimum of 43 to a maximum of 160 participants, with a median sample size of approximately 83 participants. All participants were diagnosed with CHF, primarily classified as NYHA functional class II to III. Diagnosis was based on the NYHA functional classification system, with some studies also using echocardiographic criteria such as reduced ejection fraction (EF < 40%) to define systolic heart failure. The interven-

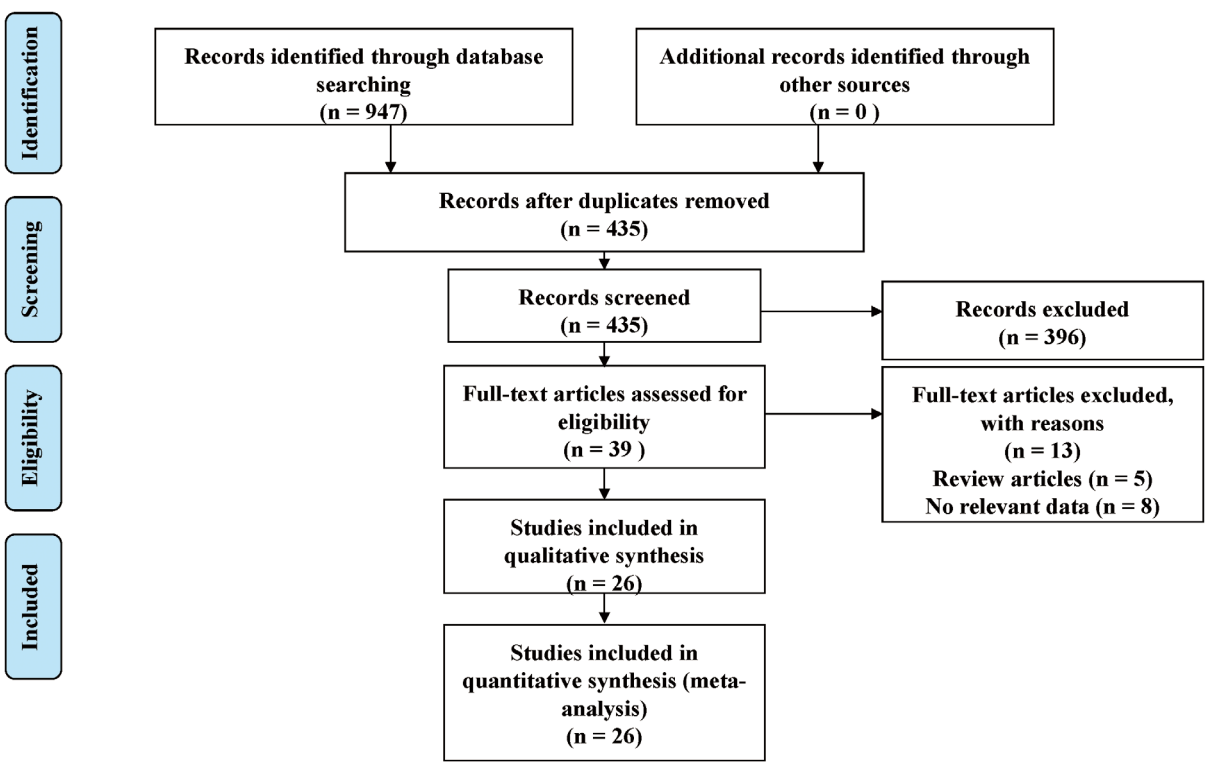

Fig. 1. Study selection.

Table 1. Studies included in the meta-analysis.

Number	Author	Year	Study design	Combination/Observation group	Conventional/Control group
1	Shiqing Zhou	2018	Randomized Controlled Trial	63	63
2	Zhanhua Gao	2019	Randomized Controlled Trial	40	40
3	Xuelong Li	2015	Randomized Controlled Trial	25	25
4	Jinping Lu	2013	Randomized Controlled Trial	38	38
5	Hong Yan	2007	Cross-Sectional Trial	23	23
6	Kang Ye	2017	Randomized Controlled Trial	60	60
7	Lan Yao	2017	Randomized Controlled Trial	60	60
8	Mingxi Zhang	2007	Randomized Controlled Trial	32	30
9	Jian Du	2014	Randomized Controlled Trial	45	45
10	Qifei Li	2022	Randomized Controlled Trial	57	57
11	Gaoren Liu	2019	Randomized Controlled Trial	45	45
12	Jianjun Jiang	2017	Randomized Controlled Trial	80	80
13	Yinping Wang	2014	Randomized Controlled Trial	30	30
14	Haixia Wang	2018	Randomized Controlled Trial	22	21
15	Panhong Lin	2019	Randomized Controlled Trial	39	39
16	Yongfeng Chen	2017	Randomized Controlled Trial	34	34
17	Wenqing Li	2016	Randomized Controlled Trial	60	60
18	Yun Zhao	2019	Randomized Controlled Trial	62	62
19	Jing Zhang	2017	Randomized Controlled Trial	62	61
20	Zhanwen Yu	2015	Randomized Controlled Trial	40	40
21	Xiurong Zhang	2018	Randomized Controlled Trial	60	61
22	Jing Feng	2019	Randomized Controlled Trial	43	43
23	Huiming Wang	2018	Randomized Controlled Trial	50	50
24	Fei Jiang	2018	Randomized Controlled Trial	40	40
25	Yuchao Li	2017	Randomized Controlled Trial	35	35
26	Jionghui Zhao	2018	Randomized Controlled Trial	68	68

tions varied among the studies but generally included a combination of herbal medicine, acupuncture, and moxibustion, tailored to warm yang and promote diuresis, as well as activate blood circulation according to traditional medicine principles. The control groups in these studies received standard CHF treatment, including ACE inhibitors, beta-blockers, diuretics, and MRAs. A few studies compared WYLBAM directly against placebo treatments. Primary outcomes focused on improvements in cardiac function, assessed through changes in LVEF) and structural changes measured by LVEDD and LVESD. Secondary outcomes included physical capacity, gauged by the 6-minute walk test, and levels of cardiac biomarkers such as BNP and NT-proBNP.

The quality of the 26 studies included in our meta-analysis was rigorously assessed for the risk of bias using the Cochrane Collaboration's tool. The results of this assessment indicated that the majority of the studies were of high quality (Fig. 2). The evaluation considered several dimensions of bias, including selection, performance, detection, attrition, and reporting biases. The findings reveal that most of the included studies exhibited a low risk of bias in these key areas, thereby lending confidence to the robustness and reliability of our meta-analysis results. This high-quality evidence base supports the conclusion that the Warm yang and promote diuresis blood-activating method (WYLBAM) is a promising complementary approach for the management of chronic heart failure.

The results of the meta-analysis revealed significant findings across the primary and secondary outcomes, suggesting that WYLBAM has a positive impact on patients with CHF. The combined effect size, represented by the blue diamond at the bottom, demonstrates an overall positive effect with an OR of 2.77 (95% CI: 2.21, 3.47), indicating that WYLBAM significantly improves clinical efficacy in patients with CHF (Fig. 3). The meta-analysis of LVEF showed a significant improvement in patients treated with WYLBAM compared to those receiving standard care. The pooled standard mean difference (SMD) was 0.96 (95% CI: 0.67 to 1.25), indicating enhanced cardiac function. Given the moderate heterogeneity observed (I^2 = 87.1%), a random-effects model was applied (Fig. 4). For LVEDD and LVESD, the analysis also showed significant reductions, suggesting beneficial effects on cardiac structure. The pooled SMD for LVEDD was −1.34 mm (95% CI: −1.98 to −0.71 mm), and for LVESD was 1.89 mm (95% CI: −3.03 to −0.75 mm), with moderate heterogeneity (I^2 = 94.7%), justifying the use of a random-effect model (Fig. 5). The

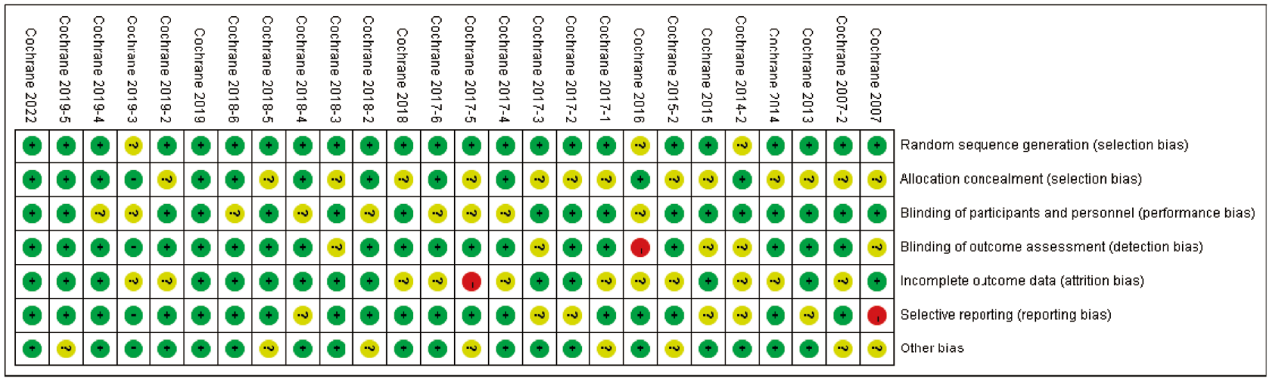

Fig. 2. Risk of Bias Assessment.

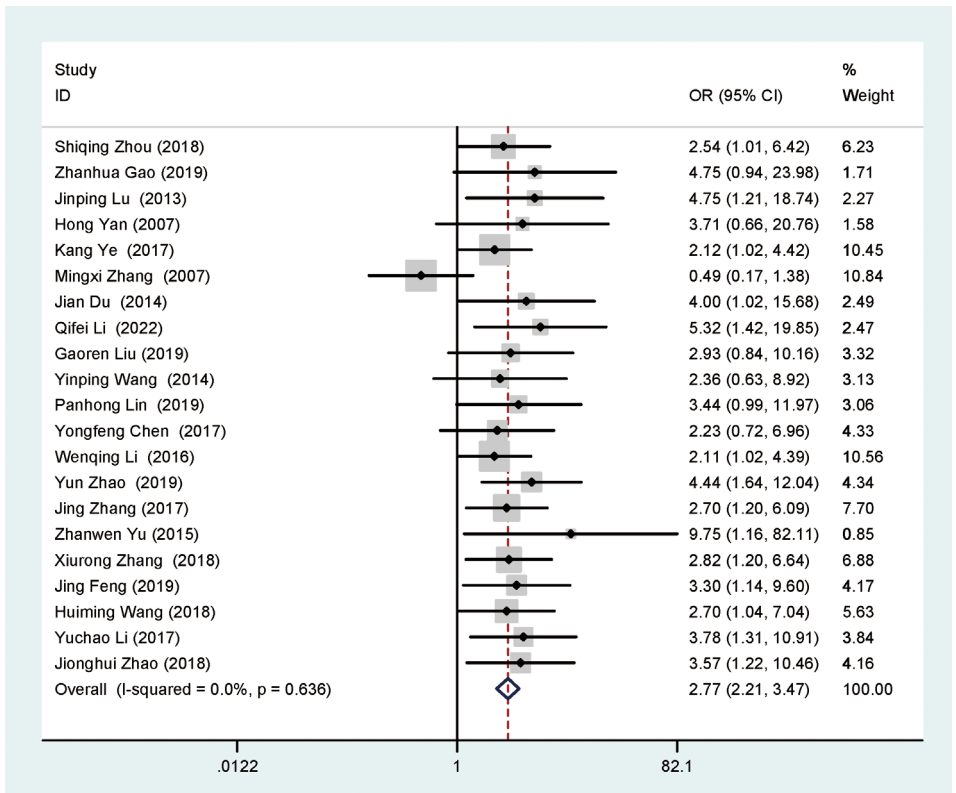

Fig. 3. Forest plot showing the SMDs in LVEF for WYLBAM in CHF, with substantial heterogeneity.
Forest plot displaying the odds ratios (ORs) and 95% confidence intervals (CIs) for the clinical efficacy rate of WYLBAM in CHF, across multiple studies.

analysis of the 6-minute walk test results demonstrated a notable improvement in exercise capacity among patients undergoing WYLBAM. The SMD between the intervention and control groups was 1.13 (95% CI: 0.47 to 1.79), with an I^2 of 88.9%, suggesting a moderate heterogeneity across studies (Fig. 6). Significant reductions in both BNP and NT-proBNP levels were observed, indicating a decrease in cardiac stress following WYLBAM treatment. The pooled SMD for BNP was −2.0 (95% CI: −2.78 to −1.23 pg/mL), and for NT-proBNP was −0.85 (95% CI: −1.23 to −0.48), both with moderate heterogeneity (I^2 = 92.3%), thus analyzed using a random-effects model (Fig. 7).

Sensitivity analyses were performed to explore the robustness of the meta-analysis findings by excluding studies with a high risk of bias or those contributing significantly to heterogeneity. These analyses did not substantially change the overall effect estimates, indicating that the results are robust despite the moderate levels of heterogeneity observed for some outcomes. Publication bias was assessed using funnel plots and Egger's test where appropriate. The funnel plots for the outcomes (LVEF, LVEDD, LVESD, 6-minute walk test, BNP, NT-proBNP) appeared

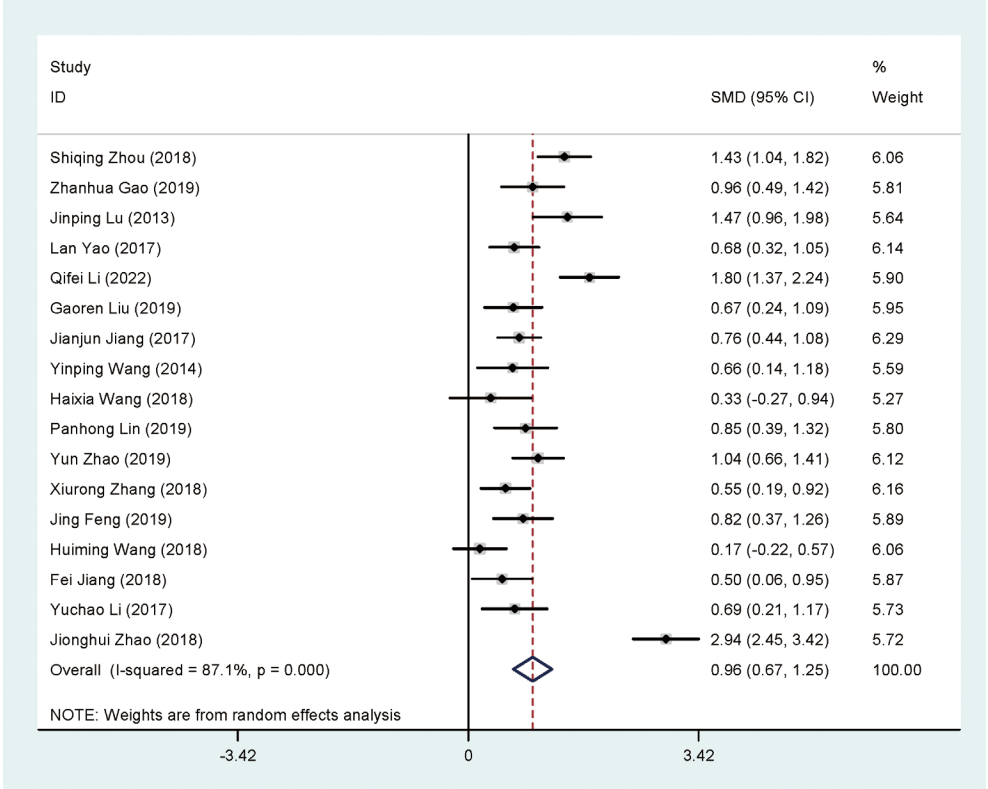

Fig. 4. Forest plot for the effect of WYLBAM on LVEDD and LVESD in CHF patients, showing high heterogeneity.

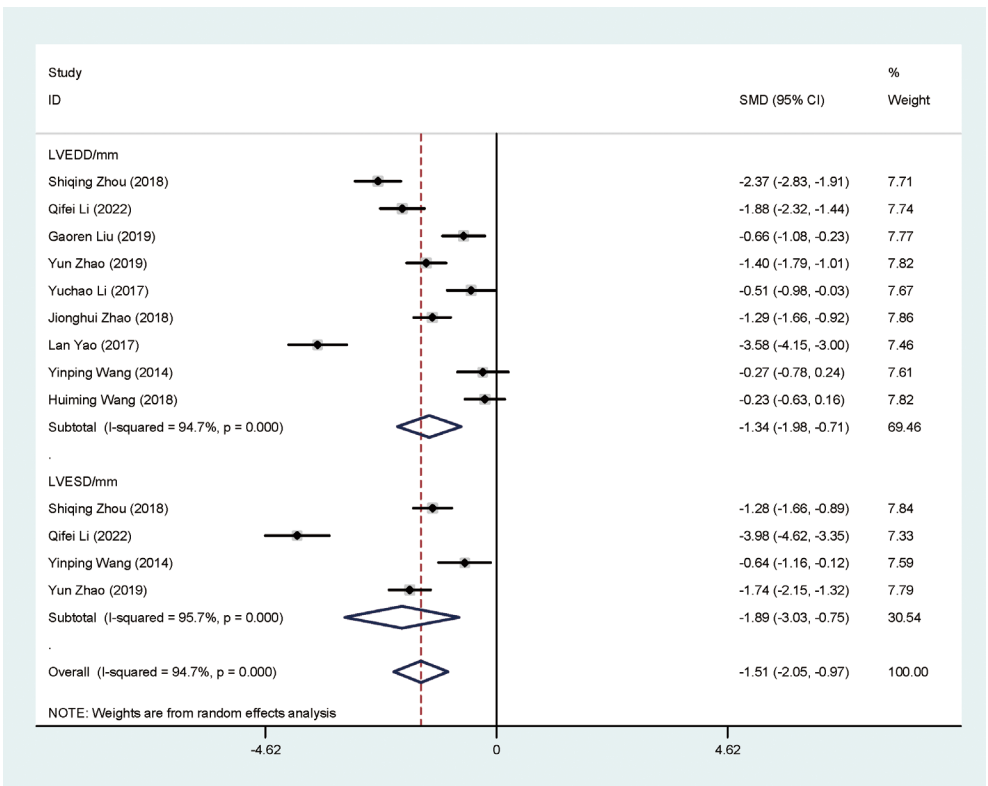

Fig. 5. Forest plot illustrating the SMDs for 6-minute walk test across four studies.

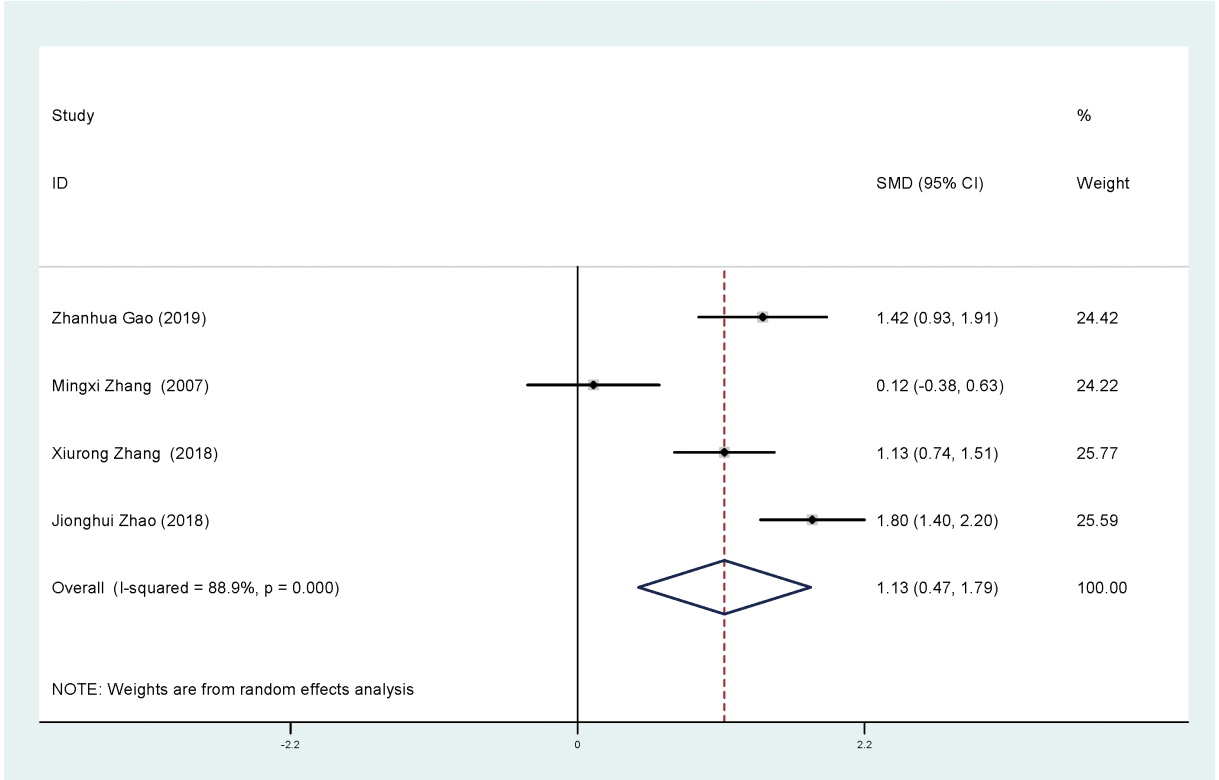

Fig. 6. Forest plot of the effects of WYLBAM on biomarkers BNP and NT-proBNP in CHF.

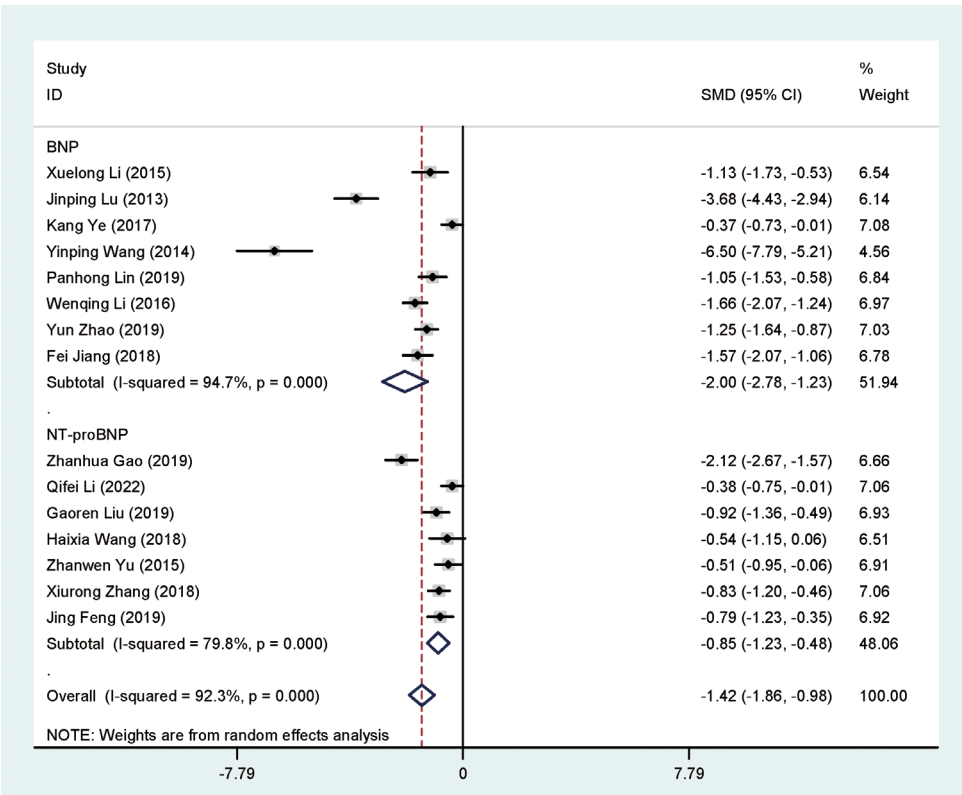

Fig. 7. Forest plot of WYLBAM effects on BNP and NT-proBNP in CHF.

symmetrical, suggesting a low risk of publication bias. This observation was supported by Egger's test, which did not indicate significant publication bias for these outcomes ($p > 0.05$ for all) (Fig. 8).

Sensitivity analyses were conducted to evaluate the robustness of our findings regarding the efficacy of WYLBAM in treating CHF. These analyses involved excluding one study at a time and recalculating the meta-analysis metrics to assess the influence of individual studies on the overall results. The outcomes remained consistent across different analyses, suggesting that our results are stable and not overly dependent on any single study (Fig. 9). Despite the presence of heterogeneity among the included studies, these sensitivity analyses confirm the reliability of our conclusion that WYLBAM can significantly improve cardiac function and physical capacity in CHF patients.

Discussion

The meta-analysis conducted presents compelling evidence on the therapeutic efficacy of WYLBAM for patients suffering from CHF. The synthesis of data from 26 rigorously selected studies, encompassing a sample size of 2,423 participants, indicates a substantial improvement in clinical efficacy rates with the application of WYLBAM compared to standard heart failure treatments. Significantly, the analysis revealed an enhancement in LVEF, a crucial determinant of cardiac performance, in the WYLBAM cohorts. This finding underscores the potential of WYLBAM to bolster cardiac contractility amongst CHF patients. Furthermore, structural cardiac improvements were evidenced by reductions in LVEDD and LVESD, suggesting a possible amelioration of cardiac remodeling processes. The clinical ramifications of these findings are further corroborated by the improved outcomes in the 6-minute walk test, which signal an augmentation in the physical capacity and functional status of the patients. Additionally, the observed decreases in biomarkers such as BNP and the NT-proBNP align with these functional improvements, suggesting a mitigated cardiac stress response. These findings collectively advocate for the consideration of WYLBAM as an adjunctive therapeutic strategy in the comprehensive management of CHF. The favorable impact on cardiac function, physical capacity, and biomarker profiles presents a case for the integration of traditional interventions with conventional medical therapy in the pursuit of optimizing patient outcomes in CHF management. The therapeutic landscape for CHF has long been dominated by conventional pharmacotherapies aimed at symptom relief, mortality reduction, and slowing disease progression (Liu et al. 2022). However, our meta-analysis suggests that the WYLBAM, a traditional medical intervention, not only complements but may enhance the efficacy of standard care in CHF treatment. The contrast between WYLBAM and standard care is particularly striking when considering improvements in LVEF and physical capacity as measured by the 6-minute walk test. These improvements are not solely numerical but represent potential qualitative leaps in patient health and daily living capabilities. The underpinnings of WYLBAM's efficacy may be multifaceted, given its holistic approach which includes herbal medicine, acupuncture, and moxibustion. These practices are hypothesized to exert synergistic effects that modulate the neurohormonal axis, reduce inflammatory

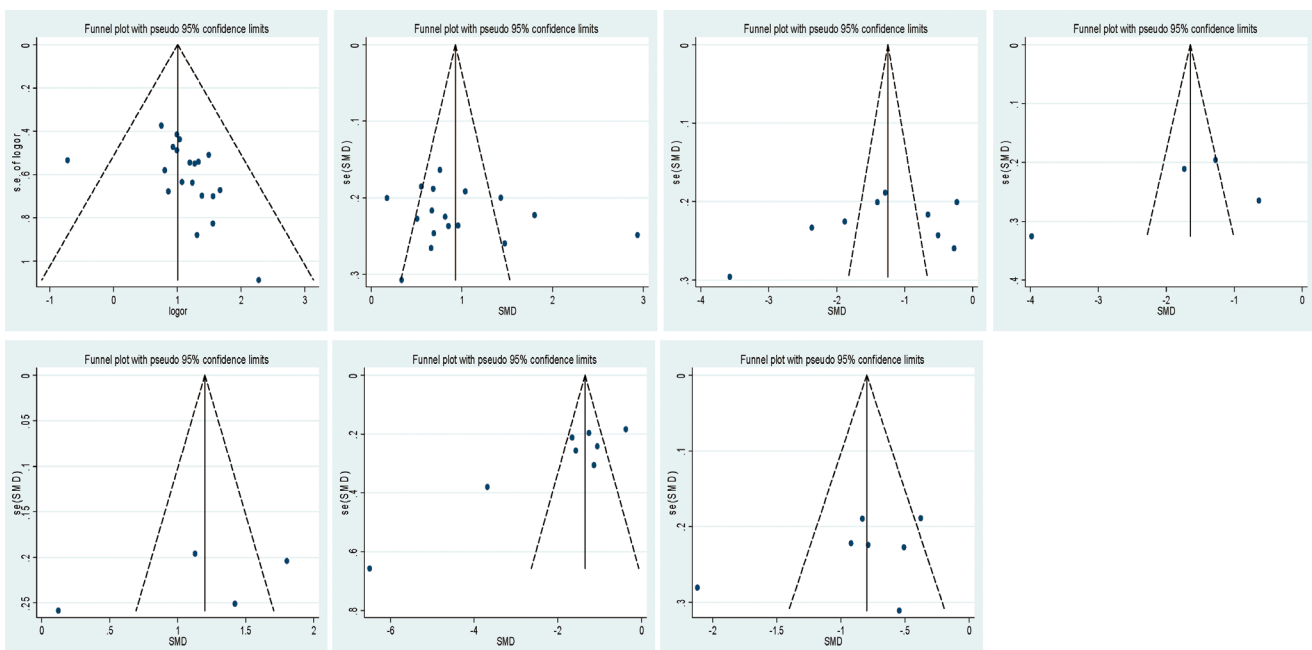

Fig. 8. Influence plots of study omission effects on WYLBAM meta-analysis in CHF.
A set of influence plots showing the impact of omitting each individual study on the overall meta-analysis estimate for various outcomes associated with WYLBAM in CHF.

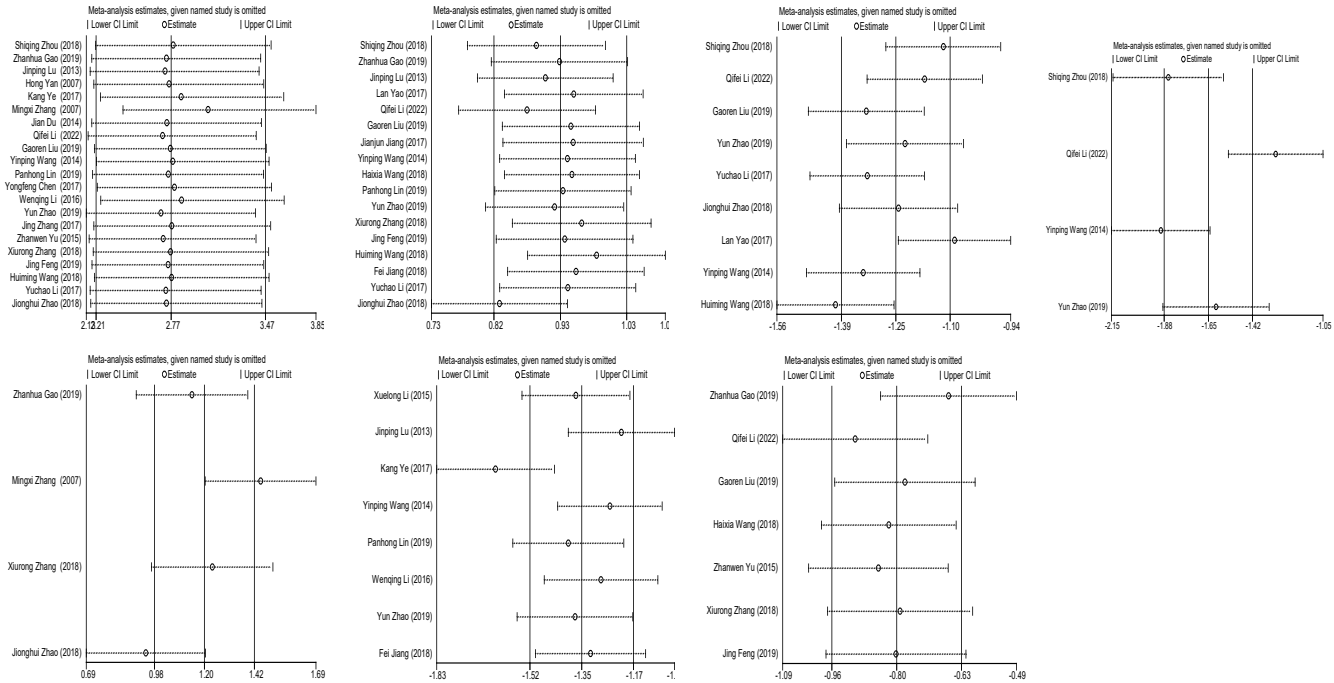

Fig. 9. Sensitivity Analysis.

responses, and improve endothelial function, which are critical pathological facets of CHF (Li et al. 2020). By potentially improving myocardial energy efficiency and reducing peripheral vascular resistance, WYLBAM might directly enhance cardiac output, thereby improving LVEF. Moreover, the observed reductions in biomarkers such as BNP and NT-proBNP are clinically significant, as these peptides are directly associated with cardiac wall stress and are prognostic indicators in heart failure (Klemens et al. 2022). Typically elevated in CHF due to increased ventricular pressure, their reduction suggests a possible alleviation of the cardiac workload and an improved cardiac filling pressure profile. The mechanism by which WYLBAM exerts this effect might involve the amelioration of cardiac fibrosis and the optimization of fluid balance, which are central therapeutic targets in CHF management (Wang et al. 2021). These biomarker reductions not only reflect a lower neurohormonal activation, which is a desired outcome in heart failure treatment, but they also may indicate a reversal of some of the maladaptive cardiac changes associated with CHF pathophysiology. Collectively, the findings invite a closer examination of traditional practices within modern medical frameworks and encourage a broader dialogue on integrating complementary therapies in standard CHF care protocols.

The strengths of our meta-analysis are grounded in a methodical and exhaustive literature search, followed by a stringent selection process adhering to the PRISMA guidelines. This approach ensured a comprehensive aggregation of relevant data, minimizing the potential for omission of pertinent studies and thereby reducing selection bias. The robustness of our analysis is further reinforced by the rigorous quality assessment of the included studies, with the majority meeting high standards of research design and execution. Notably, 25 out of 26 studies were RCTs, the gold standard in clinical research, which significantly mitigates the risk of confounding factors and provides a more reliable estimate of the treatment effect. The randomized design across the included studies lends weight to the validity of our findings, enabling us to draw more definitive conclusions about the efficacy of WYLBAM in the management of CHF. Moreover, the large combined sample size and the global representation of the data add to the generalizability of our results. This comprehensive synthesis of high-quality evidence presents a strong case for the consideration of WYLBAM as a significant complementary therapy in CHF treatment, reflecting a meticulous and well-structured investigative process that adheres to established standards of systematic review methodology.

The moderate to high heterogeneity observed across the outcomes of our meta-analysis merits careful consideration. Heterogeneity is an inherent challenge in systematic reviews and can arise from clinical diversity among studies, methodological variability, or statistical variations. Clinical heterogeneity in this context may stem from the disparate characteristics of the study populations, including differing stages of CHF as classified by the New York Heart Association (NYHA) functional classification, varied comorbid conditions, and a range of patient demographics such as age and gender. Additionally, the multifaceted nature of WYLBAM-which integrates herbal medicine, acupuncture, and moxibustion-could contribute to clinical heterogeneity, given that the specifics of these treatments (such as herb composition, acupuncture points, and moxibus-

tion sites) likely varied between studies. Methodological heterogeneity is also a consideration, as variations in study design, outcome measurement, and duration of follow-up could influence the results. For example, some studies may have employed different echocardiographic criteria or utilized various scales to measure the 6-minute walk test, contributing to variability in the reported outcomes. Moreover, the intervention's modality and the context of its delivery can introduce heterogeneity. The studies included in our analysis span a breadth of healthcare settings and cultural backgrounds, which may influence the administration and efficacy of WYLBAM. Understanding the sources of heterogeneity is crucial for interpreting the results of a meta-analysis. While random-effects models are employed to manage statistical heterogeneity, the exploration of subgroups and conducting sensitivity analyses are pivotal in elucidating the potential factors contributing to the variability observed. Future research should aim to standardize treatment protocols and outcome measurements to reduce heterogeneity and allow for more homogeneous comparisons.

The sensitivity analyses conducted during our meta-analysis provided valuable insights into the consistency of our findings. By systematically excluding individual studies and observing the effects on the overall results, we established that the positive effects of WYLBAM on CHF were not contingent upon any single study. This robustness check bolsters the reliability of the conclusion that WYLBAM offers therapeutic benefits in CHF management. In terms of publication bias, the symmetrical distribution of studies within the funnel plots and the non-significant results from Egger's test indicate minimal bias, enhancing the credibility of the meta-analysis. These findings suggest that the likelihood of unpublished negative studies skewing the results is low, providing a more balanced and accurate assessment of WYLBAM's efficacy. The integration of our findings into clinical practice could herald a paradigm shift in the management of CHF. Current treatment regimens, primarily focused on pharmacological interventions, could be supplemented with WYLBAM to enhance patient outcomes. This traditional method could be particularly valuable for patients who have suboptimal responses to conventional treatments or experience significant side effects. The application of WYLBAM in clinical settings should be done with careful consideration of individual patient factors, such as disease severity, comorbidities, and personal preferences. The observed heterogeneity across studies underscores the necessity for personalized treatment plans. Healthcare providers might need to tailor the combination of herbal medicine, acupuncture, and moxibustion therapies to best meet the unique needs of each patient. Further, given the holistic nature of WYLBAM, its integration into practice would benefit from a multidisciplinary approach, involving cardiologists, traditional medicine practitioners, and patient educators. This collaboration could ensure that patients receive a well-rounded treatment strategy that maximizes the potential benefits of both conventional and traditional therapies in the quest to improve quality of life and clinical outcomes for individuals with CHF.

Our meta-analysis, while thorough, is not without its limitations. The variability in study quality, even with the predominance of RCTs, must be acknowledged. Some studies included may have had small sample sizes or short follow-up periods, which can affect the strength of the evidence and the potential for bias. The potential for bias in individual studies cannot be overlooked, which could influence the reported efficacy of WYLBAM. While the sensitivity analysis has shown stability in the results, it is important to consider that these biases might still have had some effect on the overall findings. Another significant limitation is the generalizability of the results. The studies included in this meta-analysis were conducted in diverse geographical locations with varied cultural backgrounds, which may influence the treatment administration and patient response to WYLBAM. There were variations in age, sex, and the severity of CHF (based on NYHA classification) across the included studies. These demographic differences could influence the response to WYLBAM. Although we performed subgroup analyses to explore the impact of these variables, further research is needed to understand how specific demographic factors affect treatment outcomes. The duration of WYLBAM treatment varied among the studies, ranging from several weeks to several months. Our sensitivity analysis indicated that long-term interventions (> 12 weeks) might have a more pronounced effect on improving cardiac function and physical capacity compared to short-term treatments. Future studies should aim to standardize the duration of intervention to better assess its impact. The presence of comorbid conditions such as diabetes, hypertension, and renal impairment varied across the studies. Although our sensitivity analysis by excluding studies with high prevalence of specific comorbidities showed consistent results, the influence of these comorbidities on the overall efficacy of WYLBAM requires further investigation. Future research should include detailed reporting and stratification based on comorbidities to better understand their role. Despite using random-effects modeling to account for heterogeneity, moderate to high heterogeneity was observed in some outcomes. This could be due to clinical diversity, methodological differences, or variations in treatment protocols. Standardizing treatment protocols and outcome measurements in future studies would help reduce heterogeneity and improve the comparability of results. While our meta-analysis focused on systolic function, primarily through LVEF and leftventricular dimensions, we acknowledge the importance of assessing diastolic function in CHF. Unfortunately, the included studies did not consistently report diastolic function parameters such as E/A ratio, E/e' ratio, or left atrial volume. Future research should aim to include these measures to provide a more comprehensive evaluation of cardiac function in CHF patients. Thus, the applicability of the findings to all CHF populations may be

limited. These limitations suggest that while the results are promising, they should be interpreted with caution. They also highlight the need for more rigorous research to further validate the findings of this meta-analysis.

To build on the findings of this meta-analysis, future research should focus on conducting well-designed, large-scale RCTs. These studies should aim to minimize potential biases and should be sufficiently powered to confirm the efficacy of WYLBAM in treating CHF. Additionally, investigating the underlying mechanisms of action of WYLBAM will be crucial for understanding how it can be most effectively used in clinical practice. Longitudinal studies are needed to evaluate the long-term effects of WYLBAM on mortality, morbidity, and quality of life in CHF patients. Research should also be directed towards understanding how WYLBAM affects different subgroups within the CHF population, such as those with various comorbidities, different functional classes of CHF, and varying degrees of cardiac dysfunction. Finally, future studies should aim to standardize the components of WYLBAM treatments to ensure consistency and reproducibility of the results across different clinical settings. This standardization would also facilitate the integration of WYLBAM into guidelines for the management of CHF, should the evidence continue to support its efficacy.

Conclusion

This meta-analysis evaluated the efficacy of WYLBAM in treating CHF. The findings indicate that WYLBAM significantly improves cardiac function and structure, enhances physical capacity, and reduces biomarkers indicative of cardiac stress. Despite moderate heterogeneity among the included studies, the results are robust and suggest that WYLBAM could be a beneficial adjunctive treatment for CHF.

Author Contributions

X.L. designed the study. H.F. analyzed the data, participated in the data collection, and Y.Z. prepared the manuscript. Y.Z. helped the analysis with constructive discussions. All authors critically revised the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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