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Comparative efficacy of five traditional Chinese medicine injections for treating heart failure with reduced and mildly reduced ejection fraction: Bayesian network meta-analysis

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ABSTRACT

Background: More than half of all heart failure (HF) patients have heart failure with reduced ejection fraction (HFrEF) or mildly reduced ejection fraction (HFmrEF). The combination of traditional Chinese medicine injections (TCMIs) with Western medicine treatment (WMT) has been reported to have better efficacy than using WMT alone. However, the positive effects of TCMIs combined with WMT on HFrEF and HFmrEF require more comprehensive and systematic evidence and warrant further investigation.

Methods: The NMA searched eight databases, including four English and four Chinese, from database creation to November 10, 2022. We used the Cochrane Risk of Bias tool (ROB 2) to assess the selected studies' quality. OpenBUGS and STATA 17.0 were used for network meta-analysis.

Results: The 101 RCTs were included in the systematic review. Studies have shown that when combined with any of the five TCMIs, WMT was more efficient than WMT alone. Shenmai injection (SMI) + WMT may be the best treatment for clinical effectiveness rate (CER) improvement and b-type natriuretic peptide (BNP) reduction. Huangqi injection (HQI) + WMT was the best treatment for improving left ventricular ejection fraction (LVEF). Danhong injection (DHI) + WMT may be the best treatment for lowering left ventricular end-diastolic dimension (LVEDD). Xinmailong injection (XMLI) + WMT was likely the best treatment for increasing the 6-min walking test (6MWT). In addition, XMLI had the lowest incidence of adverse reactions (3.38%).

Conclusions: Shenfu injection (SFI), SMI, DHI, XMLI, and HQI combined with WMT have stronger efficiency in treating HFrEF and HFmrEF. However, as all studies were conducted in China, this review is limited by the inevitable selection bias, and further high-quality multicenter randomized controlled trials (RCTs) are required.

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1. Introduction

Heart failure (HF) is a clinical illness characterized by signs and/or symptoms caused by structural and/or functional heart defects

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Abbreviations

HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFmrEF	heart failure with mildly reduced ejection fraction
CER	clinical effectiveness rate
LVEF	left ventricular ejection fraction
LVEDD	left ventricular end-diastolic dimension
6MWT	6-min walking test
BNP	b-type natriuretic peptide
ADRs	adverse events
WMT	western medicine treatment
SFI	shenfu injection
SMI	shenmai injection
DHI	danhong injection
XMLI	xinmailong injection
HQI	huangqi injection
TCMIs	traditional Chinese medicine injection
RCTs	randomized controlled trials
SUCRA	surface under the cumulative ranking curve
CI	confidence interval
MD	mean difference
OR	odds ratio

and validated by objective evidence of high natriuretic peptide levels and/or pulmonary or systemic congestion [1]. Due to an aging population, survival after myocardial infarction, and a significant increase in the survival rate of HF, the prevalence of HF is on the rise. In developed nations, the prevalence of HF is expected to be between 1% and 2% of the adult population. Similarly, the burden of healthcare costs associated with HF was increasing, with the total cost estimated at $30.7 billion in 2012 and projected to increase by 127% by 2030 [2]. HF has become the leading cause of hospitalization in adults.

Based on the change in left ventricular ejection fraction (LVEF), HF is categorized into three subtypes: heart failure with preserved ejection fraction (HFpEF, LVEF $\geq$50%), heart failure with reduced ejection fraction (HFrEF, LVEF $<$ 40%), and heart failure with mildly reduced ejection fraction (HFmrEF, LVEF $\geq$40%, $<$ 50%) [1]. It is estimated that there are around 64.3 million individuals with HF in the globe, with roughly 50% having HFrEF and 10%–25% having HFmrEF [3]. HFmrEF and HFrEF have similar clinical characteristics, including age and sex distribution, blood pressure, myocardial infarction, atrial fibrillation, chronic renal disease, diabetes, and ischemic heart disease [4–6]. A growing number of studies have demonstrated a high degree of similarity between HFmrEF and HFrEF, suggesting that HFmrEF is a spectral extension of HFrEF [7].

In addition to co-morbidity, both HFrEF and HFmrEF have similar therapeutic responses to medications. Both HFmrEF and HFrEF patients have elevated levels of circulating neurohormones. Drugs that target the neurohormonal axis are beneficial for individuals with both HF categories, but not for patients with HFpEF [8,9]. Extensive registry-based research shows that angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), and β-blockers may be effective for individuals with HFmrEF in terms of treatment response [10,11]. A meta-analysis of 11 trials with 14,262 patients in sinus rhythm revealed that therapy with β-blockers decreased all-cause mortality and cardiovascular mortality in patients with HFrEF or HFmrEF sinus arrhythmias but not in those with HFpEF [12].

Drug therapy is the cornerstone of HFrEF treatment and is based on the combination of different routes of drug administration. Over the past 30 years, conventional therapies have improved survival and reduced incidence and hospitalization rates in patients with HFrEF. Still, they have not achieved the desired results, with a slight improvement in symptoms in patients with HF using Western medicine treatments (WMTs) alone and the potential for drug tolerance and adverse effects after long-term use [13]. In China, combining traditional Chinese medicine injections (TCMIs) with WMT has been broadly applied for patients with HF and multiple RCTs have examined its efficacy [14–16]. Five TCMIs, Shenfu injection (SFI), Shenmai injection (SMI), Danhong injection (DHI), Xinmailong injection (XMLI), and Huangqi injection (HQI), are commonly used to treat different types of HF. SFI protects the myocardium, improves hemodynamics, and dilates blood vessels [17]. SMI can eliminate oxygen-derived free radicals and protect myocardial cells [18]. DHI is abundant in tanshinone and tannic acid, which can reduce myocardial necrosis and regulate inflammation [19]. Astragalus, the active ingredient in HQI, can enhance myocardial contractility [20]. XMLI can increase calcium inward flow and myocardial contractility [21].

HF as a clinical syndrome covers numerous types, and there are significant differences in epidemiological features and pathophysiological processes among patients. Since HFmrEF is more like HFrEF than HFpEF in clinical characteristics and therapeutic responses, their pathophysiology characteristics are hypothesized to be comparable. There have been studies on the efficacy of one or more TCMIs on HFrEF and HFmrEF [22,23], but the wide variety of TCMIs makes it challenging to consider entirely with only one study. It is required to complement the existing studies by comparing TCMIs with different efficacy.

Network meta-analysis (NMA), as opposed to standard meta-analyses of direct comparisons between two therapies, may synthesize data from direct, indirect, and mixed comparisons [24]. Therefore, this research conducted NMA for five regularly used TCMIs for the treatment of HF: SFI, SMI, DHI, XMLI, and HQI. The study indirectly assessed the efficacy and safety of five TCMIs using a research network that included WMT as a common comparison. The five TCMIs were then rated probabilistically according to their degree of efficacy.

2. Materials and methods

2.1. Literature search

This NMA searched eight databases, which include four English databases, i.e., Pubmed, Embase, Web of Science, and Cochrane Library, and four Chinese databases, i.e., China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM), Wan-fang Database, and China National Knowledge Infrastructure (CNKI), search time limited to November 10, 2022, since database creation. We also searched for unpublished studies on Clinical Trials.gov. The top search terms used include: "Heart Failure", "Shenmai Injection", "Shenfu injection", "Xinmailong Injection", "Huangqi Injection", "Danhong injection", and "Randomized Controlled Trial". The search strategy has been refined based on database characteristics and Picos principles. The full search approach is discussed in S2 Supplemental Material.

2.2. Inclusion and exclusion criteria

All the included studies satisfied the following criteria:

Participants: 1) Regardless of gender, ethnicity, nationality, illness duration, or etiology, the diagnostic criteria of Western medicine and Chinese medicine should be based on the accepted diagnostic criteria of HF at the time the research is published; 2) The New York Heart Association (NYHA) patient categorization should range from II to IV: patients with a range of physical activity from mildly limited to unable to perform any physical action; 3) LVEF < 50%; 4) Age ≥18 years old.

Interventions: 1) In the control group, patients only received WMT, which included diuretics, digitalis preparations, ACEI, ARBs, β-receptor blockers, SGLT2i, and nitrates. 2) In addition to WMT, patients in the experimental group received one of the five TCMIs examined in this study.

Outcomes: 1) Outcomes included clinical effectiveness rate (CER), LVEF, left ventricular end-diastolic dimension (LVEDD), 6-min walking test (6MWT), b-type natriuretic peptide (BNP), Adverse events (ADRs); 2) CER must satisfy the following definitions: Markedly effective: symptoms and signs disappeared, HF was controlled, and heart function improved >2 levels or recovered to level 1; Effective: symptoms and signs were significantly relieved, and heart function improved 1 level, but less than two levels; Ineffective: symptoms and signs did not change significantly or worsened, and heart function improved less than 1 level or even deteriorated.

Studies failing to meet inclusion and/or meeting exclusion criteria will be excluded. The criteria for exclusion are listed below.

1) Studies of non-RCTs; 2) Repeatedly published studies; 3) Personal experience summary, purely theoretical research; 4) In the control group, other traditional Chinese therapies, such as acupuncture and prepared Chinese medicines, were utilized; 5) Too few cases per group reported (<20 cases per group); 6) Treatment course <7 days; 7) Studies with incorrect or incomplete data; 8) Full text of the study is not available; 9) Patients with HFrEF or HFmrEF also have other critical disorders, including as shock, respiratory failure, malignant arrhythmia, cancer, severe liver, and renal insufficiency, etc.

2.3. Data extraction and quality evaluation

After using Endnote to eliminate duplicate studies, two researchers manually selected all remaining studies according to inclusion and exclusion criteria. Using a standardized data extraction form, we extracted information from qualifying studies. Data needed include:

1. Information essential to the study: primary author, nationality, and publishing year.
2. Characteristics of the study population at baseline, including sample size, gender mix, mean age, and LVEF range.
3. Details of the intervention: type, specifications, dosage, and duration of TCMIs.
4. Details of the five outcome indicators.
5. Information about the quality evaluation of the article: method of randomization, allocation concealment, and blinding.

The sample sizes and response rates of the control and experiment groups for dichotomous results were extracted from the studies. For continuous outcomes, the mean, standard deviation, and total number of participants were retrieved.

Two investigators used the Cochrane risk-of-bias instrument for randomized trials (RoB 2) to independently evaluate bias risk in five domains for the included RCTs. The items assessed by RoB 2 are (I) randomization process: selection bias; (II) deviation from intended interventions: performance bias; (III) measurement of the outcome: detection bias; (IV) missing outcome data: attrition bias; (V) selection of the reported result: reporting bias; (VI) overall bias. Based on the scores, each bias was classified into three levels: low risk (green), some concerns (yellow), or high risk (red). A third researcher resolved any differences of opinion.

2.4. Statistical analysis

This study is a Bayesian network meta-analysis conducted using Stata (version 17.0) and OpenBUGS (version 3.2.2) for statistical analysis. In OpenBUGS 3.2.2 software, 50,000 sample iterations with 20,000 annealing and a thinning interval of 1 were produced. The odds ratio (OR) was utilized as the effect analysis statistic for dichotomous variables. For continuous variables, mean difference (MD) was used, and each effect was provided as a 95% confidence interval (CI). When the 95% CI of OR did not include one, and the 95% CI of MD did not contain zero, the differences between the two groups were deemed statistically significant.

Network plots were generated using Stata to represent the mixed effects resulting from direct or indirect comparisons of the outcome indicators of the included studies. To determine the overall ranking of each treatment, the surface under the cumulative ranking curve (SUCRA) for each treatment was computed. Assign 100% SUCRA values to the best interventions and 0% SUCRA values to the worst interventions. For outcomes including more than 15 RCTs, funnel plots were created to assess the possibility of publication bias. Global I^2-statistic and prediction interval plots were used to assess the degree of heterogeneity. Heterogeneity was considered high when the estimated I^2 value exceeded 50%. When there was significant heterogeneity between studies, RCTs with study case numbers $\geq$100 or studies published in 2010 and beyond were selected for sensitivity analysis. In addition, subgroup analyses were undertaken depending on the TCMI dose, therapy time, and age of participants.

2.5. Evaluation of the evidence

Assessing the quality of evidence for outcomes using the GRADE methodology. Initially, all included RCTs were considered high-quality evidence recommendations. The following five factors may lead to rating down the rate of evidence: risk of bias (such as inadequate allocation concealment, lack of blindness), inconsistency (narrow or no overlap in confidence intervals across studies, large I^2 values), indirectness (population differences, intervention differences, outcome measure differences), imprecision (small sample size, too wide confidence interval for effect size estimates), and Publication bias (may exist when funded by the vendor). The quality of the evidence was ranked as either high (no degradation), moderate (one level downgrade), low (two levels downgrade), or very low

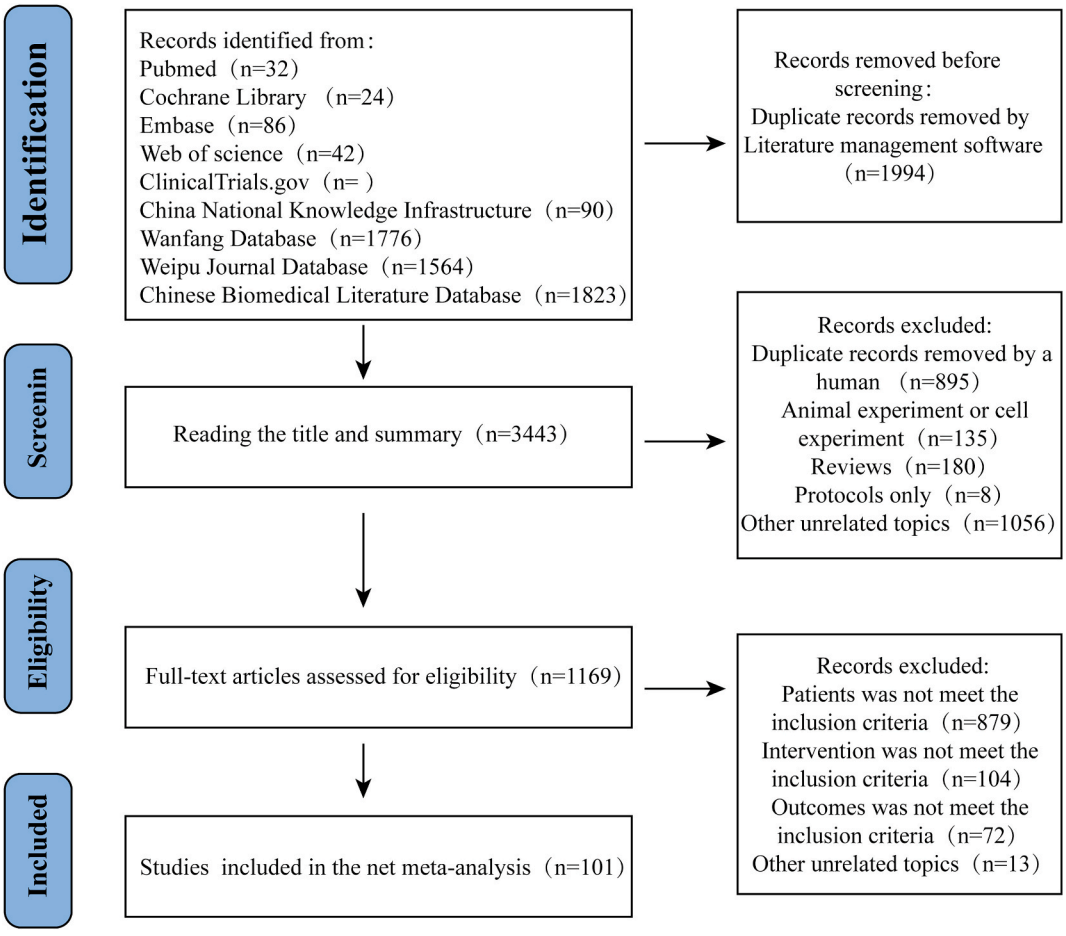

Fig. 1. Study selection flowchart.

(three levels downgrade).

3. Results

3.1. Results of the search

Based on the improved search strategy, 5437 records were initially identified. After removing duplicates, 3443 items were filtered based on title and abstract, of which 2274 were excluded. The full text of 1169 studies were read through. 101 RCT [14–16,25–122] were eventually selected for inclusion in the study, and all of these studies have been published. Fig. 1 depicts the selection study's flowchart.

3.2. Systematic review and characteristics

Of the 101 RCTs included, 8777 patients were treated with one of the five TCMIs listed in the methods combined with WMT. All patients were diagnosed with HF and had LVEF < 50%, and Fig. 2(A-E) depicts the comparative linkages between therapies and each outcome. The primary features of each study included in the analysis are summarized in Table 1. Supplementary Material S4 describes the details of TCMIs and their traditional efficacy.

3.3. Quality evaluation

Included studies were assessed for literature quality using the RoB 2. The evaluation of the risk of bias for the included studies is outlined in Fig. 3 and Supplementary Material S5. (I) randomization process: 36 RCTs reported randomized grouping methods, and 33

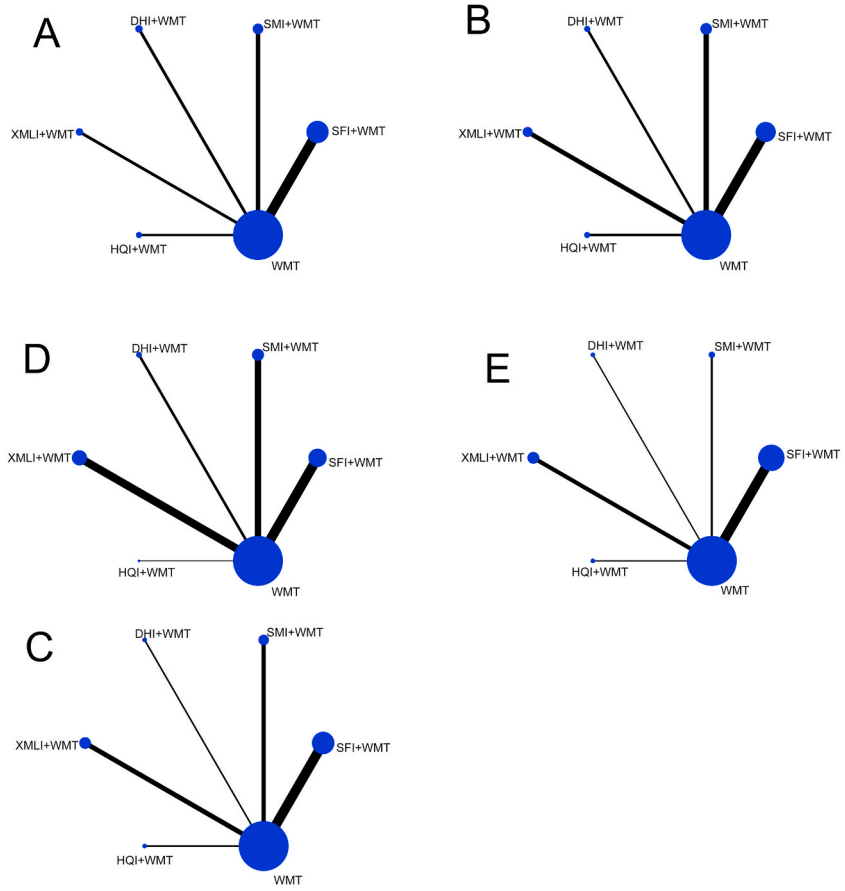

Fig. 2. Network diagrams of comparisons on different outcomes of treatments in different groups of patients with CHD-HF. A clinical effectiveness rate (CER); B left ventricular ejection fraction (LVEF); C left ventricular end-diastolic dimension (LVEDD); D 6-min walking test (6MWT); E b-type natriuretic peptide (BNP). Each node represents a type of treatment. The node size is proportional to the total number of patients receiving a treatment (in brackets). Each line represents a type of head-to-head comparison. The width of the lines is proportional to the number of trials comparing the connected treatments.

Table 1
Characteristics of the studies included.

Included studies	Sample size (E/C)	Sex (F/M)	Age (mean ± SD, years) (E/C)	Ejection fraction	NYHA (E/C) (II, III, IV)	Intervention arm(E)	Control arm(C)	Duration (day)	Outcome
An and xiao, 2019 [25]	45/45	54/36	60.12 ± 2.5/ 59.97 ± 2.23	≤40%	NA	SMI (100 ml,qd) + WMT	WMT	28	①②③④⑤
Bao and yu, 2011 [26]	30/30	32/28	53.6 ± 9.8	≤45%	14, 40, 6	SFI (50 ml,qd) + WMT	WMT	14	①②③⑦
Chen and zhou, 2010 [30]	30/30	–	53 ± 10	<45%	18, 32, 10	SMI (50 ml,qd) + WMT	WMT	14	①②③⑦
Chen et al., 2009 [31]	30/27	42/15	21-75/20-76	<45%	0, 20, 10/ 0, 18, 9	SFI (50 ml,qd) + WMT	WMT	14	①②③⑤
Chen et al., 2017 [29]	50/50	65/35	61 ± 11/62 ± 12	< 40%	NA	DHI (30 ml,qd) + WMT	WMT	10	②⑥⑤
Chen, 2010 [27]	62/60	65/57	58 ± 6/57 ± 8	≤40%	7, 37, 18/ 6, 38, 16	DHI (40 ml,qd) + WMT	WMT	30	①②③④
Chen, 2021 [28]	43/43	53/33	66.73 ± 3.41/ 67.20 ± 3.52	<50%	NA	SMI (40 ml,qd) + WMT	WMT	56	②③④
Cui et al., 2019 [32]	49/49	52/46	59.98 ± 9.11/ 61.02 ± 7.69	<40%	11, 22, 16/ 12, 24, 13	SMI (60 ml,qd) + WMT	WMT	14	①②⑥
Deng and bai, 2017 [33]	30/30	32/28	62.5 ± 12.6/ 60.3 ± 11.2	<50%	NA	SFI (50 ml,qd) + WMT	WMT	14	①
Ding, 2013 [35]	40/40	31/39	72.94 ± 7.58/ 76.43 ± 6.80	<50%	0, 29, 11/ 0, 30, 10	SFI (60 ml,qd) + WMT	WMT	14	①②⑤
Ding, 2014 [34]	20/20	21/18	67.4 ± 8.6/68.5 ± 7.9	< 50%	3, 13, 14/ 4, 12, 4	DHI (20 ml,qd) + WMT	WMT	14	①②⑤⑦
Dong, 2012 [36]	30/30	31/29	59.8 ± 10.2/ 61.7 ± 10.6	<40%	10, 12, 8/ 11, 13, 6	SFI (50 ml,qd) + WMT	WMT	14	①⑦
Gan, 2019 [37]	30/30	34/26	59.3 ± 5.7/59.8 ± 5.6	≤40%	NR	HQI (20 ml,qd) + WMT	WMT	14	①②⑤
Guo and Chen, 2006 [38]	42/42	–	52.3 (40–74)	<40%	NR	HQI (30 ml,qd) + WMT	WMT	10	①②⑦
Han, 2018 [39]	30/30	37/23	57.26 ± 6.34/ 57.21 ± 6.25	≤40%	18, 12, 0/ 17, 13, 0	SFI (40 ml,qd) + WMT	WMT	7	①
Hao et al., 2019 [40]	23/23	27/19	56 ± 12/57 ± 13	<50%	NA	XMLI (5 mg/kg, bid) + WMT	WMT	7	②④⑤
He et al., 2018 [41]	50/50	59/41	60.3 ± 12.4	< 40%	0, 34, 66	SMI (40 ml,qd) + WMT	WMT	7	②⑥
He et al., 2020 [42]	46/46	55/36	61.13 ± 12.98/ 60.87 ± 11.94	< 40%	0, 13, 33/ 0, 15, 31	SMI (50 ml,qd) + WMT	WMT	7	②⑥
He, 2017 [43]	40/40	52/28	56.6 ± 10.2/ 56.4 ± 10.3	≤40%	NA	SFI (50 ml,qd) + WMT	WMT	14	①④⑤
Hu et al., 2009 [44]	31/32	24/39	72.94 ± 7.58/ 76.43 ± 6.80	≤40%	0, 20, 11/ 0, 22, 10	SFI (40 ml,qd) + WMT	WMT	7	②
Huang et al., 2012 [45]	30/30	32/28	66.3 ± 11.2	<40%	0, 18, 12/ 0, 19, 11	SFI (60 ml,qd) + WMT	WMT	14	④
Huang et al., 2011 [46]	60/60	65/55	67.36 ± 4.07/ 69.27 ± 3.96	<45%	0, 47, 13/ 0, 48, 12	SMI (50 ml,qd) + WMT	WMT	14	①②⑤
Huang, 2009 [47]	38/38	47/29	68.22 ± 5.53	<40%	NA	SFI (40 ml,qd) + WMT	WMT	14	①②③④
Jia, 2011 [48]	21/21	30/12	58 ± 11/57 ± 11.2	≤40%	NR	DHI (30 ml,qd) + WMT	WMT	14	①②③④
Jia, 2016 [49]	75/75	67/83	65.8 ± 9.1/65.2 ± 9.4	< 40%	26, 34, 15/ 28, 36, 11	DHI (30 ml,qd) + WMT	WMT	42	1 ②
Jiang, 2021 [50]	32/32	41/23	62.08 ± 5.03/ 61.25 ± 5.19	<40%	12, 16, 4/ 19, 10, 3	SMI (50 ml,qd) + WMT	WMT	14	①⑥
Lan and Wei, 2011 [51]	30/30	33/27	57.5 ± 9.2	≤40%	4, 20, 6/6, 20, 4	SMI (50 ml,qd) + WMT	WMT	7	②④⑦
Li and he, 2013 [52]	42/42	43/41	51–79	< 50%	NA	DHI (20 ml,qd) + WMT	WMT	14	①
Li and Liu, 2017 [58]	50/50	55/45	60.09 ± 5.52/ 60.23 ± 5.61	< 40%	19, 18, 13/ 20, 18, 12	SFI (60 ml,qd) + WMT	WMT	14	①②③⑦
Li et al., 2016 [53]	60/60	72/48	61.32 ± 8.61/ 59.32 ± 8.35	<50%	18, 31, 11/ 20, 30, 10	SMI (100 ml,qd) + WMT	WMT	14	②⑤
Li et al., 2022 [14]	175/175	145/ 205	59.64 ± 6.12/ 60.15 ± 6.03	< 45%	31, 87, 57/ 29, 86, 60	XMLI (35 mg/kg, bid) + WMT	WMT	10	①②③⑥⑤
Li J.F., 2018 [54]	36/36	44/28	77.92 ± 9.43/ 77.42 ± 9.55	≤40%	NA	XMLI (5 mg/kg,bid) + WMT	WMT	14	①②④⑥⑤
Li J.P.et al., 2020 [55]	61/61	65/57	56.02 ± 4.14/ 55.98 ± 3.89	<45%	NA	SFI (20 ml,qd) + WMT	WMT	14	②⑤

(*continued on next page*)

Table 1 (*continued*)

Included studies	Sample size (E/C)	Sex (F/M)	Age (mean ± SD, years) (E/C)	Ejection fraction	NYHA (E/C) (II, III, IV)	Intervention arm(E)	Control arm(C)	Duration (day)	Outcome
Li l, 2018 [56]	29/29	35/23	52.0 ± 1.4/53.0 ± 1.6	<40%	5, 9, 15/6, 10, 13	SMI (60 ml,qd) + WMT	WMT	14	①②③⑦
Li, 2013 [57]	68/52	66/54	63.2 ± 11.3/ 62.1 ± 10.2	< 50%	0, 66, 54	SMI (50 ml,qd) + WMT	WMT	14	①②
Li, 2020 [59]	62/62	71/53	69.27 ± 8.54/ 68.71 ± 8.29	≤40%	27, 23, 12/ 24, 28, 10	XMLI (5 mg/kg,bid) + WMT	WMT	14	①②③④⑥
Lin and Bao, 2013 [60]	60/60	70/50	70.49 ± 8.42/ 76.06 ± 7.96	<45%	14, 38, 8/ 15, 36, 9	SMI (50 ml,qd) + WMT	WMT	14	①⑥
Lin et al., 2015 [61]	30/30	36/24	66.45 ± 5.96/ 64.25 ± 6.29	≤45%	11, 17, 2/ 10, 17, 3	DHI (40 ml,qd) + WMT	WMT	14	①②④⑦
Liu and fu, 2003 [62]	62/50	69/43	58 ± 18/59 ± 19	<45%	NR	HQI (30 ml,qd) + WMT	WMT	10	①②
Liu et al., 2015 [65]	60/76	91/45	44.2 ± 3.7/45.2 ± 3.5	<45%	NA	XMLI (200 mg,bid) + WMT	WMT	14	②③
Liu et al., 2017 [63]	67/67	68/66	68.98 ± 7.45/ 65.17 ± 7.32	< 50%	NA	DHI (40 ml,qd) + WMT	WMT	180	①②
Liu et al., 2018 [64]	51/51	NA	NA	<50%	NA	SFI (50 ml,qd) + WMT	WMT	14	①②③
Lv, 2010 [66]	31/30	44/17	41.5 ± 10.2/ 40.3 ± 12.5	<45%	0, 10, 21/ 0, 11, 19	SFI (50 ml,qd) + WMT	WMT	14	①②③⑤
Mao, 2019 [67]	26/26	38/14	46.87 ± 5.41	<45%	0, 4, 48	XMLI (5 mg/kg,bid) + WMT	WMT	10	①②③④
Meng and Ma, 2008 [68]	49/49	51/47	48.2/48.6	< 40%	0, 21, 28/ 0, 23, 26	HQI (30 ml,qd) + WMT	WMT	12	①②④⑦
Ni and Mao, 2006 [69]	84/80	94/70	65.4/64.7	< 45%	NR	SMI (50–100 ml,qd) + WMT	WMT	7–14	①
Pan, 2015 [70]	74/74	95/53	67.3 ± 6.2/67.4 ± 5.9	<40%	0, 30, 44/ 0, 29, 45	SFI (60 ml,qd) + WMT	WMT	14	①②④⑤
Peng et al., 2014 [71]	56/56	62/50	71.1 ± 2.8/70 .2 ± 2 .6	< 45%	20, 29, 7/ 17, 26, 13	XMLI (200 mg,bid) + WMT	WMT	14	②④
Qi and qi, 2015 [72]	60/60	82/38	63.00(45–85)/ 62.70(44–87)	<45%	0, 31, 29/ 0, 28, 32	SFI (60 ml,qd) + WMT	WMT	14	①②
Qi et al., 2021 [73]	44/44	49/39	66.18 ± 5.43/ 65.73 ± 5.45	< 50%	25, 0, 19/ 23, 0, 21	DHI (40 ml,qd) + WMT	WMT	60	①②③⑦
Que and guo, 2003 [74]	32/28	37/23	33-75/35-76	<40%	8, 21, 3/7, 19, 2	SFI (60 ml,qd) + WMT	WMT	14	①②
Ren et al., 2015 [75]	30/30	37/23	71.3 ± 6.8/70.9 ± 6.3	< 50%	5, 21, 4/6, 21, 3	SFI (50 ml,qd) + WMT	WMT	14	①②④⑥
Song, 2006 [76]	45/42	50/37	62.13 ± 12.37/ 61.90 ± 12.52	≤40%	11, 23, 11/ 11, 22, 9	SFI (60 ml,qd) + WMT	WMT	15	①②⑥
Su et al., 2018 [77]	42/41	35/48	61.1 ± 10.9/ 60.2 ± 11.8	<40%	NA	XMLI (200 mg,qd) + WMT	WMT	15	①②③④⑥
Su, 2017 [78]	30/30	27/33	55.26 ± 9.73	≤40%	19, 11/17, 13	SFI (50 ml,qd) + WMT	WMT	14	①②④⑥⑤
Sun, 2014 [80]	38/38	50/26	62.25 ± 4.3/ 63.42 ± 4.15	< 45%	NR	SMI (60 ml,qd) + WMT	WMT	14	②③④⑦
Sun, 2016 [79]	54/54	52/56	68.0 ± 8.9/67.0 ± 8.8	< 45%	NR	HQI (40 ml,qd) + WMT	WMT	14	②③⑤
Tong et al., 2021 [81]	56/56	64/48	69.17 ± 10.19/ 70.45 ± 9.86	≤40%	19, 20, 17/ 23, 19, 14	XMLI (5 mg/kg,bid) + WMT	WMT	180	①②③④⑥
Wang and Pan, 2016 [89]	32/29	23/38	73.16 ± 12.25/ 32.35 ± 11.09	≤40%	17, 15, 0/ 15, 14, 0	SFI (20 ml,qd) + WMT	WMT	14	②③
Wang and wu, 2012 [87]	40/40	51/29	54.3 ± 11.2/ 57.6 ± 12.1	<40%	4, 21, 15/ 3, 23, 14	SMI (60 ml,qd) + WMT	WMT	14	①②③④⑦
Wang et al., 2016 [84]	26/30	29/27	71.56 ± 2.47/ 70.23 ± 1.56	<50%	NR	SFI (60 ml,qd) + WMT	WMT	10 ± 2	①⑦
Wang et al., 2018 [86]	43/43	51/35	67.5 ± 6.6/68.2 ± 6.4	< 50%	8, 24, 11/ 11, 23, 9	SFI (50 ml,qd) + WMT	WMT	84	①②③④⑥
Wang et al., 2011 [83]	50/50	66/34	32 ± 9/3 1 ± 9	<50%	23, 19, 8/ 21, 23, 6	SFI (1 ml/kg/d + WMT	WMT	14	②⑤
wang et al., 2014 [85]	42/38	49/31	61.8 ± 10.3/ 60.8 ± 9.9	≤45%	0, 12, 30/ 0, 21, 17	SFI (50 ml,qd) + WMT	WMT	10	①②④⑤
Wang et al., 2021 [15]	30/30	35/25	65.43 ± 2.51/ 65.51 ± 2.13	<50%	8, 18, 4/9, 17, 4	XMLI (5 mg/kg,bid) + WMT	WMT	15	②③
Wang, 2003 [88]	35/31	50/16	60.9 ± 11.7/ 60.6 ± 10.6	≤45%	0, 26, 9/0, 24, 7	HQI (40 ml,qd) + WMT	WMT	14	①②

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Table 1 (*continued*)

Included studies	Sample size (E/C)	Sex (F/M)	Age (mean ± SD, years) (E/C)	Ejection fraction	NYHA (E/C) (II, III, IV)	Intervention arm(E)	Control arm(C)	Duration (day)	Outcome
Wang, 2014 [82]	30/30	–	–	<45%	NA	SMI (100 ml,qd) + WMT	WMT	28	①②④⑦
Wu and Chen, 2005 [93]	26/26	28/24	39.10 ± 17.92/ 41.20 ± 16.81	<45%	0, 14, 12/ 0, 15, 11	HQI (30 ml,qd) + WMT	WMT	15	①②⑦
Wu and duan, 2009 [90]	33/29	31/31	71.48 ± 5.78/ 73.59 ± 6.96	≤40%	6, 27, 0/5, 24, 0	SFI (50 ml,qd) + WMT	WMT	14	①②③⑤
Wu and Wang, 2010 [94]	44/44	49/39	70.4 ± 7.2/72.7 ± 7.2	< 45%	26, 44, 18	SFI (100 ml,qd) + WMT	WMT	14	①②③⑥
Wu et al., 2011 [91]	31/32	24/39	72.94 ± 7.58/ 76.43 ± 6.80	≤40%	20, 11/22, 10	SFI (40 ml,qd) + WMT	WMT	7	②③
Wu, 2016 [92]	43/43	52/34	63.2 ± 7.3	≤40%	19, 56, 11	SFI (1 ml/kg/d + WMT	WMT	14	②③
Xing and Nie, 2006 [95]	22/21	30/13	60.0 ± 15.6	<40%	12, 16, 15	HQI (50 ml,qd) + WMT	WMT	14	①②③
Xu E.W.et al., 2018 [96]	44/44	43/45	66.1 ± 12.3/ 65.3 ± 11.6	<50%	21, 23, 0/ 19, 25, 0	XMLI (5 mg/kg,bid) + WMT	WMT	7	①②④⑥⑤
Xu et al., 2015 [97]	25/25	32/18	64.00 ± 11.00/ 63.00 ± 10.00	≤40%	4, 11, 10/ 5, 11, 9	SFI (100 ml,qd) + WMT	WMT	7	①②③
Xu et al., 2016 [99]	40/40	45/35	75.0 ± 10.30/ 72.0 ± 9.60	<40%	NR	SFI (100 ml,qd) + WMT	WMT	14	②
Xu et al., 2014 [100]	45/40	43/42	70.00 ± 11.30/ 68.00 ± 14.60	<40%	NA	SFI (80 ml,qd) + WMT	WMT	10	①②⑦
Xu s.l et al., 2018 [98]	30/30	33/27	56.8 ± 4.52/ 55.8 ± 5.32	<50%	NA	SMI (40 ml,qd) + WMT	WMT	14	②⑦
Yang 2016 [102]	29/29	37/21	63.22 ± 5.41/ 64.25 ± 5.44	<40%	0, 11, 18/ 0, 12, 17	SMI (50 ml,qd) + WMT	WMT	14	①②⑦
Yang and wu, 2009 [103]	30/30	42/18	42.50 ± 16.81/ 40.52 ± 15.98	<45%	0, 8, 22/0, 12, 18	SFI (60 ml,qd) + WMT	WMT	14	①②⑦
Yang et al., 2016 [101]	40/40	45/35	58-72/56-70	≤40%	0, 31, 9/0, 34, 6	SMI (40–60 ml,qd) + WMT	WMT	14	②
Yao and Lu, 2010 [105]	30/30	33/27	53.6 ± 9.8	≤45%	16, 34, 10	SFI (50 ml,qd) + WMT	WMT	14	①②③⑦
Yao et al., 2014 [104]	45/46	51/40	M: 63.26 ± 5.64; F: 64.71 ± 6.78	<40%	9, 64, 18	XMLI (200 mg,qd) + WMT	WMT	7	②③⑤⑦
Yin, 2008 [106]	56/30	50/36	68 ± 5.4/68.2 ± 4.3	< 50%	NR	SFI (40 ml,qd) + WMT	WMT	14	①②
Yu et al., 2014 [108]	75/72	83/64	35–80	<40%	NA	SFI (50 ml,qd) + WMT	WMT	14	①
Yu et al., 2015 [107]	40/40	38/42	35-75/35-75	≤40%	22, 10, 8/ 22, 10, 8	SMI (100 ml,qd) + WMT	WMT	84	①②③⑦
Zhang and Lv, 2009 [114]	23/22	26/19	71-88/71-85	< 50%	NR	SFI (40 ml,qd) + WMT	WMT	14	①②
Zhang and wen, 2016 [115]	30/30	35/25	65.4 ± 7.8/64.8 ± 8.7	<50%	14, 10, 6/ 15, 9, 6	SFI (50 ml,qd) + WMT	WMT	14	②③
Zhang et al., 2014 [109]	40/40	44/36	49.9 ± 13.8/ 52.1 ± 12.6	<45%	NR	SFI (50 ml,qd) + WMT	WMT	14	①④⑤
Zhang et al., 2018 [111]	110/110	129/ 91	49.52 ± 15.25/ 48.77 ± 13.62	≤40%	61, 49/66, 44	SFI (50 ml,qd) + WMT	WMT	14	②③⑤
Zhang et al., 2021 [16]	30/30	40/20	76.78 ± 6.8/ 65.90 ± 6.7	<50%	18, 12, 0/ 15, 15, 0	SMI (60 ml,qd) + WMT	WMT	84	①②③④
Zhang, 2015 [112]	24/24	35/13	62.0 ± 7.6	≤30%	NR	XMLI (200 mg,qd) + WMT	WMT	7	①②⑦
Zhang, 2017 [110]	30/32	42/20	56.3 ± 8.2/57.9 ± 10.1	<50%	2, 16, 12/ 3, 17, 12	SFI (50 ml,qd) + WMT	WMT	14	①②③④⑦
Zhang, 2018 [113]	48/48	38/58	77.1 ± 7.96/ 75.98 ± 6.73	≤40%	0, 35, 13/ 0, 30, 18	XMLI (5 mg/kg,bid) + WMT	WMT	14	①②③⑤⑦
Zhao and Zhang,	51/46	53/44	71.5 ± 8.7	< 45%	14, 66, 17	HQI (40 ml,qd) + WMT	WMT	14	①②③⑥

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Table 1 (*continued*)

Included studies	Sample size (E/C)	Sex (F/M)	Age (mean ± SD, years) (E/C)	Ejection fraction	NYHA (E/C) (II, III, IV)	Intervention arm(E)	Control arm(C)	Duration (day)	Outcome
2015 [117]									
Zhao et al., 2014 [116]	30/30	31/29	66 (40–78)	≤45%	15, 26, 19	XMLI (5 mg/kg-10 mg/kg,bid) + WMT	WMT	14	②
Zhong, 2016 [118]	50/50	62/38	64.99 ± 9.80/ 63.68 ± 9.48	<50%	22, 28, 0/ 21, 29, 0	XMLI (5 mg/kg-10 mg/kg,bid) + WMT	WMT	14	①②④
Zhou and yan, 2013 [119]	69/68	98/39	68.2 ± 7.4/67.9 ± 5.4	< 45%	27, 33, 9/ 24, 34, 10	DHI (40 ml,qd) + WMT	WMT	14	①②⑦
Zhu and Ma, 2010 [120]	55/50	67/38	55-80/58-80	< 45%	NR	SFI (50 ml,qd) + WMT	WMT	15	①⑦
Zhu, 2009 [121]	24/22	20/26	61.7 ± 13.6	≤40%	28, 18, 0	SFI (50 ml,qd) + WMT	WMT	14	②③④⑤
Zhu, 2015 [122]	60/60	72/48	60–86	< 40%	NR	DHI (30 ml,qd) + WMT	WMT	14	1

Note: ①, clinical effectiveness rate (CER); ②, left ventricular ejection fraction (LVEF); ③, left ventricular end-diastolic dimension (LVEDD); ④, 6-min walking test (6MWT); ⑤, b-type natriuretic peptide (BNP); ⑥, Adverse events; ⑦, No adverse events occurred; Abbreviations: C, control group; E, experimental group; F, female; M, male; I, intervention; NR, not report.; WMT, Western medicine treatment.

of these RCTs [14,15,25,28,32,37,41,42,50,54,55,57–59,63,70,72,73,75,76,78,81,83,85,86,92,96,98–100,109,111,113] used the simple random number tables, 1 RCT [94] used stratified randomization, 1 RCT [33] used the lottery method, 1 RCT [88] used the randomized alignment table method; Additionally, 1 RCT [89] did not mention whether randomized groups were used; 1 RCT [44] grouped according to the order of consultation ，1 RCT [95] grouped according to the order of admission, neither of the above 2 RCTs was a randomized group. No RCTs reported allocation concealment. Thus, the randomization process for all RCTs is “some concerns”. (II)Deviation from intended interventions: 2 RCTs [67,90] reported blinding, and both were trials of single-blind methods, the use of blinding was not reported in the remaining 99 trials. 3 RCTs [69,77,88] deviated from the intended intervention and may have had an impact on the outcome and were therefore rated “high risk”, The interventions of the 9 RCTs [14,29,54,59–61,75,76,84] were consistent with the intended interventions and were therefore rated “low risk”. (III)missing outcome data: No RCTs had patients lost to follow-up. Hence, all included RCTs were rated “low risk” (IV)measurement of the outcome: The use or non-use of blinding of outcome assessors did not affect the measurement of outcomes in any of the included RCTs, so this item was rated “low risk”. (V)selection of the reported result: All included RCTs did not have access to pre-designed protocols. Therefore, this item was rated as having “some concerns”. (VI) overall bias: Included with the studies in this NMA were graded as “some concern".

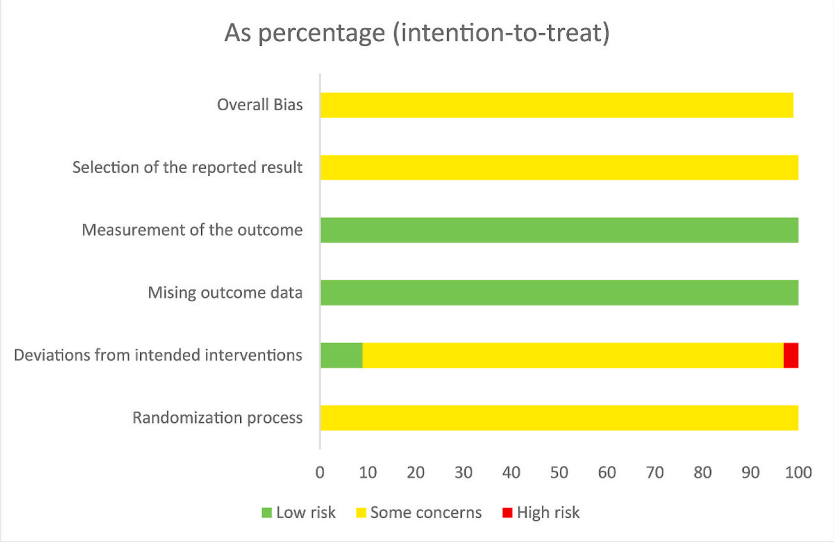

Fig. 3. Risk of bias graph.

3.4. Network meta-analysis

This NMA's contribution plot revealed that SFI + WMT vs. WMT had the highest contribution to CER, LVEF, LVEDD, BNP, and 6MWT, at 43.42 %, 39.08 %, 43.90 %, 51.85 %, and 35.48 %, respectively. Diagrams of contributions are presented in Supplemental Material S6.

3.5. Outcomes

3.5.1. CER

CER was reported by 76 RCTs comprising five TCMIs. All TCMIs used in conjunction with WMT were statistically significantly more effective than WMT alone. The results are shown below: SFI + WMT vs. WMT (OR = 4.47, 95% CI: 3.47–5.68), SMI + WMT vs WMT (OR = 4.58, 95% CI: 3.23–6.37), DHI + WMT vs. WMT (OR = 4.36, 95% CI: 2.92–6.43), XMLI + WMT vs. WMT (OR = 3.70, 95% CI: 2.52–5.33), HQI + WMT vs. WMT (OR = 3.55, 95% CI: 2.06–5.66). Table 3A shows in detail the comparison between the interventions.

3.5.2. LVEF

87 RCTs comprising five TCMIs recorded LVEF, and all TCMIs paired with WMT were significantly more effective at improving LVEF than WMT alone. The results are shown below: SFI + WMT vs. WMT (MD = 5.53, 95% CI: 2.57–8.53), SMI + WMT vs. WMT (MD = 5.91, 95% CI: 2.11–9.70), DHI + WMT vs. WMT (MD = 6.31, 95% CI: 2.94–9.75), XMLI + WMT vs. WMT (MD = 4.65, 95% CI: 1.56–7.72), HQI + WMT vs. WMT (MD = 9.10, 95% CI: 3.77–14.41). Table 3B shows in detail the comparison between the interventions.

3.5.3. LVEDD

LVEDD was observed in 41 RCTs involving five TCMIs. All TCMIs combined with WMT were statistically different and more effective in reducing LVEDD than WMT alone. The results are shown below: SFI + WMT vs. WMT (MD = −3.09, 95% CI: −4.41 to −1.77), SMI + WMT vs. WMT (MD = −4.40, 95% CI: −6.19 to −2.58), DHI + WMT vs. WMT (MD = −6.79, 95% CI: −10.09 to −3.56), XMLI + WMT vs. WMT (MD = −4.51, 95% CI: −6.22 to −2.80), HQI + WMT vs. WMT (MD = −2.75, 95% CI: −5.91 to 0.38). Table 3C shows in detail the comparison between the interventions.

3.5.4. 6MWT

31 RCTs involving five TCMIs have reported 6MWT. Compared with WMT alone, the combination of the four (SFI, SMI, DHI, XMLI) TCMIs with WMT was more effective and statistically significant in improving 6MWT, except for HQI. The results are shown below: SFI + WMT (MD = 50.36, 95% CI: 44.40–56.29), SMI + WMT (MD = 58.50, 95% CI: 48.54–68.59), DHI + WMT (MD = 50.83, 95% CI: 38.99–62.81), XMLI + WMT (MD = 156.70, 95% CI: 121.80–210.10). In addition, XMLI had better efficacy than other TCMIs and was statistically significant [vs. SFI (MD = 106.40, 95% CI: 69.56–161.60), vs. SMI (MD = 98.23, 95% CI: 59.09–155.90), vs. DHI (MD = 105.90, 95% CI: 65.29–164.60), vs. HQI (MD = −146.70, 95% CI: −205.50 to −106.10)]. Table 3D shows in detail the comparison between the interventions.

3.5.5. BNP

27 RCTs, including five TCMIs, reported BNP. All TCMIs coupled with WMT were statistically significantly more effective in reducing BNP than WMT alone. The following depicts the outcomes: SFI + WMT vs. WMT (MD = −95.27, 95% CI: −102.80 to −87.76), SMI + WMT vs. WMT (MD = -118.10, 95% CI: −131.10 to −104.90), DHI + WMT vs. WMT (MD = −120.10, 95% CI: −189.50 to −50.39), XMLI + WMT vs. WMT (MD = −70.19, 95% CI: −78.61 to −61.71), HQI + WMT vs. WMT (MD = −28.49, 95% CI: −39.20 to −17.70). Also, SMI was statistically better than SFI, XMLI, and HQI [vs. SFI + WMT (MD = −22.84, 95% CI: −37.93 to −7.68), vs. XMLI + WMT (MD = 47.92, 95% CI: 32.11–63.56), vs. HQI + WMT (MD = 89.62, 95% CI: 72.71–106.50)]. Some comparisons between TCMIs also possess statistical significance, such as SFI vs. XMLI vs. HQI, DHI vs. HQI, XMLI vs. HQI, and detailed data are shown in Table 3E.

Table 2
Surface Under the Cumulative Ranking Curve (SUCRA) results of the outcomes.

Interventions	CER (%)	LVEF (%)	LVEDD (%)	BNP (%)	6MWT (%)
SFI + WMT	73.4	51.5	36.3	64.9	51.2
SMI + WMT	74.7	57.3	65.3	89.5	75.0
DHI + WMT	66.3	63.1	94.6	83.8	53.8
XMLI + WMT	44.6	38.8	67.7	41.7	100.0
HQI + WMT	41.0	89.2	35.3	20.1	19.0
WMT	0.0	0.1	0.8	0.0	1.0

Table 3
League tables comparing interventions. CER
NOTE: WMT, Western medicine treatment; SFI, Shenfu injection; SMI, Shenmai injection; DHI, Danhong injection; XMLI, Xinmailong injection; HQI, Huangqi injection. Significant results are in bold. All the TCMIs are based on WMT.

CER

HQI+WMT	OR (95%CI)				
1.00 [0.51,1.80]	XMLI+WMT				
0.85 [0.42,1.47]	0.88 [0.50,1.47]	DHI+ WMT			
0.80 [0.42,1.41]	0.83 [0.49,1.33]	0.98 [0.57,1.58]	SMI+ WMT		
0.81 [0.44,1.36]	0.84 [0.53,1.28]	0.99 [0.60,1.55]	1.04 [0.679,1.55]	SFI+ WMT	
3.55 [2.06,5.66]	**3.70 [2.52,5.33]**	**4.36 [2.92,6.43]**	**4.58 [3.23,6.37]**	**4.47 [3.47,5.68]**	WMT

LVEF

HQI+WMT	MD (95%CI)				
4.45 [-1.74,10.64]	XMLI+WMT				
2.79 [-3.56,9.09]	-1.66 [-6.29,2.87]	DHI+WMT			
3.19 [-3.32,9.73]	-1.27 [-6.11,3.63]	0.40 [-4.65,5.51]	SMI+WMT		
3.57 [-2.57,9.66]	-0.88 [-5.19,3.38]	0.78 [-3.76,5.31]	0.38 [-4.43,5.17]	SFI+WMT	
9.10 [3.77,14.41]	**4.65 [1.56,7.72]**	**6.31 [2.94,9.75]**	**5.91 [2.11,9.70]**	**5.53 [2.57,8.53]**	WMT

LVEDD

HQI+WMT	MD (95%CI)				
1.76 [-1.84,5.33]	XMLI+WMT				
4.04 [-0.49,8.60]	2.29 [-1.39,6.01]	DHI+WMT			
1.65 [-1.98,5.24]	-0.11 [-2.59,2.36]	-2.40 [-6.14,1.31]	SMI+WMT		
0.33 [-3.08,3.73]	-1.42 [-3.59,0.75]	**-3.71 [-7.24,-0.20]**	-1.31 [-3.53,0.93]	SFI+WMT	
-2.75 [-5.91,0.38]	**-4.51 [-6.22,-2.80]**	**-6.79 [-10.09,-3.56]**	**-4.40 [-6.19,-2.58]**	**-3.09 [-4.41,-1.77]**	WMT

6MWT

HQI+WMT	MD (95%CI)				
-146.70 [-205.50,-106.10]	XMLI+WMT				
-40.78 [-57.85,-23.79]	**105.90 [65.29,164.60]**	DHI+WMT			
-48.45 [-64.11,-32.86]	**98.23 [59.09,155.90]**	-7.67 [-23.16,7.65]	SMI+WMT		
-40.31 [-53.66,-26.83]	**106.40 [69.56,161.60]**	0.47 [-12.77,13.82]	8.14 [-3.54,19.85]	SFI+WMT	
10.05 [-1.98,21.95]	**156.70 [121.80,210.10]**	**50.83 [38.99,62.81]**	**58.50 [48.54,68.59]**	**50.36 [44.40,56.29]**	WMT

BNP

HQI+WMT	MD (95%CI)				
41.70 [28.01,55.44]	XMLI+WMT				
91.65 [20.78,161.70]	49.95 [-20.38,120.00]	DHI+WMT			
89.62 [72.71,106.50]	**47.92 [32.11,63.56]**	-2.03 [-72.82,69.20]	SMI+WMT		
66.78 [53.75,79.84]	**25.08 [13.90,36.48]**	-24.87 [-94.77,45.20]	**-22.84 [-37.93,-7.68]**	SFI+WMT	
-28.49 [-39.20,-17.70]	**-70.19 [-78.61,-61.71]**	**-120.10 [-189.50,-50.39]**	**-118.10 [-131.10,-104.90]**	**-95.27 [-102.80,-87.76]**	WMT

3.6. Rank probabilities

Fig. 4 depicts the Bayesian ranking characteristics between different therapies, while Table 2 summarizes the detailed ranking findings.

For CER, SMI + WMT ranked first has the highest probability (Cumulative Probability 74.68%), followed by SFI + WMT (73.43%) and DHI + WMT (66.25%), whereas WMT alone obtained the worst effect (0.00%) (Fig. 4A and Table 2).

For LVEF, HQI + WMT has the highest probability of ranking first (Cumulative Probability 89.17%), followed by DHI + WMT (63.05%) and SMI + WMT (57.33%), whereas WMT alone obtained the worst effect (0.11%) (Fig. 4B and Table 2).

For LVEDD, DHI + WMT has the highest probability of being ranked first (Cumulative Probability 94.57%), followed by XMLI + WMT (67.73%) and SMI + WMT (65.27%), whereas WMT alone obtained the worst effect (0.83%) (Fig. 4C and Table 2).

For 6MWT, XMLI + WMT has the highest probability of ranking first (Cumulative Probability 100.00%), followed by SMI + WMT (74.97%) and DHI + WMT (53.85%), whereas WMT alone obtained the worst effect (0.98%) (Fig. 4D and Table 2).

For BNP, SMI + WMT ranked first with the highest probability (Cumulative Probability 89.49%), followed by DHI + WMT (83.82%) and SFI + WMT (64.91%), whereas WMT alone obtained the worst effect (0.00%) (Fig. 4E and Table 2).

3.7. Adverse events

A total of 17 RCTs [14,29,32,41,42,50,54,59,60,75–78,81,86,96,117] mentioned and detailed the adverse events that occurred in the control and experimental groups during the trial, such as Liver dysfunction, Episodic hypertension, Vomit (Table 4). The ADRs rates of Shenfu injection, Shenmai injection, Danhong injection, Xinmailong injection, Huangqi injection, and WMT alone were 6.82%, 9.28%, 4.00%, 3.38%, 14.43%, 5.86%, respectively.

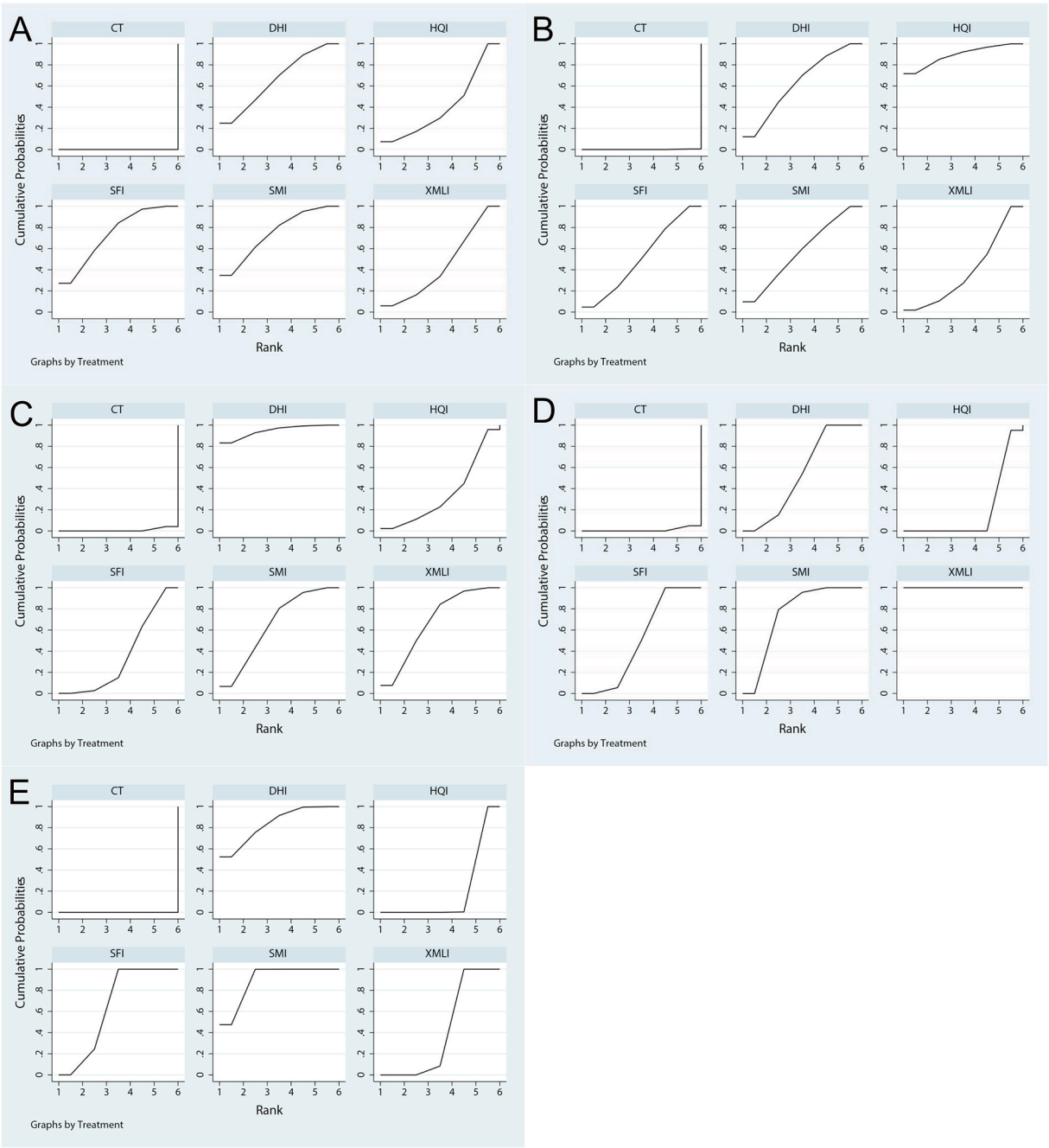

Fig. 4. Plots of the Surface Under the Cumulative Ranking Curve (SUCRA) for experimental outcomes. A clinical effectiveness rate (CER); B, left ventricular ejection fraction (LVEF); C, left ventricular end-diastolic dimension (LVEDD); D, 6-min walking test (6MWT); E, b-type natriuretic peptide (BNP).

3.8. Heterogeneity, publication bias, and GRADE assessment

The global I^2-statistic for CER, LVEF, LVEDD, BNP, and 6MWT were 0.00%, 88.8%, 79.3%, 94.6%, and 90.9%, respectively. Heterogeneity estimates are detailed in the forest diagram in Supplementary Material S7. The prediction interval plots' results indicate a 0%, 33.33%, 26.67%, 26.67%, and 26.67% probability that CER, LVEF, LVEDD, BNP, and 6MWT are affected by heterogeneity, respectively. Prediction interval charts are provided in Supplementary Material S8.

The RCTs for each of the five outcomes exceeded 15 cases, so publication bias was assessed using funnel plots, with differently colored points indicating comparisons between the five different TCMIs and WMT. As seen in Fig. 5(A-E), the slopes of all fitted straight

Table 4
Occurrence of adverse reactions of TCMIs.

Treatments	SFI	SMI	DHI	XMLI	HQI	WMT
No. of studies	4	5	1	6	1	17
Sample size	293	474	100	829	97	1793
Liver dysfunction	0	0	0	0	5	4
Erythra	0	0	3	0	0	0
Nausea	0	8	0	7	0	16
Mouth dryness	0	0	0	1	0	1
Dizziness	1	8	1	0	0	9
Headache	4	4	0	7	9	17
Dry cough	2	0	0	0	0	3
Episodic hypertension	2	2	0	0	0	0
Palpitation	2	0	0	8	0	7
Hypotension	2	8	0	1	0	17
Vomit	0	5	0	0	0	4
Weakness	0	7	0	0	0	9
Ventricular ectopic	0	2	0	0	0	2
Skin itch	0	0	0	3	0	3
Dry mouth	4	0	0	0	0	0
Death from cardiac causes	0	0	0	0	0	2
Arrhythmia	2	0	0	1	0	6
Cardiac insufficiency	1	0	0	0	0	5
Total probability	6.82%	9.28%	4.00%	3.38%	14.43%	5.86%

lines were close to the center line except for BNP (Fig. 5E). They were equally spread out on each side of the midpoint, demonstrating no significant publication bias for the four categories of CER, LVEF, LVEDD, and 6MWT (Fig. 5A–D). The points of BNP showed significant asymmetry, indicating that there may be publication bias, or other bias, for this result. The RCTs included in this NMA did not have closed loops and therefore were not tested for inconsistency.

Using the GRADE methodology, Table 5 provides the evidence grading scale for the five outcomes. The evidence varied from very low to high quality. The risk of bias was the primary reason the evidence was downgraded, followed by inconsistency and imprecision. It indicates that the included studies shared deficiencies in experimental design, such as the absence of an elucidation of allocation concealment and lack of blinding.

3.9. Sensitivity analysis and subgroup analyses

The NMA selected 29 RCTs [14,27,29,41,46,49,53,55,57–60,62–65,69–72,79,81,83,108,111,118–120,122] with case numbers ≥100, including 3990 patients/84 RCT [14–16,25–30,32–37,39–43,45,46,48–61,63–67,70–73,75,77–87,89,91,92,94,96–102,104,105,107–113,115–120,122] published in 2010 and later, including 7636 patients for sensitivity analysis. Confirmed that the benefit of TCMIs combined with WMT was more effective in all outcomes compared to WMT alone. The NMA also showed that the best interventions for increasing 6MWT and reducing LVEDD, and BNP were: DHI + WMT, XMLI + WMT, and SMI + WMT, respectively, consistent with the original NMA (see Supplementary Material S9 for sensitivity analyses). In the original NMA, the best TCMI for improving CER and LVEF were SMI + WMT and HQI + WMT, respectively, while excluding RCTs with cases less than 100, the best TCMI for CER was SFI + WMT, after excluding RCTs with a year of publication before 2010 the best TCMI for LVEF was XMLI + WMT. Subgroup analysis showed that in RCTs with low dose TCMIs (≤50 ml qd/≤30 ml qd/≤10 mg/kg.qd), treatment duration less than or equal to 14 days, patient's mean age less than 60 years in RCTs, the effectiveness of TCMIs + WMT was more statistically significant in terms of CER, LVEF, LVEDD, 6MWT, and BNP. However, it is possible that the majority of RCTs being treated for less than or equal to two weeks may account for this discrepancy. The subgroup analysis findings are reported in Supplemental Material S10.

4. Discussion

This NMA included 101 RCTs with a total of 8777 patients who had HFrEF or HFmrEF. Patients received one of five TCMIs in addition to conventional treatment. Directly comparing the efficacy of TCMIs + WMT to that of WMT alone, and indirectly comparing the efficacy of the five TCMIs (SFI, SMI, DHI, XMLI, and HQI), helps determine the optimal combination for improving various outcomes in the target population. Almost all TCMIs paired with WMT were more effective than WMT alone for CER, LVEF, LVEDD, 6MWT, and BNP in patients with HFrEF and HFmrEF, except for HQI + WMT, which showed no statistically significant difference in the improvement of LVEDD and 6MWT from WMT alone, perhaps owing to the limited number of HQI RCTs. All 9 RCTs [37,38,62,68,79,88,93,95,117] on HQI were included in the analysis, 3 [79,95,117] of them reported LVEDD and 1 [68] reported 6MWT.

SMI was ranked first in CER and BNP when the findings of NMA and the results of SUCRA were combined. HQI, DHI, and XMLI were ranked first in LVEF, LVEDD, and 6MWT, respectively. Utilizing these TCMIs according to the patient's situation can successfully alleviate the signs and symptoms of HF. Meanwhile, the quality of evidence evaluation of outcome indicators using the GRADE approach showed moderate strength of evidence for CER, low strength of evidence for LVEF, LVEDD, and 6MWT, and insufficient strength of evidence for BNP. This outcome offers us moderate confidence that TCMIs coupled with WMT are more efficacious than

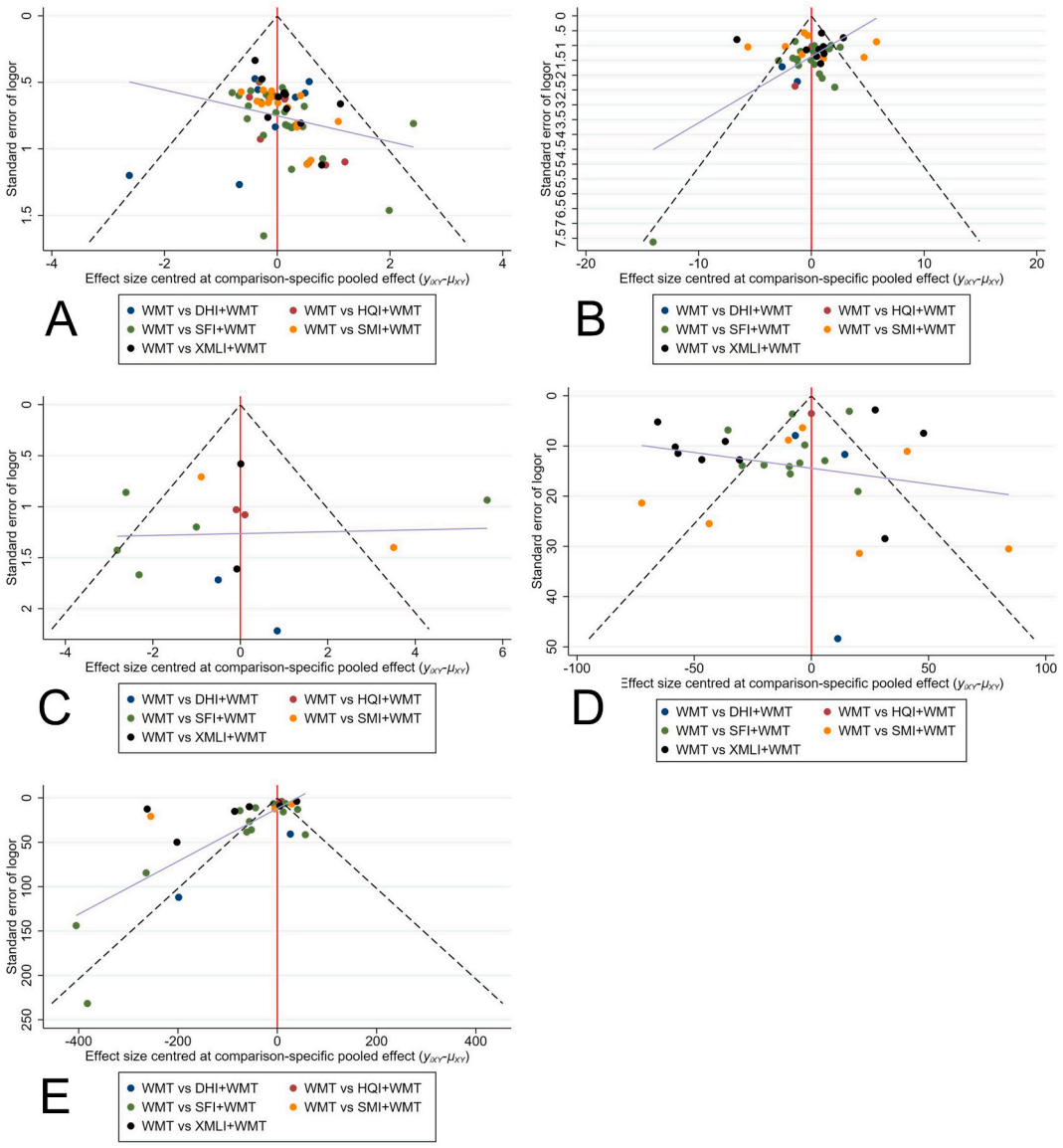

Fig. 5. Funnel plots of outcomes, A clinical effectiveness rate (CER); B, left ventricular ejection fraction (LVEF); C, left ventricular end-diastolic dimension (LVEDD); D, 6-min walking test (6MWT); E, b-type natriuretic peptide (BNP).

Table 5
GRADE assessment for the outcomes.

Outcome	No. of studies (Design)	Quality assessment					
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
CER	76 (RCT)	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊕○ Moderate
LVEF	87 (RCT)	Serious	Serious	Not serious	Not serious	Undetected	⊕⊕○○ Low
LVEDD	41 (RCT)	Serious	Serious	Not serious	Not serious	Undetected	⊕⊕○○ Low
6MWT	31 (RCT)	Serious	Serious	Not serious	Not serious	Undetected	⊕⊕○○ Low
BNP	27 (RCT)	Serious	Serious	Not serious	serious	Undetected	⊕○○○ Very Low

WMT alone at enhancing CER in patients with HFrEF and HFmrEF. Additionally, conclusions reached from LVEF, LVEDD, and 6MWT with poor-quality evidence and BNP with extremely poor-quality evidence should be viewed with caution.

Among all RCTs included in this NMA, a total of 28 RCTs explicitly mentioned the absence of ADRs, 17 RCTs specifically described the occurrence of ADRs, and 56 RCTs did not mention whether ADRs occurred. The incidence of ADRs was lowest in the case of Xinmailong injection when compared to other TCMIs. Compared to the WMT group, the incidence of ADRs in the TCMIs group did not show any statistically significant differences. However, to ensure that physicians have something to refer to when using it clinically, the investigators should document it in detail and give it attention. Doing the following will reduce the occurrence of ADRs. Firstly, the drip rate should be strictly controlled according to the drug instructions. Too fast a drip rate may lead to phlebitis, while too slow a drip rate will result in chemical changes such as hydrolysis, oxidation, and PH value changes in the herbal injection, which may cause adverse reactions; secondly, for patients with an allergy history, the drip should be slow in the first 15 min, and the patient's response should be closely observed; finally, the drug should be selected according to the patient's symptoms and reasonably combined with western medicines and pay attention to avoid possible mutual reaction [123].

According to traditional Chinese medicine (TCM), blood stasis is the primary pathophysiology of chronic heart failure (CHF), and it is a sign of a qi and yang shortage in the heart [124]. By the etiology of CHF, TCM physicians often prescribe Chinese herbs with the effects of "benefiting Qi, warming Yang, energizing Blood, and encouraging water" [125]. The five TCMIs selected in this study were derived from these herbs. Shenmai injection is derived from the Chinese herbal soup "shenmai drink" in the ancient Chinese medical book "Zheng yin mai zhi", which consists of two herbal medicines, red ginseng, and maitake, and the active substances include ginsenoside, maitake saponin, and maitake flavonoid. It has the benefit of strengthening the heart and restoring the pulse, promoting qi, and repairing detoxification [126]. Based on the results of pharmacological studies, Shenmai injection has been demonstrated to primarily enhance cardiac contractility and conductivity by decreasing cellular Na + -K + -ATPase activity, modifying Na + -K+ and Na + -Ca2+ exchange, and increasing Ca2+ inward flow. It also reduces the neuroendocrine activity of plasma renin activity, angiotensin II, aldosterone, endothelin (ET), cardiac natriuretic peptide (ANP), BNP, and TNF-α [127]. The active ingredient in Huangqi injection is derived from Huangqi. In Chinese medicine, Huangqi is considered to have the effect of tonifying Qi and raising Yang. Modern pharmacological studies have shown that polysaccharides, flavonoids, and saponins in Huangqi can lower blood pressure, prevent myocardial fibrosis, improve the diastolic and systolic functions of the heart, and achieve cardiac strengthening effects through a two-way regulatory development [128,129]. The active ingredients in Danhong injection are tanshinone, safflower phenol, and tanshin polyphenolic acid salt, extracted from two Chinese herbs, Danshin and safflower [130]. They have the effect of activating blood circulation and relieving pain. The results of modern pharmacological studies show that Danhong injection can inhibit platelet aggregation, promote myocardial blood perfusion, and improve myocardial blood oxygen supply; in addition, Danhong injection can inhibit the synthesis and secretion of angiotensin, prevent the inward flow of Na+, lower blood, reduce the load on the heart, and improve myocardial tissue remodeling [131]. The ingredient in Xinmailong injection is extracted from an American cockroach, in traditional Chinese medicine, it is a worm category, with the effects of dispersing stagnation and eliminating stagnation, detoxifying, and diuretic. Modern pharmacological studies have shown that small-molecule bioactive peptides in American cockroaches have effects on enhancing myocardial contraction and inhibiting myocardial remodeling [132].

Most cardiovascular disorders eventually lead to HF, and its yearly survival rate is comparable to cancer [133]. Additionally, HF is associated with poor life quality and high healthcare costs, it is also the primary reason for hospitalization for those over 65 [2]. Combining Chinese and Western medicine treatments has become a crucial part of the therapy of HF in China, as stated in the "2018 Chinese Heart Failure Diagnostic and Therapy Guidelines", which explicitly includes TCMIs treatment in the HF treatment protocol. TCMI is the sterile preparation of herbs that have been extracted and purified for injection into the body in the form of a solution, emulsion, powder, or concentrated solution, which have the advantages of convenient medication administration, rapid efficacy, and significant curative effect. In recent years, the combined treatment of WMT with TCMIs for HF has been increasingly reported, and the research on its mechanism is more extensive and comprehensive, especially in regulating neurological and endocrine levels and improving ventricular remodeling. TCMIs have shown better advantages in improving patients' symptoms, improving efficacy, and reducing side effects associated with traditional Western medicine treatment [134]. However, TCMIs face a relative lack of evidence on efficacy and safety. The NMA evaluates the effectiveness and safety of five TCMIs to provide some reference and evidence-based medical evidence to support future clinical use protocols.

Studies have been conducted in the past which include patients with both HFrEF and HFmrEF as subjects [23]. However, the TCMIs used in these patients were not the same as the five TCMIs selected for this study (SFI, SMI, DHI, XMLI, HQI). Even though a portion of the TCMIs in both studies were identical, our study increased the number of included RCTs and utilized sensitivity analysis to strengthen the reliability of the data, employing subgroup analysis to further investigate the impacts of prospective variables on effectiveness. This research also enhanced the inclusion and exclusion criteria for patients and therapies to decrease variability among RCTs and enhance the trustworthiness of the findings.

This NMA has various inherent limitations. Firstly, only 33 of the included RCTs specified the randomized grouping method, and only two reported a blinded approach. Moreover, none reported allocation concealment information, which may increase the risk of bias and lead to exaggerated efficacy and lower quality of evidence. Secondly, all RCTs were done in China, limiting the findings' generalization. Furthermore, most RCTs did not report the prognosis of patients, including hospitalization and cardiovascular event rates. As a result, it was impossible to determine if TCMIs improved patient prognosis. Extreme differences in treatment duration between RCTs may account for the wide variation in treatment outcomes.

5. Conclusion

In conclusion, SFI, SMI, DHI, XMLI, and HQI combined with WMT have stronger efficiency in treating HFrEF and HFmrEF. Meanwhile, among them, SMI with a prominent tonic effect was effective in improving CER and reducing BNP; HQI and DHI with a tonifying effect and activating blood were effective in improving LVEF and LVEDD; XMLI with tonifying and the diaphoretic effect was effective in improving 6MWT. However, the evidence strength for CER was moderate, while for the rest it was low or very low. In addition, there are some limitations in this study. Additional high-quality, multicenter RCTs are required to verify this conclusion and provide more objective and reliable evidence-based medical support for the therapeutic implementation of TCMI.

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Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Yu Zheng: Data curation, Formal analysis, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. **Huizhen Zheng:** Formal analysis, Methodology. **Zhihua Guo:** Formal analysis, Funding acquisition, Investigation, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23194.

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