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© 2023 Xingmeng, Guohua, Hui, Wulin, Huiwen, Maoxia, Runmin and Lili. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms. Clinical efficacy and safety of adjunctive treatment of chronic ischemic heart failure with Qishen Yiqi dropping pills: a systematic review and meta-analysis

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Objectives: Our study was to evaluate the effect of Qishen Yiqi Dropping Pills (QSYQ) on the prognosis of chronic ischemic heart failure(CIHF) and its safety. **Methods:** Databases including CNKI, Wanfang, VIP, CBM, PubMed, Web of Science, The Cochrane Library and EMbase were searched from their inception to April 2023 to screen relevant randomized controlled trials (RCTs). Primary indicators included readmission rates, rates of major adverse cardiovascular events (MACE), and all-cause mortality rates. The quality of the literature was assessed according to the Cochrane Reviewers' Handbook 5.0 and the Modified Jadad Scale (with a score of 4–7 rated as high quality). Meta-analysis was performed using the meta-package created by R software version 4.2.3, continuous data were compared using SMDs, and dichotomous and ordered data were compared using ORs; and the I^2 test was used to assess the heterogeneity.

Results: Fifty-nine studies out of 1,745 publications were finally included, totalling 6,248 patients. Most studies were poorly designed and had some publication bias, with only 26 high-quality papers (Jadad score \geq 4). Metaanalysis showed that the combined application of QSYQ was able to reduce the readmission rate [OR = 0.42, 95% CI (0.33, 0.53), P < 0.001], all-cause mortality rate [OR = 0.43, 95% CI (0.27, 0.68), P < 0.001], and the incidence of MACE [OR = 0.42, 95% CI (0.31, 0.56), P < 0.001]. Also, the treatment method can improve clinical effectiveness [OR = 2.25, 95% CI (1.97, 2.58), P < 0.001], increase 6-min walking distance (6MWD) [SMD = 1.87, 95% CI (1.33, 2.41), P < 0.0001] and left ventricular ejection fraction (LVEF) [SMD = 1.08, 95% CI (0.83, 1.33), P < 0.0001], and decrease the Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores [SMD = -2.03, 95% CI (-3.0, -1.07), P < 0.0001], BNP levels [SMD = -2.07, 95% CI (-2.81, -1.33), P < 0.0001] and NT-ProBNP levels [SMD = -2.77, 95% CI (-4.90, -0.63), P<0.05]. A total of 21 studies (n = 2,742) evaluated their adverse effects, of which 13 studies reported no adverse effects and 8 studies reported minor adverse effects.

Conclusion: Our results suggest that the combined application of QSYQ can further improve patients' cardiac function and exercise tolerance, improve their quality of life, and ultimately improve patients' prognosis with a favorable safety profile. Nonetheless, limited by the quality and high heterogeneity of the literature, we must be conservative and cautious about the present results.

Systematic Review Registration: PROSPERO (CRD42023449251).

KEYWORDS

Qishen Yiqi dripping pills, chronic ischemic heart failure, prognosis, clinical efficacy, readmission, meta-analysis

1. Introduction

Heart failure (HF) is a serious manifestation and advanced stage of various cardiovascular diseases and is a serious life-threatening complex clinical syndrome (1). Epidemiologic data show that the global prevalence of HF in adults is 1%-3%, but the prevalence is expected to increase in the future due to the aging of the population and the use of effective evidence-based therapies to prolong the lives of patients with HF (2). Even with long-term treatment with internationally standardized medications, patients still suffer from recurrent exacerbation of symptoms such as dyspnea, edema, and fatigue as well as poor quality of life, and mortality and readmission rates remain high (3). Studies have shown that in a given population, the 1-year risk of death in patients with HF ranges from 15% to 30%, with a 5-year risk of death as high as 75% (2). HF has become a serious public health concern worldwide due to its high morbidity and mortality (4). Among many factors, ischemic heart disease (IHD) represents the etiology of HF in 40% of the global HF population. Several studies have shown that the presence of coronary artery disease is associated with a higher risk of death and a worse prognosis in patients with HF after hospital discharge (2, 5). IHD-induced HF is independently associated with mortality compared with nonischemic causes (6, 7). Therefore, there remains an urgent need to find an adjunctive treatment that can improve quality of life and further effectively reduce rehospitalization and mortality rates.

Chronic heart failure belongs to the category of "heart failure" in Chinese medicine, and the basic pathogenesis is qi deficiency and blood stasis (8). Benefiting qi, activating blood circulation, and inducing diuresis constitute the mainstays of treatment for it. In recent years, Chinese medicine has received increasing attention in the treatment of HF with its unique theories and remarkable efficacy. QiShen YiQi Drop Pills (QSYQ) is one of the representative Chinese medicinal preparations, which is made of Astragalus mongholicus, Salvia miltiorrhiza, Panax notoginseng, and Dalbergia wood oil, and it is considered to have the effects of benefiting Qi, invigorating blood circulation, and dredging blood vessels. Approved by the State Food and Drug Administration (SFDA) in 2003 (National Drug Approval Number: Z20030139), QSYQ was recommended by the "Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in Traditional Chinese Medicine" for the comprehensive treatment of HF or IHD in the type of qi deficiency and blood stasis (9). Existing systematic evaluations (8, 10, 11) provide evidencebased medical evidence for the clinical application of QSYQ to a certain extent, but there are still many shortcomings: (1) To the best of our knowledge, all systematic evaluations have selected surrogate indicators for efficacy evaluation and lacked clinical endpoint indicators and long-term prognostic indicators, such as readmission rate and mortality. Despite the economic efficiency, sensitivity, and accessibility of alternative indicators in clinical studies which have some clinical value (12), they could not provide the most direct evidence to support the improvement of the long-term prognosis of patients with HF by QSYQ. (2) Newly published high-quality randomized controlled trials were not included. A randomized, double-blind, placebo-controlled trial (CACT-IHF) (13) involving 32 centers in China and including 640 patients with chronic ischemic heart failure (CIHF) has been publicly published, and there is no doubt that this trial will have an unprecedented impact on the clinical evidence-based evaluation of QSYQ. (3) Previous systematic evaluations have not conducted further assessment analyses of CIHF. Given these, we conducted an updated systematic evaluation and meta-analysis that included the CACT-IHF trial and used readmission rate, all-cause mortality, and adverse cardiovascular events as the main evaluation indexes, and explored for the first time the clinical efficacy of the adjunctive treatment of CIHF with QSYQ.

2. Materials and methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) statement and has been registered in PROSPERO (registration number: CRD42023449251).

2.1. Ethics approval and consent to participate

This study did not involve animal or patient experimentation and did not require ethical approval or informed consent from participants.

2.2. Inclusion criteria and exclusion criteria

The PICOS principles were strictly followed as the eligibility criteria and the followings are included.

2.2.1. Study type

This study included published randomized controlled trials (RCTs) of QSYQ-assisted treatment of CIHF, both nationally and internationally, which were required to have similar study methods, complete general data and statistical analysis with uniform metrics.

2.2.2. Study object

Diagnostic criteria for chronic heart failure were based on the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure (14); previous history of myocardial infarction or revascularization, or diagnosis of coronary artery disease confirmed by coronary angiography; and New York Heart Association (NYHA) functional class II–IV. Patients had balanced comparable baseline data.

2.2.3. Intervention measures

The control group was treated with conventional western medications recommended by international guidelines, including those recommended for HF (14, 15) such as ACEI/ARB, β -blockers, aldosterone receptor antagonists, ARNI, and SGLT-2i, as well as those recommended for coronary artery disease (16), such as aspirin, clopidogrel, ticagrelor, calcium antagonists, nitrates, ivabradine, nicorandil, and trimetazidine. Nonetheless, in the QSYQ group, patients also took QiShen YiQi Drops Pills (manufactured by Tianjin Tasly Pharm. Co., Ltd, taken orally, 0.5 g, TID) apart from the medicines taken by the control group. The conventional western medicines may not be consistently taken for each study, and the only difference between the QSYQ group and the control group was whether or not QSYQ was applied. In addition, neither group took any other medications that might interfere with the assessment indicators.

2.2.4. Exclusion criteria

(1) Repeated reports, studies with inaccurate or incomplete literature; (2) Irrelevant studies such as individual cases or empirical reports; (3) Animal experiments, pharmacological mechanism studies; (4) Guidelines, reviews, and systematic evaluations; (5) Descriptive studies only without clinical controlled trials; (6) Nonrandomized controlled trials; (7) Inconsistent study subjects; (8) Inconsistent evaluation indexes.

2.2.5. Outcome indicators

Primary efficacy assessment indicators include ① Re-admission rates (RARs); ② All-cause mortality (ACM); ③ Major adverse cardiovascular events (MACE were defined as cardiogenic death, cardiogenic shock, myocardial infarction, revascularization, and severe arrhythmia, etc.).

Secondary efficacy assessment indicators include ④ The Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores; ⑤ Clinical efficacy rates (CERs): Clinical efficacy assessment criteria were formulated in accordance with the "Guidelines for Clinical Research of New Traditional Chinese Medicines" and the NYHA grading. Clinical efficacy is divided into three categories: Significant: Complete relief of symptoms and signs or improvement of cardiac function by more than 2 levels; Effective: Partial relief of symptoms and signs or improvement of cardiac function by 1 level;

Ineffective: No significant improvement or aggravation of signs and symptoms, and improvement of cardiac function by less than 1 level; (6) 6-min walking distance (6MWD); (7) Left ventricular ejection fraction (LVEF); (8) Brain natriuretic peptide(BNP); (9) N-terminal prohormone of BNP(NT-pro BNP); (10) Left ventricular end-diastolic dimensions (LVEDD); (11) Left ventricular end-systolic dimensions (LVESD); (12) Left ventricular end-diastolic volume (LVEDV); (13) Left ventricular end-systolic volume (LVESV).

⁽¹⁾ Safety indicators include the incidence of adverse reactions such as itchy skin or rash, nausea, vomiting, and dizziness.

2.3. Search strategy

A comprehensive and systematic search from 8 databases was conducted to retrieve RCTs from inception to 04/22/2023. The following databases are included: PubMed, Cochrane Library, Embase, Web Of Science, Wanfang Database, China Scientific Journal Database (VIP), China National Knowledge Infrastructure (CNKI), and China Biology Medicine (CBM). We also attempted to search ongoing RCTs, such as the Chinese Clinical Trial Registry, to ensure a comprehensive and exhaustive collection of literature. Search terms included "QiShen YiQi", "QiShen YiQi Dripping Pills", "Heart Failure", "Cardiac Failure", "cardiac insufficiency", "chronic heart failure", etc., and their synonyms. A search strategy combining medical subject terms and free words was adopted. In addition, we manually searched references of published systematic reviews in order to conduct a comprehensive search for other relevant studies. Also, we provide search strategies about Pubmed (Table 1).

2.4. Article selection and data extraction

Based on the inclusion and exclusion criteria, two researchers (Qu HW and Li RM) screened the literature independently and in parallel using EndnoteX9 software to minimize subjective selection bias, and resolved disagreements by consulting a third party member (Wang XM). Studies that clearly did not meet the inclusion criteria were excluded first by reading titles and abstracts. Then the full texts of the remaining studies were

TABLE 1 Search strategy for pubMed.

		Search item
	#1	"Heart Failure"[Mesh]
	#2	[heart failure(Title/Abstract)] OR [Cardiac Failure(Title/Abstract)] OR [Heart
		Decompensation(Title/Abstract)] OR [Decompensation, Heart(Title/
		Abstract)] OR [Heart Failure, Right-Sided(Title/Abstract)] OR [Heart Failure,
		Right Sided(Title/Abstract)] OR [Right-Sided Heart Failure(Title/Abstract)]
		OR [Right Sided Heart Failure(Title/Abstract)] OR [Myocardial Failure(Title/
		Abstract)] OR [Congestive Heart Failure(Title/Abstract)] OR [Heart Failure,
		Congestive(Title/Abstract)] OR [Heart Failure, Left-Sided(Title/Abstract)] OR
		[Heart Failure, Left Sided(Title/Abstract)] OR [Left-Sided Heart Failure(Title/
		Abstract)] OR [Left Sided Heart Failure (Title/Abstract)]
	#3	#1 OR #2
	#4	[Qishen Yiqi Dripping Pills (Title/Abstract)] OR [Qishen Yiqi Dripping Pill
		(Title/Abstract)] OR [Qishen Yiqi DropPill(Title/Abstract)] OR [Qishen Yiqi
		(Title/Abstract)] OR [Qishen Yiqi droplet(Title/Abstract)] OR [Qishen Yiqi
		Pills(Title/Abstract)]
ĺ	#5	#3 AND #4

carefully read to decide on inclusion or exclusion. Finally, all the included studies were cross-checked to ensure eligibility.

Two researchers (Wang XM and Qu HW) independently and in parallel extracted data including article title, first author, year of publication, country, journal, participant's age, gender, sample size of QSYQ and control groups, intervention, treatment duration, methodological information, efficacy evaluation indexes, and adverse effects. The authors of the original studies were contacted by e-mail or telephone when necessary to obtain the missing but essential information for the studies.

2.5. Quality evaluation

The quality of included studies was independently assessed and checked by two researchers (Qu HW and Li RM), and disagreements were resolved through consultation with a thirdparty person (Wang XM). Assessment was performed using the Cochrane Risk of Bias Assessment Tool (17), which covers seven areas: Randomized sequence generation, allocation concealment, blinding of investigators and subjects, blinding of outcome assessors, completeness of outcome data, selective reporting, and other biases. All of these were assessed as "low risk of bias", "high risk of bias", or "unclear risk of bias". The quality of the studies was evaluated using the modified Jadad scale, which includes four aspects: Randomized sequence generation, allocation concealment, blinding, withdrawal and exit. The scores were 2, 2, 2, and 1, respectively. The quality of RCTs with a score of 1-3 was rated as low, and the quality of RCTs with a score of 4-7 was rated as high.

2.6. Statistical analysis

This meta-analysis was performed based on the metapackage (18) created by R software version 4.2.3. The dichotomous data were compared using the odds ratios (OR) values; the continuous data were compared using the standardized mean difference (SMD) due to the differences in participants' cardiac function between studies. To make the best use of the data, a maximum likelihood ratio fitted to the cumulative ratios model was used for the ordinal ranked data and the efficacy categories were described by the odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated. Z-tests were used to assess the combined statistical results, and P < 0.05 was considered statistically significant. Heterogeneity between studies was assessed using the I^2 statistic and the χ^2 -based Cochran Q test. When heterogeneity was not significant ($I^2 < 50\%$ or p > 0.05), a fixed-effects model was used for the combination of effect sizes; otherwise, a random-effects model was used. In addition, we calculated 95% prediction intervals to assess the true range of influence of QSYQ across future studies based on the method recommended by IntHout et al. (19).

The courses of treatment varied among the included studies, and to explore the sources of heterogeneity, we performed

subgroup analysis of 6MWD, LVEF, BNP, NT-proBNP, and LVEDD according to the courses of treatment. Multifactorial meta-regression analysis were also performed for 6MWD, and LVEF according to mean age as well as quality of the literature. Then, pooled analysis was further conducted for high-quality (Jadad score \geq 4) studies. As heterogeneity remained high across subgroups, the Galbraith plots and Baujat plots were used to identify potential sources of heterogeneity between studies, and the data were recombined after excluding outlier studies. Publication bias was assessed by plotting contour-enhanced funnel plots for indicators that included more than ten studies; Egger's linear regression test was carried out to detect the publication bias in continuous-type data, and Harbord test and Peters' test were implemented to detect the publication bias in dichotomous data (20). If publication bias was detected (P <0.05), contour-enhanced funnel plots were trimmed and filled to explore the causes of funnel plots asymmetry, and effect sizes were recombined for the corrected funnel plots. Sensitivity analysis was also performed to analyze the robustness of the results.

3. Results

3.1. Characteristics of the included studies

A total of 1,745 papers were retrieved from 9 databases. After eliminating duplicates (n = 848), 656 papers were excluded by reading titles and abstracts. Then, the full text of the remaining 241 papers was read through to exclude the studies with the following inadequacies: non-ischemic heart failure (n = 164), cohort studies (n = 2), non-randomized controlled trials (n = 6), overlapping data (n = 3), inconsistent outcome metrics (n = 3), and unavailability of full text (n = 4). Fifty-nine papers (13, 21– 78) were ultimately included for meta-analysis, involving 6,248 patients with CIHF who met the criteria. The literature screening flowchart is shown in Figure 1.

Of the 59 included studies, only one (13) was published in English and provided the largest sample size (n = 640), while the remaining 58 were published in Chinese, with sample sizes ranging from 40 to 300; both males and females participated in the studies, with a mean age range of 53.9–86 years. Among the studies involving prognostic indicators, the duration of follow-up ranged from 8 weeks to 48 weeks, with most of the studies focusing on 24 weeks or 48 weeks, but no studies with follow-up longer than 48 weeks. The majority of patients had a cardiac function classification falling within the NYHA class II–III. **Supplementary Table S1 (Supplementary materials)** summarizes the basic characteristics of the 59 studies.

3.2. Quality evaluation of included studies

The results of the quality assessment of the 59 selected papers are shown in Figure 2 and Supplementary Figure S1. Only 3 (13, 32, 58) of the 59 studies described the randomization method in



details, 23 studies (27, 34, 38, 39, 46, 50, 51, 55, 60, 62–65, 67–69, 71–76, 78) used an appropriate randomization method (randomized numeric table method), and 1 study (66) used an inappropriate randomization method (dynamic randomized grouping and different medication administration); only 3 studies (13, 32, 58) described the allocation scheme concealment and double blinding; only 2 studies (58, 74) reported lost visits or missing cases (n = 21); all studies failed to selectively report outcome indicators or other biases. Twenty-six documents (13, 27, 32, 34, 38, 39, 46, 50, 51, 55, 58, 60, 62–65, 67–69, 71–76, 78) were rated as high quality (Jadad score \geq 4) according to the modified Jadad scale.

3.3. Impact of QSYQ on outcome indicators

3.3.1. Re-admission rates (RARs)

Fifteen studies (n = 2,080) compared RARs in the QSYQ group (n = 1,056) and the control group (n = 1,024); the results of the fixed-effects model ($I^2 = 0\%$, P = 0.78 > 0.1) showed that QSYQ

significantly reduced the RARs, [OR = 0.42, 95% CI (0.33, 0.53), Z = -7.26, P < 0.001] (Figure 3A).

3.3.2. All-cause mortality(ACM)

Nine studies (n = 1,679) compared ACM in the QSYQ group (n = 842) and the control group (n = 837), and the results of the fixed-effects model ($I^2 = 0\%$, P = 0.59 > 0.1) showed that QSYQ dramatically reduced the ACM, [OR = 0.43, 95% CI (0.27, 0.68), Z = -3.57, P < 0.001] (Figure 3B).

3.3.3. Incidence of MACE

Eight studies (n = 1,493) compared the incidence of MACE in the QSYQ group (n = 749) and the control group (n = 744), and the results of the fixed-effects model ($I^2 = 32\%$, P = 0.17 > 0.1) showed that QSYQ decreased the incidence of MACE significantly, [OR = 0.42, 95% CI (0.31, 0.56), Z = -5.82, P < 0.001] (Figure 3C).

3.3.4. MLHFQ scores

Seventeen studies (n = 2,032) compared the MLHFQ Scores, and the results of a random-effects model ($I^2 = 96\%$, P < 0.01)



demonstrated that combined QSYQ significantly improved patients' quality of life, [SMD = -2.03, 95% CI (-3.00, -1.07), Z = -4.12, P < 0.0001] (Figure 4A).

3.3.5. Clinical efficacy rates (CERs)

Thirty-three studies (n = 3,289) compared CERs, and results from a fixed-effects model ($I^2 = 0\%$, P = 0.879 > 0.1) showed that the QSYQ group was 2.25 times more likely to have an improvement of one grade or more in NYHA cardiac function classification than the control group, suggesting that the combined application of QSYQ was efficacious, [OR = 2.25, 95% CI (1.97, 2.58), Z = 11.77, P < 0.001] (Figure 4B).

3.3.6. 6MWD

Thirty-three studies (n = 3,597) reported 6MWD, and results from a random-effects model ($I^2 = 97\%$, P < 0.01) showed that combined QSYQ markedly improved 6MWD, [SMD = 1.87, 95% CI (1.33, 2.41), Z = 6.81, P < 0.0001] (Figure 5).

3.3.7. LVEF

Forty-five studies (n = 4,748) compared LVEF, and the results of a random-effects model ($I^2 = 91\%$, P < 0.01,) showed that QSYQ was able to significantly enhance LVEF, [SMD = 1.08, 95% CI (0.83, 1.33), Z = 8.44, P < 0.0001] (Figure 6).

3.3.8. BNP

Sixteen studies (n = 1,606) compared BNP levels, and the results of a random-effects model ($I^2 = 96\%$, P < 0.01) showed that QSYQ was able to significantly reduce BNP levels, [SMD = -2.07, 95% CI (-2.81, -1.33), Z = -5.48, P < 0.0001] (Figure 7A).

3.3.9. NT-ProBNP

Eighteen studies (n = 1,807) reported NT-proBNP levels, and the results of a random-effects model ($I^2 = 96\%$, P < 0.01) showed that

QSYQ was able to significantly decrease the levels of NT-proBNP, [SMD = -2.77, 95% CI (-4.90, -0.63), Z = -2.54, P < 0.05] (Figure 7B).

3.3.10. LVEDD

Eighteen studies (n = 2,018) reported LVEDD, and a randomeffects model ($I^2 = 88\%$, P < 0.01) showed that QSYQ was able to significantly reduce LVEDD, [SMD = -0.92, 95% CI (-1.21, -0.63), Z = -6.21, P < 0.0001] (Figure 8A).

3.3.11. LVESD

Nine studies (n = 1,036) reported LVESD, and a random-effects model ($I^2 = 86\%$, P < 0.01) showed that QSYQ was able to significantly reduce LVESD, [SMD = -1.02, 95% CI (-1.38, -0.66), Z = -5.53, P < 0.0001] (Figure 8B).

3.3.12. LVEDV

Seven studies (n = 795) compared LVEDV, and the results of the random effects model ($I^2 = 95\%$, P < 0.01) showed that QSYQ was able to reduce LVEDV, but not statistically significant, [SMD = -1.49, 95% CI (-3.29, 0.31), Z = -1.62, P > 0.05] (Figure 8C).

3.3.13. LVESV

Eight studies (n = 873) compared LVEDD, and the results of the fixed-effects model ($I^2 = 0\%$, P = 0.69 > 0.01) showed that QSYQ was able to significantly reduce LVESV, [SMD = -0.41, 95% CI (-0.55, -0.28), Z = -5.93, P < 0.001] (Figure 8D).

3.3.14. Safety

Adverse reactions were reported as an assessment indicator in 21 of 59 studies (n = 2,742), among which 13 studies mentioned that no adverse reactions occurred during the course of treatment in both QSYQ and control groups, and 8 studies reported in details about adverse reactions that occurred during the course of treatment such

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Study	Experime Events T	otal E	vents	Total	Odds Ratio	OR	95%-CI	Weight
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$ \begin{array}{c} \text{Cu2010} & \text{i} & i$	Wu2018	10	50	22	50	-	0.20	[0.02, 2.10]	9 10/
$ \begin{array}{c} \text{Curdu22} \\ \text{Curdu22} \\ \text{Xie}2010 & 1 & 40 & 3 & 33 \\ \text{Xie}2010 & 12 & 46 & 18 & 37 \\ \text{Niu}2013 & 12 & 46 & 18 & 37 \\ \text{Lvz019} & 10 & 49 & 21 & 49 \\ \text{Lvz019} & 10 & 49 & 21 & 49 \\ \text{Chang2022} & 1 & 40 & 9 & 40 \\ \text{Chang2022} & 1 & 40 & 9 & 40 \\ \text{Yang2022} & 6 & 30 & 13 & 29 \\ \text{Wu2020} & 25 & 319 & 36 & 319 \\ \text{Wu2020} & 25 & 319 & 36 & 319 \\ \text{Wu2020} & 25 & 319 & 36 & 319 \\ \text{Wu2020} & 25 & 319 & 36 & 319 \\ \text{Heterogeneity: } l^2 = 0\%, r^2 = 0, p = 0.78 \\ \text{Common effect model} & 1056 \\ \text{Lu2022} & 1 & 40 & 8 & 40 \\ \text{Lvz011} & 1 & 54 & 8 & 54 \\ \text{Lvz019} & 1 & 548 & 549 \\ \text{Common effect model} & 1056 \\ \text{Common effect model} & 144 \\ \text{Lvz019} & 1 & 49 & 449 \\ \text{Lvz021} & 1 & 548 & 844 \\ \text{Lvz022} & 1 & 40 & 8 & 405 \\ \text{Lu2022} & 1 & 40 & 8 & 405 \\ \text{Lu2022} & 1 & 40 & 8 & 405 \\ \text{Common effect model} & 144 \\ \text{Lvz019} & 1 & 49 & 449 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 0 & 55 & 159 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 12 & 319 & 15 & 319 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 12 & 319 & 15 & 319 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 12 & 319 & 15 & 319 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 12 & 319 & 15 & 319 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 3 & 319 & 42 & 319 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 3 & 319 & 42 & 319 \\ \text{Common effect model} & 842 \\ \text{Song2020} & 3 & 319 & 42 & 319 \\ \text{Common effect model} & 749 & 744 \\ \text{Heterogeneity: } l^2 = 32\%, r^2 = 0.1762, p = 0.17 \\ \end{array}$	0012018	10	40	22	25		0.32	[0.13, 0.77]	0.170
$ \begin{array}{c} x_{12} x_{12} x_{12} x_{12} x_{13} \\ x_{12} x_{22} x_{13} x_{14} x_{14} \\ x_{12} x_{22} x_{12} x_{14} x_{14} \\ x_{12} x_{22} x_{14} x_{14} x_{14} \\ x_{14} x_{22} x_{24} x_{25} x_{15} x_{15} x_{14} \\ x_{14} x_{22} x_{24} x_{14} x_{14} x_{14} \\ x_{14} x_{14} \\ x_{14} x_{14} x_{14} \\ x_{14} x_{14} x_{14} \\ x_{14} x_{14} \\$	Cuizozo	1	40	3	35		0.27	[0.03; 2.76]	1.4%
Nu2013 12 46 18 37 12 46 18 37 12 46 18 37 12 46 18 37 12 46 18 37 12 46 18 37 12 47 14 14 12 11 41 14 12 12 10 10 10 10 10 10 10 10 10 10 10 10 10	Xie2010	12	60	22	60		0.43	[0.19; 0.98]	8.1%
L 22019 10 44 21 11 41 Zhang2020 44 42 11 41 Huang2022 1 0 54 3 54 Huang2022 1 10 6 610 Yang2022 6 6 30 13 29 W2020 8 40 12 40 W2020 8 40 12 40 Have an 2020 25 319 36 319 Common effect model 1056 Prediction interval Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0$.78 0.01 0.1 1 1 0 Study Experimental Control Study Experimental Control Study Experimental Control Common effect model 842 837 Kie2010 3 13 147 4 144 Lu2022 1 40 8 40 Lu2022 1 40 8 40 Control Events Total Control Common effect model 842 837 Xie2011 45 2 36 5 36 Common effect model 749 744 Heterogeneity: $l^2 = 32\%$, $\tau^2 = 0.762$, $p = 0.17$ 0.1 0.51 2 10 0.1 0.51 2 10 0.43 [0.27; 0.48] 100.02 0.42 [0.33; 0.56] 100.02 0.42 [0.33; 0.56] 100.02 0.55 1 55 0.79 [0.36; 1.72] 24.6 0.67 95%-Cl Weig 0.67 95%-Cl Weig 0.67 95%-Cl Weig 0.1 0.51 2 10 $0.1 0.51 2 100.43 [0.27; 0.68] 100.02 0.36 [0.07; 2.04] 8.3 0.43 [0.27; 0.68] 100.02 0.36 [0.07; 2.04] 8.3 0.43 [0.27; 0.68] 100.02 0.42 [0.33; 0.55] 100.02 0.1 0.51 2 10 0.1 0.51 2 100.1 0.51 2 100.4 0 [0.5; 1.21]0.4 0 [0.5; 1.24]0.5 0 [0.5; $	Niu2013	12	46	18	37		0.37	[0.15; 0.94]	6.8%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Lv2019	10	49	21	49		0.34	[0.14; 0.84]	7.7%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhang2020	4	42	11	41		0.29	[0.08: 0.99]	4.6%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhang2021	0	54	3	54 -		0.13	0.01: 2.68	1.6%
Lu2022 1 1 40 9 40 10 10 10 10 10 10 10 10 10 10 10 10 10	Huang2022	1	10	6	10 -		0.07	[0,01,0.84]	2.5%
Yang2022 i i yo yo<	Liu2022	1	10	å	40		0.07	[0.01, 0.04]	4 0%
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Llu2022	, c	40	12	40		0.09	[0.01, 0.74]	4.0%
W12020 3 40 12 40		0	30	13	29		0.31	[0.10; 0.96]	4.0%
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Wu2020	8	40	12	40		0.58	[0.21; 1.63]	4.4%
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mao2020	25	319	36	319	; • • 	0.67	[0.39; 1.14]	15.2%
Common effect model Prediction interval Heterogeneity: $l^2 = 0\%$, $t^2 = 0$, $p = 0.78$ 0.01 0.1 1 10 100 Study Experimental Events Total Events Total Control Events Total Odds Ratio OR 95%-Cl Weig 0.73 0.11 0.01 0.11 0.01	Zhang2021	38	147	61	144		0.47	[0.29; 0.78]	20.9%
Prediction interval Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0, p = 0.78$	Common effect model	1	056		1024	÷	0.42	[0.33; 0.53]	100.0%
Heterogeneity: $l^2 = 0\%$, $r^2 = 0$, $p = 0.78$ 0.01 0.1 1 1 00 100 Study Experimental Control Xu2021 1 54 8 54 Chang2020 1 2 319 15 319 Song2020 0 55 1 55 Chang2013 1 49 3 47 Fan2019 1 49 4 49 Common effect model 842 837 Common effect model 842 837 Common effect model 842 837 Kie2015 2 36 5 36 Xu2021 2 30 319 42 319 Song2020 3 355 10 55 Xu2021 3 147 68 144 Heterogeneity: $l^2 = 0\%$, $r^2 = 0.0452$, $p = 0.59$ Study Common effect model 749 744 Heterogeneity: $l^2 = 32\%$, $r^2 = 0.1762$, $p = 0.17$ Common effect model 749 Common effe	Prediction interval					—		[0.33; 0.56]	
Experimental Events Total	Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0.7	78				1		
Experimental StudyControl Events Total Events TotalOdds RatioOR95%-Cl Weig $Xu2021$ 154854					0.	01 0.1 1 10	100		
StudyEvents Total Events TotalOdds RatioOR95%-CI WeigXu2021154854		Experin	nental	c	ontrol				
Xu2021 1 54 8 54 1 1 1 0.01; 0.90] 13.5 Zhang2021 3 147 4 144 1 1 1 1 0.01; 0.90] 13.5 Mao2020 12 319 15 319 1 1 1 1 0.01; 0.90] 13.5 Song2020 0 55 1 55 1 0.55 Liu2022 1 40 8 40 1 1 0.01; 0.90] 13.5 Oragonal control contecont control control conterval control control cont	Study	Events	Total	Events	5 Total	Odds Ratio	OF	95%-C	Weigh
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Xu2021	1	54	2	54	i	0.11	[0 01· 0 90]	13 5%
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	7u2021	2	147		1 1 1 1		0.11		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Zhang2021	3	147	4	+ 144 - 240		0.73		
Song2020 0 0 55 1 55 1 55 0 0 0 0 0 55 1 0 55 0 0 0 0	Mao2020	12	319	15	5 319	÷ •	0.79	[0.36; 1.72]	24.8%
Liu2022 1 1 40 8 40 $0.10 \ [0.01; 0.86] 13.4$ Lv2019 1 49 3 47 $0.32 \ [0.06; 0.43] [0.03; 2.18] 6.7$ Shang2013 1 49 3 47 $0.33 \ [0.07; 2.04] 8.3$ Common effect model 842 837 $0.10 \ [0.01; 0.86] 13.4$ Heterogeneity: $I^2 = 0.0452$, $p = 0.59$ Study Events Total Events Total 0 0dds Ratio 0 R 95%-Cl Weig Xie2015 2 36 5 36 $0.11 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.51 \ 2 \ 0.10 \ 0.11 \ 0.51 \ 0.10 \ 0.11 \ 0.51 \ 0.11 \ 0.11 \ 0.51 \ 0.10 \ 0.11 \ 0.51 \ 0.10 \ 0.11 \ 0.51 \ 0.10 \ 0.11 \ 0.51 \ 0.10 \ 0.11 \ 0.51 \ 0.11 \ 0.51 \ 0.11 \ 0.11 \ 0.51 \ 0.10 \ 0.11 \ 0.51 \ 0.11 \ 0.51 \ 0.11 \ 0.11 \ 0.51 \ 0.11 \ 0.51 \ 0.11 \ 0.51 \ 0.11 \ 0.51 \ 0.11 \ 0.51 $	Song2020	0	55	1	55		0.33	[0.01; 8.21	2.6%
Lv2019 1 49 4 49 Fan2019 6 69 12 69 Zhang2013 1 49 3 47 Xie2010 2 60 5 60 Prediction interval Heterogeneity: $l^2 = 0.0452$, $p = 0.59$ Xie2015 2 36 5 36 Xu2021 6 54 23 54 Zhang2021 43 147 68 144 Mao2020 30 319 42 319 Liu2022 1 40 8 40 Liu2022 2 1 40 8 40 Liu2022 3 1 40 8 40 Liu2022 3 1 40 8 40 Liu2022 3 1 40 8 40 Liu2022 49 7 47 Common effect model 749 744 Prediction interval Heterogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ All the terogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$	Liu2022	1	40	6	3 40		0.10	[0.01; 0.86]	13.4%
Fan201966691269 12 69 12 14 14 13 47 14 14 13 47 14 14 13 47 13 10.03 3.051 5.2 Xie2010260560 10 10.51 2 10.02	Lv2019	1	49	4	49		0.23	[0.03; 2.18]	6.7%
Zhang2013 1 49 3 47 0.31 $[0.03; 3.05]$ 5.2 Xie2010 2 60 5 60 0 0.31 $[0.03; 3.05]$ 5.2 Common effect model 842 837 0.1 0.51 2 0.38 $[0.07; 2.04]$ 8.3 Prediction interval Heterogeneity: $l^2 = 0.0452$, $p = 0.59$ 0.1 0.51 2 0.43 $[0.27; 0.68]$ 100.0 Study Experimental Control Odds Ratio OR 95%-Cl Weig Xie2015 2 36 5 36 0.36 $[0.07; 2.02]$ 3. Xie2014 6 54 23 54 0.43 $[0.7; 2.02]$ 3. Xia2021 43 147 68 144 0.46 $[0.29; 0.75]$ 0.36 $0.7; 2.02]$ 3. Mao2020 30 319 42 319 49 0.42 0.22 $0.04; 1.09]$ 0.22 0.024 $0.05; 1.24]$ 0.42 $0.05; 1.24]$ 0.42 $0.05; 1.24]$ 0.42 $0.05; 1.24]$ 0.42	Fan2019	6	69	12	2 69		0.45	[0.16; 1.28]	18.8%
Xie2010 2 60 5 60 0.38 [0.07; 2.04] 8.3 Common effect model 842 837 0.1 0.51 2 10 0.43 [0.27; 0.68] 100.0 [0.20; 1.01] Prediction interval Experimental Control Odds Ratio OR 95%-Cl Weight 0.36 [0.07; 2.02] 3. Xie2015 2 36 5 36 0.43 [0.07; 2.02] 3. Xie2015 2 36 5 36 0.43 [0.07; 2.02] 3. Xie2015 2 36 5 36 0.10 0.17 [0.06; 0.46] 14. Mao2020 30 319 42 319 44 0.46 [0.29; 0.75] 33. Wang2022 2 49 8 49 44 44 0.42 [0.01; 0.86] 5. Wang2013 2 49 7 47 44 44 44 0.42 10.15; 1.24] 4. Heterogeneity: $l^2 = 32\%, \tau^2 = 0.1762, p = 0.17$ 744 44 44 10.51 2	Zhang2013	1	49	3	3 47	_	0.31	[0.03: 3.05	5.2%
Common effect model842837 0.43 [0.27; 0.68] 100.0Prediction interval Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0452$, $p = 0.59$ 0.1 0.51 2 10 0.43 [0.27; 0.68] 100.0StudyExperimental Events Total Events TotalControl Odds Ratio 0.43 [0.27; 0.68] 100.0Xie20152 365 36 0.1 0.51 2 10 0.36 [0.07; 2.02] 3.Xie20152 365 36 0.43 [0.27; 0.68] 100.0Xie20146 5423 54 0.1 0.51 2 10 0.36 [0.07; 2.02] 3.Nao202030 31942 319 0.43 [0.27; 0.68] 100.0Song20203 55 10 55 0.44 [0.29; 0.75] 33.Nang20222 498 49Liu20221 408 40Zhang20132 497 47Prediction interval Heterogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ 0.1 0.51 2 10	Xie2010	2	60	5	5 60		0.38	0.07; 2.04	8.3%
Prediction interval Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0452$, $p = 0.59$ Out (0.21), 0.05]Out (0.21), 0.05]StudyExperimental Events TotalControl Events TotalOdds RatioOR95%-CIXie20152<36	Common effect mode	1	842		837		0.43	10 27 0 68	100.0%
Treatedom interval Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0452$, $p = 0.59$ (1.10, 51 2)Experimental Control StudyOdds RatioOR 95%-CI WeigXie20152 365 360.10.36 [0.07; 2.02] 3.Xu20216 5423 540.10.11 [0.06; 0.46] 14.Zhang202143 14768 14440.46 [0.29; 0.75] 33.Mao202030 31942 3190.1Song20203 55 1055Liu20221 408 40Zhang20132 497 47Common effect model749744Prediction interval Heterogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ 0.1	Prediction interval	-1	042		007	- -	0.40	[0.27, 0.00]	100.07
Experimental StudyControl Events TotalControl Events TotalOdds RatioOR95%-CI WeightXie20152365360.360.07; 2.02]3.Xu202165423540.170.06; 0.46]14.Zhang202143147681440.460.29; 0.75]33.Mao202030319423190.680.42; 1.12]26.Song202035510550.260.07; 1.00]6.Wang20222498490.220.04; 1.09]5.Liu20221408400.220.04; 1.09]5.Zhang20132497470.420.021; 0.86]5.Prediction interval Heterogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ 0.10.51210	Heterogeneity: $I^2 = 0\%$,	$t^2 = 0.0452$	2, p = 0.	.59				[0.20, 1.01]	
StudyEventsTotalEventsTotalOdds RatioOR95%-CIWeightXie2015236536 $$		Experim	ental	C	ontrol	0.1 0.51 2 10			
Xie2015236536Xu20216542354Zhang20214314768144Mao20203031942319Song20203551055Wang2022249849Liu2022140840Zhang2013249747Common effect model7497440.42Prediction interval Heterogeneity: $l^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ 0.10.51210	Study	Events	Total	Events	Total	Odds Ratio	OF	8 95%-C	l Weigl
Xu2021 6 54 23 54 0.17 [0.06; 0.46] 14. Zhang2021 43 147 68 144 0.46 [0.29; 0.75] 33. Mao2020 30 319 42 319 0.68 [0.42; 1.12] 26. Song2020 3 55 10 55 0.10 [0.06; 0.46] 14. Wang2022 2 49 8 49 0.46 [0.29; 0.75] 33. Liu2022 1 40 8 40 0.22 [0.04; 1.09] 5. Zhang2013 2 49 7 47 0.10 [0.01; 0.86] 5. Ocamon effect model 749 744 0.42 [0.05; 1.24] 4. O.1 0.51 2 10 0.42 [0.11; 1.15] [0.11; 1.15]	Xie2015	2	36	5	36		0.36	6 [0.07: 2.02	3.39
Zhang2021 43 147 68 144 0.46 [0.29; 0.75] 33. Mao2020 30 319 42 319 0.46 [0.29; 0.75] 33. Song2020 3 55 10 55 0.46 [0.29; 0.75] 33. Wang2022 2 49 8 49 0.46 [0.29; 0.75] 33. Liu2022 1 40 8 40 0.22 [0.04; 1.09] 5. Zhang2013 2 49 7 47 0.10 [0.01; 0.86] 5. Ocemon effect model 749 744 0.42 [0.31; 0.56] 100. Prediction interval 0.1 0.51 2 10 0.42 [0.31; 0.56] 100.	Xu2021	6	54	23	54	i	0 1	10.06: 0.46	14.29
LiningLor 40 147 60 16 1029, 0.10 133 355 10 55 0.26 10.07; 1.00 6. 0.22 [0.04; 1.09] 5. 0.10 [0.01; 0.86] 5. 0.10 [0.01; 0.86] 5. 0.24 [0.05; 1.24] 4. Common effect model 749 744 744 60 0.42 [0.31; 0.56] 100. [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.15] [0.11; 1.	Zhang2021	43	147	69	144		0.14	S [0 20 0 75	3 33 80
Machazor 30 315 42 315 0.000 $[0.42; 1.12]$ 26. Song2020 3 55 10 55	Mac2020	20	310	10	310		0.40	8 [0 / 2 · 1 / 2	1 26 50
Song2020 3 55 10 55 $+$ 0.26 [0.07; 1.00] 6. Wang2022 2 49 8 49 $-+-$ 0.22 [0.04; 1.09] 5. Liu2022 1 40 8 40 $-+-$ 0.10 [0.01; 0.86] 5. Zhang2013 2 49 7 47 $-+-$ 0.24 [0.05; 1.24] 4. Common effect model 749 744 $$ $$ 0.42 [0.31; 0.56] 100. Prediction interval $$ $ $	Na02020	30	519	42	519		0.00	5 [0.42, 1.12]	.j 20.5
vvang2022 2 49 8 49 ************************************	Song2U2U	3	55	10	55		0.20		y 0.6
Liu2022 1 40 8 40 \bullet 1 40 8 40 8 40 \bullet 1 40 8 40 8 40 \bullet 1 40 8 40 8 40 8 40 8 40 8 40 8 40 8 40	Wang2022	2	49	8	49		0.22	2 [0.04; 1.09	g 5.3°
Zhang2013 2 49 7 47 0.24 0.24 0.05 ; 1.24 4. Common effect model 749 744 0.42 0.31 ; 0.56] 100. 0.11 ; 1.15] Prediction interval 0.1 0.51 2 100 0.11 ; 1.15]	Liu2022	1	40	8	40		0.10	0 [0.01; 0.86	6] 5.4°
Common effect model 749 744 Prediction interval Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ 0.1 0.5 1 2 10 0.42 [0.31; 0.56] 100. [0.11; 1.15]	Zhang2013	2	49	7	47		0.24	1 [0.05; 1.24	-] 4.8º
Prediction interval [0.11; 1.15] Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ 0.1 0.51 2 10	Common effect model		749		744	\$	0.42	2 [0.31: 0.56	1 100.0
Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.1762$, $p = 0.17$ 0.1 0.5 1 2 10	Prediction interval					÷		[0.11; 1.15	5
0.1 0.51 2 10	Heterogeneity: $I^2 = 32\%$	$r^2 = 0.1762$	2, p = 0	.17					-
						0.1 0.51 2 10			
	7								

as hypotension, dizziness, headache and nausea. However, these reactions were common and relatively mild. None of the studies reported serious adverse effect that affected the course of the study, such as electrolyte disorders, severe hepatic and renal deficits, etc. Therefore, the addition of QSYQ did not cause significant or dramatic adverse events, and had a good safety and tolerability profile compared to the control group (Table 2).

3.4. HFrEF

10, 3, 5, 8, 6, 13, 20, 6, 9 and 6 studies compared RARs, incidence of MACE, ACM, CERs, MLHFQ scores, 6MWD,

LVEF, BNP, NT-ProBNP, and LVEDD, respectively, with respect to HFrEF, and the results were consistent with the above. [RARs: $I^2 = 0\%$, OR = 0.43, 95% CI (0.32, 0.58), P < 0.01; incidence of MACE: $I^2 = 38\%$, OR = 0.56, 95% CI (0.36, 0.89), P < 0.01; ACM: $I^2 = 1\%$, OR = 0.48, 95% CI (0.28, 0.81), P < 0.01; CERs: $I^2 = 0\%$, OR = 1.97, 95% CI (1.48, 2.61), P < 0.01; MLHFQ scores: $I^2 = 98\%$, SMD = -2.49, 95% CI (-4.68, -0.29), P < 0.01; 6MWD: $I^2 = 96\%$, SMD = 1.63, 95% CI (0.87, 2.39), P < 0.01; LVEF: $I^2 = 93\%$, SMD = 1.03, 95% CI (0.66, 1.39), P < 0.01; BNP: $I^2 = 93\%$, SMD = -1.28, 95% CI (-2.09, -0.48), P < 0.01; NT-ProBNP: $I^2 = 84\%$, SMD = -1.29, 95% CI (-1.69, -0.88), P < 0.01; LVEDD: $I^2 = 88\%$, SMD = -1.03, 95% CI (-1.21, -0.84), P < 0.01].

Study	Total Mean SD To	otal Mean SD	Difference	SMD 95%-CI Weigl
Wu2013	30 30.71 12.2500	30 72.82 6.0400	→ :	-4.30 [-5.25; -3.36] 5.7
Zhang2013	30 39.37 10.2300	30 42.33 10.9300		-0.28 [-0.78; 0.23] 5.9
Lin2014	29 37.31 3.9300	27 40.44 4.2000		-0.76 [-1.30; -0.22] 5.9
lang2017	70 26.59 4.7500	70 35.11 5.0800		-1.72 [-2.11; -1.33] 6.0
Zhang2017	44 40.37 8.9300	42 47.21 10.3600		-0.70 [-1.14 ; -0.27] 6.0
Zhang2019	88 24.90 4.9000	81 27.05 5.5300		
Zhang2020	45 50.45 6.1400	45 59.57 6.6200		
Liu2021	51 23 67 3 8100	51 27 65 3 9400		-3.43 $[-4.10, -2.74]$ $5.8-1.02$ $[-1.43; -0.61]$ 6.0
Yang2021	32 14 98 1 2900	28 23 36 1 2500		-6.50 [-7.81: -5.20] 5.4
Yao2021	42 18.97 9.5200	42 32.07 10.9500		-1.27 [-1.74; -0.79] 6.0
Lian2022	30 31.57 1.9600	30 35.03 2.2800		-1.61 [-2.19; -1.02] 5.9
Shi2022	30 32.40 9.0000	30 42.40 14.5700		-0.82 [-1.34; -0.29] 5.9
Whang2022	51 23.06 2.1100	51 27.53 2.4000		-1.96 [-2.44; -1.49] 5.9
Zhang2022	48 19.89 5.2900	45 33.15 9.5100		-1.72 [-2.20; -1.25] 5.9
Zhu2022	48 32.06 1.7400	46 50.56 3.0900		-7.36 [-8.51; -6.21] 5.6
Random effects mor	319 23.36 17.2300	319 26.54 17.6700		-0.18 [-0.34, -0.03] 8.0
Prediction interval Heterogeneity: $I^2 = 96\%$	$\tau^2 = 4.0348, p < 0.01$			[-6.44; 2.38]
Study	logOR SE(ogOR)	-5 0 5 Odds Ratio	OR 95%-Cl Weight
Bao2020	1 0895	0.4165		2.07 [1.31: 6.72] 2.7%
Cai2010	1 3 1 8 0	0.4717		2.37 [1.31, 0.72] $2.7%$
	0.7669	0.4/1/		2.7 + [1.40, 3.42] = 2.1%
	0.7666	0.3303		2.15 [1.11, 4.16] 4.2%
Chen2011	0.6913	0.4103		2.00 [0.89, 4.46] 2.8%
Ding2020	0.8516	0.5692		2.34 [0.77; 7.15] 1.5%
Fu2019	1.0519	0.4602		2.86 [1.16; 7.06] 2.2%
Hao2015	1.3491	0.3610		3.85 [1.90; 7.82] 3.7%
Hu2017	1.1825	0.5599		3.26 [1.09; 9.78] 1.5%
Jia2012	0.6740	0.4360	+ =	1.96 [0.83; 4.61] 2.5%
Li2017	1.0149	0.4061		2.76 [1.24; 6.12] 2.9%
Ma2019	0.5283	0.3179	+	1.70 [0.91; 3.16] 4.7%
Mao2018	1.2512	0.3700		3.49 [1.69; 7.22] 3.5%
Qi2010	0.8154	0.5018	+	2.26 [0.85; 6.04] 1.9%
Ren2017	0.1512	0.4128	<u>+</u>	1.16 [0.52; 2.61] 2.8%
Shao2014	0.7139	0.4613		2.04 [0.83; 5.04] 2.2%
Shi2021	0.6407	0.3831		1.90 [0.90; 4.02] 3.2%
Su2021	0.9703	0.4225		2.64 [1.15: 6.04] 2.7%
Wang2010	0.3907	0.3050		1.48 [0.81: 2.69] 5.1%
Wang2011	0 2345	0 4405		1 26 0 53 3 00 2 5%
Wang2018	0.6923	0 3934		2 00 [0 92 4 32] 3 1%
Wang2019	0.9852	0.4753		2.68 [1.05; 6.80] 2.1%
Wang2020	1 0818	0.4161		2.00 [1.00, 0.00] 2.170
Wu2015	0.6153	0.2540		1 85 [1 12: 3 05] 7 3%
1442019	0.6737	0.2343		1.06 [0.03: 4.13] 3.3%
Wu2018	1 6046	0.3790		5 44 [2 00: 14 20] 2 0%
VVU2020	1.6946	0.4009	1	5.44 [2.09, 14.20] 2.0%
Xiang2015	0.8667	0.4401		2.38 [1.00; 5.64] 2.5%
Xiao2020	1.0275	0.4051		2.79 [1.26; 6.18] 2.9%
Yin2014	0.4741	0.6067		1.61 [0.49; 5.28] 1.3%
Yu2015	0.8734	0.4324		2.39 [1.03; 5.59] 2.5%
Yuan2016	0.6659	0.2871		1.95 [1.11; 3.42] 5.8%
Zeng2018	1.5706	0.4931		4.81 [1.83; 12.64] 2.0%
Zhang2012	0.5140	0.3058	+- 	1.67 [0.92; 3.04] 5.1%
Zhang2021	1.0777	0.4207		2.94 [1.29; 6.70] 2.7%
Common effe	ct model		\$	2.25 [1.97; 2.58] 100.0%
Prediction in	lei vai			[1.90; 2.59]
Heterogeneity:	$I^2 = 0\%, \tau^2 = 0, p = 0.88$	0.1	0.5 1 2 10	
Heterogeneity:	$I^2 = 0\%, \tau^2 = 0, p = 0.88$			

3.5. Prediction interval

Prediction intervals are not often reported but are more insightful and well suited to assess differences in intervention effects across settings (19). We observed that the prediction intervals and their respective 95% CIs in RARs, CERs, and LVESV almost overlapped, which may be related to the low heterogeneity of the studies. However, in other metrics, such as 6MWD, the combined effect size was 1.87 with a 95% CI (1.33, 2.41); yet, the prediction intervals ranged from -1.34 to 5.09 and contained values of zero or below zero. Similar results were observed in ACM (0.20, 1.01), incidence of MACE (0.11, 1.15), MLHFQ scores (-6.44, 2.38), LVEF (-0.60, 2.76), BNP (-5.35, 1.21), NT-ProBNP (-12.80, 7.26), LVEDD (-2.20, 0.37), LVESD (-2.31, 0.27), LVEDV (-8.12, 5.14). These suggest that QSYQ may not always be beneficial to patients in clinical practice, and may even be mildly harmful.

3.6. Subgroup analysis and meta-regression analysis

We performed subgroup analysis of 6MWD, LVEF, BNP, NTproBNP, and LVEDD according to regimen, and in all subgroups

Study	Total	Exp Mean	erimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight
time = 2–4w										
An2010	64	460.00	36.1100	64	442.00	31.1900		0.53	[0.18; 0.88]	3.1%
Zhang2012	79	358.00	40.0000	79	280.00	34.0000		2.09	[1.70; 2.48]	3.1%
Gu2014	65	459.21	35.1000	65	441.98	30.1800	+	0.52	[0.17; 0.87]	3.1%
Xiang2015	43	359.00	36.0000	43	263.00	28.0000		2.95	[2.33; 3.57]	3.0%
Yuan2016	90	364.00	21.0000	90	279.00	22,0000		3.94	3.43: 4.441	3.1%
Hu2017	28	398 18	102 0400	28	314 46	95 0800		0.84	[0.29] 1.38]	3.0%
Ren2017	58	426 15	68 1500	42	388.62	60.8500		0.57	[0.17:0.98]	3.1%
Bao2020	45	120.10	93 1000	45	365 70	105 6000		0.50	$\begin{bmatrix} 0.17, 0.00 \end{bmatrix}$	3 1%
Ding2020	-40	424.30	42 9000	-40	260.60	20,4000		1 1 0	$\begin{bmatrix} 0.17, 1.01 \end{bmatrix}$	2.0%
	20	410.40	43.8000	20	402.25	39.4000		1.10		3.0%
vvu2020	40	433.78	24.7200	40	402.35	21.3900		1.35	[0.86, 1.83]	3.1%
Su2021	44	411.89	69.6300	44	364.48	73.5200		0.66	[0.23; 1.09]	3.1%
Zhang2021	45	439.64	66.6300	45	409.84	59.6970		0.47	[0.05; 0.89]	3.1%
Li2022	60	520.35	25.6600	60	420.45	23.4500		4.04	[3.41; 4.67]	3.0%
Random effects model	689			673			\diamond	1.51	[0.80; 2.21]	39.8%
Heterogeneity: $I^2 = 96\%, \tau^2$	= 1.64	19, p < (0.01							
time = 8w	40	442.00	66 7000	40	264.40	75 1000		0.07	[0.00:4.40]	2 40/
	40	412.80	00.7000	40	304.40	15.1000		0.67	[0.22; 1.13]	3.1%
Shi2012	42	427.00	26.8000	42	322.00	26.5000		3.90	[3.16; 4.64]	3.0%
Ma2013	24	530.50	16.6000	24	482.20	15.8000		2.93	[2.10; 3.76]	2.9%
Qin2013	60	550.40	40.7000	54	480.80	30.6000		1.91	[1.46; 2.35]	3.1%
Yu2015	40	431.60	13.3000	40	330.50	14.0000		7.33	[6.09; 8.58]	2.7%
Wang2018	48	562.50	41.3000	48	464.70	32.8000		2.60	[2.05; 3.15]	3.0%
Random effects model	254			248				3.18	[1.40: 4.96]	17.8%
Heterogeneity: $I^2 = 96\%, \tau^2$	= 4.80	11, p < (0.01						,	
time = 12w										
Wu2015	120	430.20	33.5000	120	333.90	36.7000	+	2.73	[2.38; 3.09]	3.1%
Xie2015	36	449.10	60.3000	36	378.20	57.4000		1.19	[0.69; 1.69]	3.1%
Wang2016	20	569.61	40.6100	20	463.62	34.7100		2.75	[1.86; 3.64]	2.9%
Liu2017	30	425.00	26.0000	30	399.00	22.0000		1.07	[0.52; 1.61]	3.0%
Wu2017	30	368.30	65.2000	30	265.80	71.6000		1.48	[0.90; 2.05]	3.0%
Sona2018	40	365.00	40.0000	40	286.00	34.0000		2.11	1.56: 2.66	3.0%
Wu2018	50	368.00	18 0000	50	285.00	20,0000		4 33	3 60 5 06	3.0%
Cai2019	35	470.91	181 4200	33	395.48	119 6200		0.48	[-0.00; 0.97]	3.1%
Wang2020	47	470.68	81 3200	45	102.48	73 6700		0.40	$\begin{bmatrix} 0.00, 0.07 \end{bmatrix}$	3 1%
Bandom offosts model	41	470.00	01.5200	404	402.40	13.0700		4.07	[0.44, 1.50]	3.1/0
candom effects model	400			404				1.07	[1.09; 2.05]	21.3%
Heterogeneity: $I^- = 94\%$, τ^-	= 1.35	04, p < 0	0.01							
ime = 24w										
Nu2013	30	473.60	21.6500	30	353.87	65.4000		2.43	[1.75; 3.10]	3.0%
Yin2014	20	344.50	136.5000	20	425.50	128.5000		-0.60	[-1.23: 0.04]	3.0%
Cui2020	40	537.00	151,9000	35	451.00	130,5000		0.60	[0.13: 1.06]	3.1%
Xu2021	54	520.32	25,6500	54	420 55	23,5000		4 03	[3.36 4 69]	3.0%
Mao2020	310	374 47	103 0900	310	340 71	104 5700		0.32	[0.17:0.48]	3.1%
Random effects model	463	517.71	.00.0000	452	540.71	134.5700		1 3/	[-0.27·2.96]	15.2%
Heterogeneity: $I^2 = 97\% r^2$	= 3.31	18 n < 1	0.01	-10				1.54	[0.21, 2.30]	10.4 /0
neterogeneity. 7 – 3770, t	- 5.51	10, p < t								
Random effects model	1814			1783			🗇	1.87	[1.33; 2.41]	100.0%
Prediction interval									[-1.34; 5.09]	
Heterogeneity: $I^2 = 97\%$, τ^2	= 2.41	23, p < 0	0.01				1 1 7			
Test for subgroup difference	es: $\chi_3^2 =$	3.26, df	= 3 (p = 0.	35)			-5 0 5			
5										

the results were consistent with those described above. Although negative results were obtained in some subgroups (subgroup 24 weeks in 6MWD, subgroup 24 weeks in LVEF, subgroups 8 weeks and 12 weeks in NT-proBNP, and subgroup 8 weeks in LVEDD), there still showed a trend toward improvement. As the heterogeneity remained high, we performed meta-regression analysis of 6MWD and LVEF according to the quality of literature and mean age. The results showed that mean age (p = 0.0082 <0.01) and literature quality (p = 0.0031 < 0.01) contributed to 24.49% of the heterogeneity $(tau^2 = 1.7636, R^2 = 24.49\%)$ for 6MWD, and, literature quality (p = 0.0007 < 0.001) contributed to 20.07% of the heterogeneity (tau² = 0.5364, R^2 = 20.07%) for LVEF. We therefore pooled high-quality literature and analyzed it by age and duration of treatment. We found a significant decrease in heterogeneity in the 60-65-year-old and 12 weeks-duration subgroups for 6MWD, and in the more-than-70-year-old and 2-4 weeks-duration subgroups for LVEF. Effect sizes did not change significantly across groups. There was no evidence that the quality of literature and mean age contributed to the heterogeneity of BNP, NT-proBNP, and LVEDD (P > 0.05) (Table 3).

3.7. Sensitivity analysis

A sensitivity analysis was conducted to verify the stability and accuracy of the meta-analysis results. In the indicator LVEDV, the overall heterogeneity decreased (from 95% to 75%) after the document Yu 2015 was deleted, and the result of the combined effect size was reversed to be statistically significant (P < 0.01). We found that this document contributed to the largest heterogeneity through the Baujat plot. Among the other indicators, there was no significant

Study	Total N	Exper Nean	imental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight
time = 4w										
Xiang2015	43 5	52.00	6.8000	43	47.00	5.1000		0.82	[0.38; 1.27]	2.3%
Hu2017	28 4	12.96	4.8500	28	39.46	3.3400	<u>-</u>	0.83	[0.28; 1.38]	2.2%
Che2018	50 6	50.27	8.6500	50	52.73	7.5500		0.92	[0.51; 1.33]	2.3%
Mao2018	60 4	17.20	2.2000	60	42.50	2.3000		2.08	[1.63; 2.52]	2.2%
Liu2019	27 5	50.43	5.9600	27	40.56	6.6500		1.54	[0.93; 2.15]	2.1%
Bao2020	45 4	46.10	3.9000	45	42.40	4.0800	1 <u>=</u>	0.92	[0.48; 1.35]	2.3%
Ding2020	28 4	46.33	6.1400	28	41.23	3.2600		1.02	[0.46; 1.58]	2.2%
Zhang2020	40 6	50.31	6.8400	40	52.65	7.4800	-	1.06	[0.59; 1.53]	2.2%
Su2021	44 4	17.11	2.8400	44	42.18	4.5100		1.30	[0.84; 1.76]	2.2%
Zhang2021	45 4	13.89	4.0180	45	40.27	2.9720	=	1.02	[0.58; 1.46]	2.3%
LI2U22	470	53.65	5.2000	470	58.42	6.2500		0.90	[0.53; 1.28]	2.3%
Heterogeneity: $l^2 = 620$	470 2 - 0.080	E E	0.01	470				1.12	[0.89; 1.35]	24.3%
Heterogeneity: $T = 02.70, \pi$	- 0.005	5, p <	0.01							
time = 8w										
lia2012	40 F	52 80	7 4000	40	45 40	10 6000	<u> </u>	0.80	[0.35:1.26]	2.2%
Shi2012	42 5	51 60	2 9000	42	45 10	3 9000		1 87	[1.36:2.39]	2.2%
Ma2013	24 5	53 20	4 4000	24	49.00	4 0000		0.98	[0.38.1.58]	2.1%
Qin2013	60 5	53.20	5.6000	54	49.00	3,8000	1	0.86	[0.48: 1.25]	2.3%
Yu2015	40 5	56.40	3.2000	40	48.20	3.0000	· · · · · ·	2.62	[2.01: 3.22]	2.1%
Li2017	47 4	15.38	3.4800	47	39.82	2.7800		1.75	[1.27: 2.23]	2.2%
Wang2018	48 4	15.20	4.2000	48	37.10	2.3000		2.37	[1.85; 2.90]	2.2%
Song2020	55 5	57.22	6.8300	55	55.75	6.2200		0.22	[-0.15; 0.60]	2.3%
Random effects model	356			350				1.42	[0.84; 2.01]	17.7%
Heterogeneity: $I^2 = 92\%$, τ^2	² = 0.646	67, p <	0.01						- /	
time = 12w										
Shao2014	36 4	16.20	6.4000	37	43.10	5.7000		0.51	[0.04; 0.97]	2.2%
Han2015	30 4	48.37	3.9100	30	45.07	2.9400		0.94	[0.41; 1.48]	2.2%
Xie2015	36 4	16.30	8.2000	36	36.20	9.1000		1.15	[0.65; 1.65]	2.2%
Wu2015	120 5	55.70	8.7000	120	47.70	5.1000		1.12	[0.85; 1.39]	2.4%
Liu2017	30 5	53.90	3.6000	30	42.10	3.2000		3.42	[2.61; 4.23]	1.9%
Zeng2018	35 6	50.33	8.6100	35	52.80	6.9700		0.95	[0.45; 1.45]	2.2%
Jia2018	29 6	59.80	11.5400	29	58.08	7.3200		1.20	[0.63; 1.76]	2.2%
Wu2018	50 5	51.10	7.3000	50	46.10	8.3000		0.63	[0.23; 1.04]	2.3%
Cal2019	35 4	17.09	11.2600	33	47.03	10.6600		0.01	[-0.47; 0.48]	2.2%
Ma2019	73 5	51.36	6.1100	73	47.53	6.0200		0.63	[0.30; 0.96]	2.3%
Wang2019	40 4	15.59	8.5000	40	41.48	6.2000		0.55	[0.10; 0.99]	2.2%
Wang2020	47 5	51.47	7.3500	45	47.53	6.8100	=	0.55	[0.13; 0.97]	2.3%
VVU2020	40 5	28.61	3.4700	40	46.07	2.3300		4.20	[3.40; 5.00]	1.9%
	40 0	JJJ.∠J	6.8500	40	40.02	TU.8300		0.01		2.3%
Shi2021	51 6	51 74	5 1000	51	47.09	4 4700		1.63	$\begin{bmatrix} 0.22, 1.19 \end{bmatrix}$	2.270
5112021 Fu2019	36 5	53 01	3 5900	36	43.00	3 2800		3 39	[2 66: 4 12]	2.2%
Random effects model	771	55.91	3.3300	768	42.12	3.2000		1 27	[2.00, 4.12]	37 3%
Heterogeneity: $I^2 = 92\%$	$^{2} = 1.232$	0 0 0	0.01	700				1.21	[0.75, 1.02]	51.570
ficterogeneity. 7 = 52.70, t	- 1.202	.0, p <	0.01							
time = 24w										
Wu2013	30 5	55.77	2.0600	30	55.53	1.7800		0.12	[-0.38: 0.63]	2.2%
Yin2014	20 5	52.50	11.5000	20	55.50	8.5000		-0.29	[-0.91: 0.33]	2.1%
Cui2020	40 4	16.00	11.5000	35	45.00	10.3000		0.09	[-0.36; 0.54]	2.2%
Lin2021	50 4	48.88	5.1200	50	43.36	5.2200		1.06	[0.64; 1.48]	2.3%
Xu2021	54 6	53.63	5.2200	54	58.45	6.2400		0.89	[0.50; 1.29]	2.3%
Zhang2021	147 4	47.12	3.9100	144	46.37	1.6100		0.25	[0.02; 0.48]	2.4%
Mao2020	319 4	13.78	11.0100	319	43.44	9.5600		0.03	[-0.12; 0.19]	2.4%
Random effects model	660			652			\diamond	0.32	[-0.03; 0.67]	15.9%
Heterogeneity: $I^2 = 83\%$, τ^2	2 = 0.175	55, p <	0.01							
time = more than 24w										
vvang2010	89 5	5.00	6.3000	76	48.00	6.2000		1.11	[0.78; 1.44]	2.3%
Feng2015	43 4	44.70	3.6000	43	42.60	4.5000		0.51	[0.08; 0.94]	2.3%
Random effects model	132	0.5	0.02	119				0.83	[0.24; 1.42]	4.6%
Heterogeneity: $I^2 = I9\%$, τ^2	= 0.143	9, p =	0.03							
Dandam offeste medal	2200			2250				4 00	10 02. 4 221	100.0%
Prediction interval	2389			2009				1.08	[0.63; 1.33]	100.0%
Heterogeneity: $I^2 = 9104$	2 = 0.679	1 n -	0.01						[-0.00; 2.76]	
Test for subgroup difference	= 0.076 es: $\gamma^2 = 1$	18.86	df = 4 (p - 1)	< 0.01)			-4 -2 0 2 4			
	x4			0.01)			. 2 5 2 4			
FIGURE 6										
Forest plot of LVEF.										
-										

change in heterogeneity and effect size, which suggests that the results of the meta-analysis were stable. See specific details at **Supplementary Figure S2–S4**.

3.8. Heterogeneity analysis

The vast majority of subgroup analysis still had high heterogeneity, so we plotted Galbraith plots and Baujat plots

(Figure 9 and Supplementary Figure S5). We found 11, 26, 16, 12, 9, 10, 5, and 2 studies to be the major sources of heterogeneity for MLHFQ scores, 6MWD, LVEF, BNP, NT-ProBNP, LVEDD, LVESD, and LVEDV, respectively. Heterogeneity was eliminated or significantly reduced by deleting the above outlier studies before re-performing the pooled analysis, but the combined effect sizes did not change significantly. [MLHFQ scores: SMD = -1.00, 95% CI (-1.19, -0.81), $I^2 = 28\%$, P_{heterogeneity} = 0.23; 6WMD: SMD =

Study	Total	Experimental Mean SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weigh
time = 4w Zhang2012 Xiang2015 Yuan2016 Ren2017 Zhang2021 Random effe Heterogeneity	79 43 58 45 ects model 315 : $l^2 = 98\%$, $\tau^2 = 3.96$	908.00 65.0000 377.00 62.0000 1062.00 61.0000 171.60 98.5000 355.92 53.7100 08, p < 0.01	79 43 90 42 45 299	1050.00 756.00 1495.00 351.50 379.05	180.0000 98.0000 124.0000 239.3000 50.3990	**	-1.04 -4.58 -4.41 -1.04 -0.44 -2.28	[-1.38; -0.71] [-5.40; -3.76] [-4.96; -3.87] [-1.46; -0.61] [-0.86; -0.02] [-4.05; -0.52]	6.4% 6.0% 6.3% 6.4% 6.4% 31.4%
time = 8w Ma2013 Qin2013 Li2017 Random effe Heterogeneity	24 60 47 ects model 131 : $J^2 = 93\%$, $\tau^2 = 1.79$	142.00 20.6000 140.60 20.5000 136.52 14.3500 67, <i>p</i> < 0.01	24 54 47 125	186.00 186.50 217.39	18.8000 20.7000 19.8700	*	-2.19 -2.21 -4.63 -2.99	[-2.92; -1.47] [-2.68; -1.74] [-5.41; -3.84] [-4.56; -1.43]	6.1% 6.3% 6.0% 18.5%
time = 12w Chen2011 Wu2015 Wang2016 Song2018 Wu2018 Random effe Heterogeneity	$\begin{array}{c} 43 \\ 120 \\ 20 \\ 40 \\ 50 \\ 17 \\ 17 \\ 273 \\ 17 \\ 292\%, \tau^2 = 0.96 \end{array}$	4172.00 415.0000 1412.00 466.0000 170.61 40.6100 905.00 65.0000 76.00 10.3000 77, <i>p</i> < 0.01	47 120 20 40 50 277	5921.00 2436.00 238.62 1050.00 110.00	512.0000 493.0000 44.7100 181.0000 13.6000	¢# ***	-3.70 -2.13 -1.56 -1.06 -2.80 -2.24	[-4.39; -3.01] [-2.45; -1.81] [-2.28; -0.84] [-1.53; -0.59] [-3.35; -2.24] [-3.14; -1.34]	6.1% 6.4% 6.1% 6.3% 31.3%
time = more Wu2013 Yin2014 Feng2015 Random effe Heterogeneity	than 24w 30 20 43 ects model 93 $1/^2 = 58\%, \tau^2 = 0.093$	437.10 61.6100 204.50 176.5000 524.80 150.7000 27, <i>p</i> = 0.09	30 20 43 93	450.53 294.50 712.60	68.0400 196.5000 235.8000	¢ ≢ # #	-0.20 -0.47 -0.94 -0.56	[-0.71; 0.30] [-1.10; 0.16] [-1.39; -0.49] [-1.02; -0.10]	6.3% 6.2% 6.3% 18.8%
Random effe Prediction in Heterogeneity Test for subgro	ects model 812 hterval : $l^2 = 96\%$, $\tau^2 = 2.198$ bup differences: $\chi_3^2 =$	91, <i>p</i> < 0.01 18.90, df = 3 (<i>p</i> < 0.	794 01)			-4 -2 0 2	-2.07 7 4	′ [–2.81; –1.33] [–5.35; 1.21]	100.0%
Study	Total	Experimental Mean SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight
						: 1			
time = 4w Mao2018 Bao2020 Su2021 Zhang2021 Random e Heterogenei	60 45 44 45 ffects model 194 ty: <i>l</i> ² = 0%, τ ² = 0, <i>p</i> =	751.20 518.6000 1951.95 579.5100 1951.71 509.8700 1839.39 508.4330 = 0.75	60 45 44 45 194	1214.20 2298.32 2298.21 2086.98	944.3000 140.5100 371.5000 598.1490	1	-0.60 -0.67 -0.77 -0.44 -0.62	[-0.97; -0.24] [-1.09; -0.24] [-1.20; -0.34] [-0.86; -0.02] [-0.82; -0.41]	5.6% 5.6% 5.6% 5.6% 22.4%
time = 4w Mao2018 Bao2020 Su2021 Zhang2021 Random ei Heterogenei time = 8w Jia2012 Shi2012 Yu2015 Song2020 Random ei Heterogenei		751.20 518.6000 1951.95 579.5100 1951.71 509.8700 1839.39 508.4330 = 0.75 478.60 214.7000 1422.00 420.0000 685.20 14.2000 330.12 89.4000 3599, p < 0.01	60 45 44 45 194 40 42 40 55 177	1214.20 9 2298.32 4 2298.21 2 2086.98 9 774.20 2 2536.00 4 934.60 4 96.52	244.3000 140.5100 371.5000 598.1490 290.6000 176.0000 13.6000 - 94.3900	+	-0.60 -0.67 -0.77 -0.44 -0.62 -1.15 -2.46 -17.77 [-1.80 -5.69	[-0.97; -0.24] [-1.09; -0.24] [-1.20; -0.34] [-0.86; -0.02] [-0.82; -0.41] [-1.62; -0.67] [-3.03; -1.89] -20.62; -14.91] [-2.24; -1.35] [-13.41; 2.02]	5.6% 5.6% 5.6% 22.4% 5.6% 5.6% 5.1% 5.6% 21.9%
time = 4w Mao2018 Bao2020 Su2021 Zhang2021 Random ef Heterogenei time = 8w Jia2012 Yu2015 Song2020 Random ef Heterogenei time = 12w Shao2014 Xia2015 Liu2017 Sun2018 Xiao2020 Liu2021 Random ef Heterogenei	$\begin{cases} 60\\ 45\\ 44\\ 45\\ ffects model 194\\ ty: l^2 = 0\%, \tau^2 = 0, p = $	751.20 518.6000 1951.95 579.5100 1951.71 509.8700 1839.39 508.4330 = 0.75 478.60 214.7000 1422.00 420.0000 685.20 14.2000 330.12 89.4000 330.12 89.4000 330.12 89.4000 3599, <i>p</i> < 0.01	60 45 44 194 40 55 177 37 36 30 60 48 35 246	1214.20 9 2298.21 2 2298.21 2 2086.98 9 774.20 2 2536.00 4 934.60 4 96.52 878.00 2 1273.00 9 190.69 8 43.31 563.00 2	944,3000 140,5100 371,5000 598,1490 290,6000 176,0000 94,3900 94,3900 30,300 200,4000 30,3300 222,1300 226,0000		-0.60 -0.67 -0.77 -0.44 -0.62 -1.15 -2.46 -17.77 -1.80 -5.69 -0.56 -1.38 -0.66 -1.77 -14.58 -0.66 -3.20	$ \begin{bmatrix} -0.97; & -0.24 \\ [-1.09; & -0.24 \\] \\ [-1.20; & -0.34 \\] \\ [-0.86; & -0.02 \\] \\ [-0.82; & -0.41 \\ \end{bmatrix} \\ \begin{bmatrix} -1.62; & -0.67 \\] \\ [-3.03; & -1.89 \\ -20.62; & -14.91 \\] \\ [-2.24; & -1.35 \\] \\ [-1.341; & 2.02 \\] \\ \begin{bmatrix} -1.02; & -0.09 \\] \\ [-1.90; & -0.86 \\] \\ [-1.18; & -0.14 \\] \\ [-2.19; & -1.34 \\] \\ -16.73; & -12.44 \\] \\ [-1.14; & -0.18 \\] \\ [-7.54; & 1.15 \\ \end{bmatrix} $	5.6% 5.6% 5.6% 22.4% 5.6% 5.6% 5.6% 21.9% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6%
time = 4w Mao2018 Bao2020 Su2021 Zhang2021 Random ei Heterogenei Song2020 Random ei Heterogenei time = 8w Jia2012 Yu2015 Song2020 Random ei Heterogenei time = 12w Shao2014 Xie2015 Liu2017 Sun2018 Xiao2020 Liu2021 Xu2021 Xu2021 Xu2021 Xu2021 Random ei Heterogenei	$\begin{cases} 60\\ 45\\ 44\\ 45\\ ffects model 194\\ ty: I^2 = 0\%, \tau^2 = 0, p = 0, p = 0, p = 0, p = 0, r^2 $	751.20 518.6000 1951.95 579.5100 1951.71 509.8700 1839.39 508.4330 = 0.75 478.60 214.7000 1422.00 420.0000 685.20 14.2000 330.12 89.4000 3599, p < 0.01 682.60 288.8000 492.10 198.6000 745.70 525.6000 140.58 25.7800 512.33 22.8900 421.00 199.0000 1998, p < 0.01 438.00 203.4000 3034.02 110.0100 311.66 43.2000 5139.63 121.0500 076, p < 0.01	60 45 44 49 194 40 42 40 42 40 42 40 55 177 36 30 00 48 33 00 48 52 246 35 50 54 41 44 283	1214.20 9 2298.32 2 2298.21 2 2086.98 9 324.60 9 34.60 496.52 9 878.00 1 770.10 1 1273.00 9 496.52 9 843.31 563.00 1 698.00 1 3231.00 1 427.52 6 676.77 1	944.3000 140.5100 571.5000 598.1490 290.6000 13.6000 13.6000 94.3900 200.4000 991.6000 30.3300 22.1300 20.13300 20.13300 20.13300 20.13300 20.13300 20.13300 20.13300 20.13000 20.13000 20.13000 20.13000 20.13000 20.13000 20.1300000000000000000000000000000000000		-0.60 -0.67 -0.77 -0.44 -0.62 -1.15 -2.46 -17.77 -1.80 -5.69 -0.56 -1.38 -0.66 -1.38 -0.66 -1.77 -14.58 -0.66 -3.20 -3.20 -1.23 -1.77 -2.59 -0.88 -1.60	$ \begin{bmatrix} -0.97; & -0.24 \\ [-1.09; & -0.24] \\ [-1.20; & -0.34] \\ [-0.86; & -0.02] \\ [-0.82; & -0.41] \\ \end{bmatrix} \\ \begin{bmatrix} -1.62; & -0.67 \\ [-3.03; & -1.89] \\ -20.62; & -14.91] \\ [-2.24; & -1.35] \\ [-1.3.41; & 2.02] \\ \end{bmatrix} \\ \begin{bmatrix} -1.02; & -0.09 \\ [-1.90; & -0.86] \\ [-1.18; & -0.14] \\ [-2.19; & -1.34] \\ -6.73; & -12.44 \\ [-1.14; & -0.18] \\ [-7.54; & 1.15] \\ \end{bmatrix} \\ \begin{bmatrix} -1.72; & -0.73 \\ [-2.33; & -1.30] \\ [-3.11; & -0.64] \\ [-3.23; & -0.87] \\ \end{bmatrix} \\ \begin{bmatrix} -1.22; & -0.64 \\ [-2.33; & -0.87] \end{bmatrix}$	5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 21.9% 5.6% 5.6% 5.6% 33.3% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6%

1.12, 95% CI (0.93, 1.31), $I^2 = 0\%$, $P_{heterogeneity} = 0.57$; LVEF: SMD = 0.89, 95% CI (0.81, 0.97), $I^2 = 15\%$, $P_{heterogeneity} =$ 0.24; BNP: SMD = -2.10, 95% CI (-2.33, -1.86), $I^2 = 0\%$, $P_{heterogeneity} = 0.48$; NT-ProBNP: SMD = -0.87, 95% CI (-1.01, -0.73), $I^2 = 29\%$, $P_{heterogeneity} = 0.19$; LVEDD: SMD = -0.65, 95% CI (-0.80, -0.50), $I^2 = 18\%$, $P_{heterogeneity} = 0.28$; LVESD: SMD = -1.06, 95% CI (-1.33, -0.79), $I^2 = 42\%$, $P_{heterogeneity} = 0.16$; LVEDV: SMD = -0.53, 95% CI (-0.71, -0.34), $I^2 = 27\%$, $P_{heterogeneity} = 0.24$].

3.9. Publication bias

Publication bias was detected by plotting funnel plots (Figure 10), which were visually asymmetric for RARs, CERs, MLHFQ scores, 6MWD, LVEF, NT-proBNP, and LVEDD, and the results of the Harbord test, Peters' test, or Egger's test provided corresponding support evidences. (RARs: Harbord test P < 0.01, Peters' test P < 0.01; CERs: Egger's test P = 0.0167 < 0.05; MLHFQ scores: Egger's test, P < 0.001; CERs: Egger's test, P < 0.001; LVEF: Egger's test



P < 0.001; NT-proBNP: Egger's test, P < 0.001; LVEDD: Egger's test, P = 0.0373 < 0.05). No significant publication bias was found in index BNP (Egger's test, P = 0.0676 > 0.05). The contour-enhanced funnel plots for the above 8 metrics were further trimmed and filled. The results (Figure 11) showed that 6 studies and 9 studies were added to the white area (not statistically significant, P > 0.1) in the funnel plots for RARs and CERs, respectively. In the funnel plots for MLHFQ scores, 6MWD, BNP, and NT-proBNP, 8, 9, 1, and 3 studies were added to the gray area, respectively. In the funnel plot for LVEF, 8 studies were added to the white area and 10 studies were added to the gray area, respectively. 1 study was added to the white area and 3 studies were added to the gray area in the funnel

plot for LVEDD, respectively. In RARs, CERs, 6MWD, LVEF, LVEDD, and BNP, the effect sizes OR/SMD of recombination were not significantly altered after trimming and filling the funnel plot [RARs: OR = 0.46, 95% CI (0.37, 0.58), P < 0.001; CERs: OR = 1.97, 95% CI (1.74, 2.22), P < 0.001; 6MWD: SMD = 1.02, 95% CI (0.34, 1.71), P < 0.01; LVEF: SMD = 0.52, 95% CI (0.21, 0.84), P < 0.01; BNP: SMD = -1.88, 95% CI (-2.67, -1.08), P < 0.001; LVEDD: SMD = -0.65, 95% CI (-1.00, -0.30), P < 0.001]. However, there was a significant change in SMD of MLHFQ scores and NT-proBNP, which reversed to be statistically insignificant [MLHFQ scores: SMD = -0.58, 95% CI (-1.77, 0.60), P = 0.334; NT-proBNP: SMD = -1.10, 95% CI (-3.93, 1.74), P = 0.449].

First	QSYQ	Control	Adverse reactions in the
author/	group	group	QSYQ group
year			
Cao 2012	0/64 (0%)	2/65 (3.08%)	NA
Jia 2012	0	0	NA
Zhang 2012	0	0	NA
Qin 2013	0	0	NA
Wu 2013	0	0	NA
Shao 2014	0	0	NA
Hao 2015	9/60 (15%)	24/60 (40%)	Hypotension, decreased heart rate
Xie 2015	0	0	NA
Xiang 2015	0	0	NA
Hu 2017	0	0	NA
Li 2017	0	0	NA
Ren 2017	0	0	NA
Wu 2017	0	0	NA
Wang 2018	5/48	4/48 (8.33%)	Sinus bradycardia, hypotension, dry
	(10.41%)		cough, gastrointestinal distress
Cai 2019	0	0	NA
Ma 2019	7/73	6/73 (8.22%)	Hypotension, nausea, headache,
	(9.59%)		electrolyte disturbances
Xiao 2020	3/48	6/48 (12.5%)	Hypotension, dizziness, headache,
	(6.25%)		nausea and vomiting
Zhang 2020	3/40	2/40 (5.0%)	Hypotension, headache, nausea and
	(7.5%)		vomiting
Shi 2021	4/51	5/51 (9.80%)	Hypotension, dizziness, nausea
F1	(7.84%)		
Zhang 2021	0	0	NA
Mao 2020	16/319	18/319	Cold, dizziness, nausea and vomiting,
	(5.01%)	(5.64%)	hematochezia, hyperkalemia, liver
			aysiunction

TABLE 2 The side effects of included trails.

3.10. GRADE assessment

By GRADE assessment, ACM, incidence of MACE, and LVESV were rated as moderate evidence, RARs and BNP were rated as low-quality evidence, while the rest of the indicators were rated as very low-quality evidence. Reasons for downgrading: (1) Regarding the risk of bias, only three papers

TABLE 3 Meta-analysis results of high-quality studies.

described in details the implementation of randomization, allocation concealment, and blinding, whereas most of the studies just adopted appropriate randomization methods without specifying them. (2) In terms of inconsistency, a high degree of heterogeneity was found during the analysis, which were considered to be attributed to multiple factors such as study population, gender, disease duration, drug dispensing, and variable study quality. (3) Different degrees of publication bias were detected by drawing funnel plots (**Table 4**).

4. Discussion

To our knowledge, to date, this is the first and largest systematic evaluation and meta-analysis assessing the improvement of prognosis of patients with CIHF by the proprietary Chinese medicine QSYQ, and more comprehensive alternative metrics were pooled to evaluate its clinical efficacy and safety. The results of the meta-analysis showed that the combination of QSYQ with conventional Western medicine improved the prognosis of patients by reducing the RARs, the incidence of MACE, and ACM. This may be attributed to the improvement in cardiac function, exercise tolerance and quality of life, as well as the protective effect on cardiac structures. In terms of safety, no serious adverse events were reported in 21 studies comprising 2,742 patients, suggesting that QSYQ is relatively safe and well tolerated.

Despite the fact that standardized medications recommended by current international guidelines have been established as the cornerstone of treatment for HF and IHD, there is still a high residual risk in patients with CIHF (13). A large body of published evidence suggests that the coexistence of HF and coronary artery disease carries a high risk of adverse cardiac events and death, and that the risk of death increases progressively with the worsening of coronary artery disease (79); deterioration of patients' cardiac function, and socioeconomic

Metrics	Subgroups	Studies	Participants	SMD (95% CI)	l ² (%)	P _{Heterogeneity}
6MWD	Overall	13	1,637	1.33 (0.63, 2.03)	95	< 0.01
Subgroup analysis by age	<60	4	359	2.45 (0.66, 4.25)	97	< 0.01
	60-65	8	1,218	0.61 (0.42, 0.81)	57	0.02
	>65	1	60	2.43 (0.75, 3.10)	-	-
Subgroup analysis by treatment course	2-4 weeks	5	444	1.37 (0.07, 2.68)	96	< 0.01
	8 weeks	1	80	0.67 (0.22, 1.13)	-	-
	12 weeks	3	232	0.84 (0.46, 1.23)	50	0.14
	24 weeks	4	881	1.82 (0.13, 3.52)	98	< 0.01
LVEF	Overall	24	2,899	0.75 (0.56, 0.94)	86	< 0.01
Subgroup analysis by age	<60	6	599	0.87 (0.45, 1.30)	81	<0.01
	60-65	12	1,604	0.70 (0.44, 0.95)	86	< 0.01
	65-70	4	526	0.62 (-0.05, 1.29)	90	< 0.01
	>70	2	170	1.01 (0.69, 1.33)	0	0.74
Subgroup analysis by treatment course	2-4 weeks	7	624	1.01 (0.84, 1.17)	0	0.9
	8 weeks	3	284	0.92 (0.04, 1.79)	92	< 0.01
	12 weeks	8	719	0.75 (0.42, 1.08)	77	<0.01
	24 weeks	6	1,272	0.40 (0.04, 0.75)	85	<0.01



deprivation lead to a worse quality of life, and a poor quality of life is strongly associated with recurrent readmissions and a higher mortality rate (80). Against this background, it is urgent to explore additional adjunctive therapies to mitigate this risk. The development of Traditional Chinese medicine (TCM) has provided more possibilities and options to improve the prognosis of CIHF patients (81). As a traditional Chinese medicine compound preparation, QSYQ has been widely used in China in the combined treatment of HF patients, owing to its efficacy of "benefiting qi and activating blood circulation", and has achieved good therapeutic effects. A newly published reappraisal analysis of systematic reviews on QSYQ (82) points out the current lack of attention to the impact of QSYQ on mortality and readmission rates in patients with HF, even in one of the largest systematic evaluations incorporating 85 studies (11). With the popularization of the concept of heart failure vulnerable period (83) and the emphasis on the prognosis of patients with HF, more and more relevant studies have been published. Thus, we re-pooled and performed a meta-analysis with the prognostic index as the primary outcome indicator, and conducted a more adequate analysis of heterogeneity and a publication bias test.

The endpoint indicator is the real disease outcome, which is the event that patients are most concerned about and has the most immediate interests to them. The indicator can objectively reflect the real effect of the intervention, having great clinical significance and clinical reference value (84). Our results showed



that QSYQ combined with conventional Western medications reduced RARs, incidence of MACE, and ACM in CIHF patients, and did not reveal significant heterogeneity, and the results remained stable even after being corrected for publication bias. In addition, we comprehensively summarized the alternative metrics that have been shown to be associated with poor prognosis in patients with CIHF, such as LVEF, which reliably reflects left heart function, 6MWD, which reflects the patient's exercise tolerance (85), as well as quantitative markers of HF, BNP and NT-ProBNP (86). Our results suggest that QSYQ adjunctive therapy for CIHF is favorable. However, it must be alarmed that a high degree of heterogeneity was observed in all of the above mentioned proxies. Although subgroup and meta-regression analyses were performed, heterogeneity was not significantly eliminated. By looking at the Galbraith plots and the Baujat plots, we hypothesized that the heterogeneity between studies might involve multiple factors. On the one hand, the lack of study design may not only lead to differences in the evaluation of the intervention effect, but also create a higher risk of bias and lower the level of evidence in our study. On the other hand, the clinical heterogeneity could not always be further explored and addressed due to the lack of access to exhaustive clinical data from the original studies (11). For example, the patients' age, gender, disease duration, comorbidity characteristics, the dose and frequency of the specific drugs used, and the drug

combinations or TCM dialectic typing, etc., we cannot rule out the interfering effect of these factors on the clinical efficacy. This limits to some extent the extrapolation of the results of this study. By trimming and filling the contour-enhanced funnel plots, we found that the cause of the funnel plot asymmetry may not be entirely attributable to publication bias. It is well known that systematic exaggeration of effect sizes resulting from small studies with poor study design can lead to funnel plot asymmetry and can introduce greater heterogeneity (87, 88). In addition, it is not uncommon for potential publication bias and heterogeneity to interact when both are coexisting (11, 89).

In addition, as can be seen from the wide prediction intervals, QSYQ may not always be beneficial and is even sometimes slightly detrimental in clinical applications. Just like conventional Western medicines, not every patient exhibits full tolerance, but we must also recognize the limitations of incorporating the principles of TCM. It is challenging to fully reconcile individualized treatment based on "one person, one prescription" and "dialectical treatment", which are characteristics of TCM, with patient screening, which is centered on disease diagnosis (13). A clinical efficacy evaluation system guided by the combination of Western medicine diseases and TCM syndromes may provide an idea for future development (90, 91). In conclusion, we call for future RCTs to be pre-registered on relevant websites and to strictly follow the "CONSORT Extension for Chinese Herbal Medicine Formulas 2017" statement (92) for standardized study design. It

TABLE 4 GRAI	DE-based assess	ment of evid	dence quality.									
Quality asse Importance	ssment						No	of pati	ents	Effect	Qua	lity
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	QSYQ + CT	Ъ	Relative (95% Cl)	Absolute		
Rehospitaliza	tion											
15	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias ^b	140/1,056 (13.3%)	260/ 1,042 (25%)	OR 0.42 (0.33- 0.53)	127 fewer per 1,000 (from 100 fewer to 151 fewer)	⊕⊕OO Low	Critical
All-cause mo	rtality											
6	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/842 (3.2%)	60/837 (7.2%)	OR 0.43 (0.27- 0.68)	40 fewer per 1,000 (from 22 fewer to 51 fewer)	⊕⊕⊕O Moderate	Critical
MACE									-			
8	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	No serious imprecision	None	89/749 (11.9%)	171/744 (23%)	OR 0.42 (0.31- 0.56)	118 fewer per 1,000 (from 87 fewer to 145 fewer)	⊕⊕⊕O Moderate	Critical
MLHFQ (bett	er indicated by	lower value	(S)									
17	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	No serious imprecision	Reporting bias ^b	1,026	1,006	1	SMD 2.03 lower (3.0-1.07 lower)	⊕000 Very low	Important
Clinical effica	cy (better indic	ated by low	er values)									
33	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias ^b	1,657	1,632	1	OR 2.25 higher (1.97–2.58 higher)	⊕⊕OO Low	Important
6MWD (bette	r indicated by	lower values	2)									
33	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	No serious imprecision	Reporting bias ^b	1,814	1,783	1	SMD 1.87 higher (1.33–2.41 higher)	0000 Very low	Important
LVEF (better	indicated by lo	wer values)										
45	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	No serious imprecision	Reporting bias ^b	2,389	2,359	1	SMD 1.08 higher (0.83-1.33 higher)	⊕000 Very low	Important
BNP (better i	ndicated by lov	ver values)										
16	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	No serious imprecision	None	812	794	1	SMD 2.07 lower (2.81-1.33 lower)	⊕OOO Very low	Important
NT-ProBNP (k	setter indicated	by lower ve	alues)									
18	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	No serious imprecision	Reporting bias ^b	206	006	1	SMD 2.77 lower (4.90–0.63 lower)	0000 Very low	Important
LVEDD (bette	r indicated by	lower values	(5									
18	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	No serious imprecision	Reporting bias ^b	1,010	1,008	1	SMD 0.92 lower (1.21–0.63 lower)	⊕OOO Very low	Important
LVESD (bette	r indicated by l	ower values	(
6	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	No serious imprecision	None	518	518	1	SMD 1.02 lower (1.38–0.66 lower)	0000 Very low	Important
											J	Continued)

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Quality ass Importance	essment						Z	. of pati	ents	Effect	Quali	ty
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	QSYQ + CT	Ь	Relative (95% Cl)	Absolute		
LVEDV (bette	r indicated by	lower values	(\$									
7	Randomised trials	Serious ^a	Very serious ^c	No serious indirectness	Serious ^d	None	404	391	I	SMD 1.49 lower (3.29 lower-0.31 higher)	0000 Ir Very low	nportant
LVESV (bette	r indicated by I	ower values	(
8	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	No serious imprecision	None	443	430	I	SMD.41 lower (0.55-0.28 lower)	⊕⊕⊕⊖ Iı Moderate	nportant
There are large Asymmetric fu The heterogen	e deviations in ran nnel plot showing eity test $P < 0.01$,	Idom allocatio 3 publication t 1 ² > 75%.	on, allocation hiding, and	d blind design.								

is recommended to focus on the efficacy of QSYQ in patients with a specific HF type, such as HFpEF, or a certain TCM syndrome, such as qi deficiency and blood stasis, while negative findings and unfavorable results should not be concealed. In clinical practice, we need to follow our own rules of TCM development and integrate modern evidence-based medicine concepts, and develop a detailed and individualized dialectical medication plan according to the actual situation of patients based on the available evidence-based practice, rather than blindly applying it to all patients.

HF was categorized according to LVEF into heart failure with reduced ejection fraction (HFrEF, LVEF ≤40%), heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 41%-49%) and heart failure with preserved ejection fraction (HFpEF, LVEF \geq 50%) (15). Several RCTs have found that patients with HFmrEF are similar to HFrEF in terms of treatment benefit (15), and both have similar pathophysiologic characteristics. Based on this, patients with HFmrEF were also included in this study. Analysis of HFrEF showed that treatment method that combines QSYQ with conventional Western medicines improved its prognosis and improved all indicators. However, we did not perform a subgroup analysis of HFpEF due to the lack of available clinical data. Although HFpEF and HFrEF have similar symptoms and signs, HFpEF has not benefited from conventional drug treatment (93, 94). Due to the heterogeneity and complexity of the pathogenesis and comorbidities, no substantial breakthroughs have been made in its pathogenesis and treatment options, and its continued prevalence and poor prognosis should not be underestimated (95). Current studies point to multiple mechanisms of systemic inflammatory response and its induced endothelial dysfunction, oxidative stress, abnormal cardiac energy metabolism, and microvascular dysfunction that lead to increased myocardial fibrosis, myocardial remodeling, and diastolic dysfunction (95). A study innovatively found that epicardial adipose tissue (EAT) promotes myocardial inflammation by activating inflammatory vesicle-mediated cellular pyroptosis in adipocytes and constructs an EATmyocardium axis, which provides a new strategy and a new way of thinking for the treatment of HFpEF (94). Previous studies have pointed out that astragalus with Salvia miltiorrhiza is a core drug for the treatment of HFpEF because it can regulate oxidative stress and glycolipid metabolism through multicomponents and multi-targets (96). Similarly, a meta-analysis showed that QSYQ improves cardiac function and exercise tolerance in patients with HFpEF (10). This suggests that although QSYQ is beneficial in treating HFpEF, it does not provide the most direct support for its effect in improving prognosis. Further studies with large-scale, multicenter RCTs are still needed in the future.

In addition, diabetes mellitus is one of the leading causes of HF, and the mortality is significantly increased when HF is complicated by diabetes mellitus. They are independent risk factors for each other (97). Reactive oxygen species (ROS)-mediated oxidative stress, glucose-lipid metabolism disorders caused by insulin resistance, perfusion insufficiency due to endothelial dysfunction, autonomic dysfunction, and activation of multiple inflammatory

FABLE 4 Continued

95% confidence interval contains 0.

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responses may be potential mechanisms of diabetic heart failure (98, 99). In the inflammatory response, NOD-like receptor protein 3 (NLRP3) inflammatory vesicles activated by multiple pathways, such as high-glucose and high-fat stimuli, oxidative stress, endoplasmic reticulum stress, and calcium overload, induce the secretion of a large number of pro-inflammatory cytokines through the cascade of inflammation, which then mediate the process of cellular pyroptosis and promote myocardial injury and fibrosis (94, 100). Several studies have shown that QSYQ ameliorates myocardial injury by inhibiting excessive autophagy and NLRP3 inflammatory vesicles (101) and protects cardiomyocytes from high glucose-induced injury (97). Also, it can promote the repair of diabetic myocardial ischemic injury by up-regulating the levels of Sirt1 and eNOS, increasing NO bioavailability, preserving endothelial function, improving neovascularization, and inhibiting myocardial fibrosis and myocardial apoptosis (102). This shows that the proprietary Chinese medicine QSYQ has great therapeutic potential. More notably, compared with the traditional hypoglycemic effect of empagliflozin (EMP), its prognostic improvement and cardioprotective effect on HF patients are more compelling (98). Therefore, it will be interesting and valuable to investigate whether the combination of EMP with QSYQ can bring more therapeutic opportunities and greater benefits for patients with diabetes and HF.

Over the past decade or so, several studies have been conducted in an attempt to elucidate the underlying mechanisms by which QSYQ improves IHD. In a rat model of HF constructed by coronary artery ligation, it was found that QSYQ had a significant myocardial protective effect on HF rats, which may improve the degree of myocardial fibrosis by inhibiting the TGF- β 1/Smads pathway, and decrease myocardial cell apoptosis by inhibiting the caspase-3 signaling pathway (103). The results of a network pharmacology showed that the active ingredients in QSYQ, such as astragaloside, Salvianic acid A, and ginsenoside Rg1, could synergistically regulate the targets in the HIF-1 signaling pathway to inhibit the expression of this signaling pathway and protect cardiomyocytes (104). It has also been suggested that QSYQ may inhibit the oxidative damage of myocardial tissues in HF model rats by activating the Nrf2/HO-1 signaling pathway, and thus exert its protective effect on cardiomyocyte damage (105). In summary, the above preclinical findings support to some extent the protective and ameliorative effects of QSYQ on CIHF, which are realized through multiple targets and pathways.

In short, the tremendous advantages of TCM in synergistic treatment of HF have attracted more and more attention from researchers. Moreover, research on TCM has evolved from the original macro syndrome differentiation and treatment to elucidating its role and mechanism from multiple dimensions, such as molecular biology and metabolomics. Individualized precision therapy for HF guided by evidence-based medicine evidence is becoming an objective and universally accepted model of care in treatment protocols. However, standardized and scientific TCM clinical efficacy evaluation system and highquality clinical trials are still expected to provide solid support for TCM to prevent and treat HF in order to increase the contribution of TCM.

We must acknowledge the limitations of this study:(1) Although we systematically assessed the effect of QSYQ on prognosis and clinical symptoms in CIHF for the first time, the overall quality of the included studies was low and most of them did not use placebo controls, which somewhat compromised the level of evidence and affected the reliability of our results; (2) The lack of available specific data did not allow us to further analyze heterogeneity and publication bias or to assess differences in the efficacy of QSYQ in specific populations by further subgroup analysis. (3) HFpEF subtypes were not analyzed. (4)The observation time of most studies was limited to less than 1 year, so rigorously designed large-sample clinical trials with long-term follow-up are still needed to further evaluate its efficacy.

5. Conclusions

The available evidence suggests that the combined application of QSYQ can further improve CIHF patients' cardiac function, exercise tolerance, and quality of life, alleviate clinical symptoms, and ultimately improve their prognosis with a favorable safety profile. However, limited by the quality and high heterogeneity of the literature, we must be more conservative and cautious about the present results and approach QSYQ dialectically. We look forward to the implementation of rigorously designed and highquality RCTs to further refine our conclusions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

WX: Data curation, Project administration, Software, Writing – original draft, Writing – review & editing. DG: Funding acquisition, Supervision, Validation, Writing – review & editing. GH: Methodology, Supervision, Writing – review & editing. GW: Methodology, Writing – review & editing. QH: Data curation, Writing – review & editing. FM: Supervision, Writing – review & editing. LR: Supervision, Writing – review & editing. RL: Supervision, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023. 1271608/full#supplementary-material

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