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Efficacy and safety of Qili Qiangxin Capsule in the adjuvant treatment of ischemic cardiomyopathy with heart failure: a systematic review and meta-analysis

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ABSTRACT

Objective To evaluate the efficacy and safety of Qili Qiangxin Capsule (QLQXC) combined with western medicine in patients with ischemic cardiomyopathy (ICM) comorbid with heart failure (HF) for clinical application.

Methods We searched relevant references in Chinese databases including China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (VIP), Wanfang Database, and China Biology Medicine (CBM), as well as English databases including PubMed and Embase, from the foundation of the database to January 8, 2023, without language restrictions. All statistical analyses, including subgroup and sensitivity analyses, were performed using the Review Manager (version 5.4) and Stata (version 15.0).

Results QLQXC combined with western medicine significantly increased the endpoints of overall response rate (ORR) ($P < 0.000\,01$), left ventricular ejection fraction (LVEF) ($P < 0.000\,01$), the score of Minnesota Living with Heart Failure Questionnaire (MLHFQ) ($P = 0.000\,2$), and 6-minute walking distance (6MWD) ($P < 0.000\,01$), decreased left ventricular end-diastolic diameter (LVEDD) ($P < 0.000\,01$), left ventricular end-systolic diameter (LVESD) ($P = 0.03$), and pro-brain natriuretic peptide (pro-BNP) ($P < 0.000\,01$), and reduced the incidence of rehospitalization ($P = 0.000\,3$) and adverse events (AEs) ($P = 0.000\,6$) compared with those under the conventional western therapy alone. Nonetheless, no significant difference was observed in reducing the mortality between the QLQXC combined with western medicine group and the western medicine group ($P = 0.30$).

Conclusion The combination therapy of QLQXC with western medicine can potentiate cardiac function and raise the quality of life in patients with ICM comorbid with HF.

1 Introduction

Ischemic heart disease (IHD), also known as coronary artery disease, is a fatal disease with the pathological features of plaque formation in coronary arteries. As the leading cause of death due to cardiovascular diseases, its economic burden in China is soaring [1]. Coronary artery disease can turn into ischemic cardiomyopathy (ICM), where if the coronary artery is obstructed for a prolonged period, the ability to provide oxygen and nutrition to the myocardium declines continually [2]. The pathological features of ICM include myocardial stunning, myocardial scar, and hibernating myocardium, followed by myocardium replacement fibrosis and ventricular remodeling [3].

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ICM is highly correlated with adverse cardiac events such as fatal tachyarrhythmias, sudden cardiac death, and heart failure (HF) [4]. Consequently, irreversible left ventricular dysfunction, reduced left ventricular ejection fraction (LVEF), and inferior quality of life were the characteristics of ICM [5].

Currently, the evidence-based treatment for patients with ICM and HF is medical therapy and vascular reconstruction surgery (VRS) [6]. However, the clinical practice of VRS remains controversial. Moreover, the results of two large-scale clinical trials suggested that percutaneous coronary intervention or coronary-artery-bypass-grafting did not significantly improve functional ability and reduce the incidence of all-cause mortality or hospitalization for patients with HF [7]. Compared with optimal goal-directed medical therapy, the long-term survival rate and mortality of coronary-artery-bypass-grafting were worse [8]. In addition, the search for better medical therapy is imperative, given the high perioperative mortality and high cost of vascular reconstruction surgery.

Qili Qiangxin Capsule (QLQXC) is a Chinese patent medicine developed based on the theory of collateral disease, with the effects of tonifying Qi, warming Yang, activating blood, and promoting diuresis (Qi, Yang, and blood are the basic theories of Chinese medicine). A large-scale multicenter, double-blind, randomized controlled trial (RCT) demonstrated that the QLQXC significantly reduced the level of pro-brain natriuretic peptide (pro-BNP) and improved cardiac function in HF patients [9]. Subsequent studies have shown that the QLQXC can also improve the cardiac function of patients with various cardiomyopathies, such as dilated and diabetic cardiomyopathy [10, 11]. Thus, we hypothesized that QLQXC could improve the cardiac dysfunction and quality of life in patients with ICM comorbid with HF.

At present, the efficacy of the combination therapy of conventional treatment (diuresis, preventing ventricular remodeling, etc.) and the QLQXC for patients with ICM and HF has not been evaluated. Thus, this evidence-based study assessed the efficacy and safety of the combination therapy for ICM and HF patients for the first time, providing the latest evidence for clinical therapy.

2 Materials and methods

2.1 Protocol and registration

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12], and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD 42023389546).

2.2 Information sources and search strategy

We searched Chinese databases including China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database, and China Biology Medicine (CBM), and English databases including PubMed and Embase, from the foundation of the database to January 8, 2023, without language restrictions. Next, we searched the ClinicalTrials.gov (https://clinicaltrials.gov) and Chinese Clinical Trial Register (www.chictr.org.cn) for all RCTs investigating QLQXC on patients with ICM accompanied by HF. To ensure the integrity of the retrieved results, we used the "PIS" in the Population, Intervention, Comparison, Outcome, and Study design (PICOS) principle to improve our search formula using the following Medical Subject Headings (MeSH) terms: P = "ischemic cardiomyopathy", I = "Qili Qiangxin Capsule", and S = "randomized controlled trial", and adjusted the formula following different retrieval principles in various databases. For example, we used the following formula in the PubMed: ("Qili Qiangxin Capsule" OR "Qili Qiangxin Capsules" OR "Qili Qiangxin" OR "Qili-Qiangxin" OR "QLQXC") AND ("Ischemic cardiomyopathy" OR "Ischemic cardiomyopathies" OR "Ischemia cardiomyopathy" OR "Ischemia cardiomyopathies" OR "cardiomyopathy" OR "cardiomyopathies" OR "ICM") AND ("randomized controlled trial" OR "randomised controlled trial" OR "randomized trial" OR "randomised trial" OR "randomized" OR "RCT"). The complete search formulas for each database were provided in Supplementary Figure S1.

2.3 Study selection and data extraction

Two investigators retrieved all articles by screening the titles and abstracts and browsing full texts independently. Any controversy concerning the selection of research was resolved by a third-party reviewer for judgment.

2.3.1 Inclusion criteria (i) The studies were RCTs with an ethical review. (ii) The participants were aged over 18, graded as class II – IV according to the New York Heart Association (NYHA), had a history of coronary heart disease, and were diagnosed as ICM with HF [13]. (iii) The intervention compared the effects of conventional therapy and the combination therapy of conventional treatment with QLQXC (the conventional treatment included diuretics, blood lipid-lowering therapy, blood pressure lowering therapy, and antiplatelet therapy). (iv) The studies reported primary or secondary outcomes. The overoll response rate (ORR), LVEF, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and pro-BNP were the primary outcomes to evaluate the efficacy and superiority of QLQXC on the cardiac function. Adverse events (AEs), mortality, rehospitalization, 6-minute walking distance (6MWD), and Minnesota Living with Heart Failure Questionnaire (MLHFQ) were the secondary outcomes to evaluate the safety and advantage of QLQXC on the quality of life.

2.3.2 Exclusion criteria (i) The research lacked a randomization nature. (ii) The studies were animal experiments, cell-based experiments, retrospective research, cohort research, review literature, and case reports. (iii) The intervention included any other proprietary Chinese medicine or Chinese herbs. (iv) The studies contained repetitive data.

2.4 Risk of bias and quality assessment

We used the Cochrane risk of bias assessment tool to evaluate the risk of bias in individual studies, including the bias of selection (random sequence generation and allocation concealment), performance, detection, attrition, reporting, and others [14]. Furthermore, we adopted the modified Jadad score to assess the quality of every trial [15]. The quality evaluation items include randomization, allocation concealment, blinding, and data withdrawal. For the items of blinding, randomization, and allocation concealment, 2 points were given to the adequate method, and 1 and 0 points would be given to the unclear and inadequate method, respectively. For the item of data withdrawal, 1 point was given to the trials that depicted the reason for data loss. If there was no item, 0 point was given. Trials with a score of 1 – 3 were considered to be of low quality, while those with a score of 4 – 7 were considered to be of high quality.

2.5 Statistical analysis

We analyzed the results of LVEF, LVEDD, LVESD, pro-BNP, 6MWD, and MLHFQ as continuous variables, and recorded the mean and standard deviation (SD) before and after the intervention. ORR, AEs, mortality, and re-hospitalization events were estimated as discontinuous variables, and the number of participants in every event was reported. The continuous data were reported as the mean difference (MD), and the discontinuous data were reported as the risk ratio (RR) with 95% confidence intervals (CI).

I^2 testing was used to assess the heterogeneity. Substantial heterogeneity was revealed if $I^2 > 50\%$, and the random-effects model was used to pool the RR; otherwise, the fixed-effects model was used to pool the MD. A funnel plot was drawn to examine the publication bias if the study included 10 RCTs or more. Egger's test was employed to evaluate the symmetry of the funnel plot, with $P < 0.01$ considered statistically significant.

We performed subgroup analyses of highly heterogeneous outcomes following categories of mean age of the participants, follow-up period, publication date, and treatment. For the ORR endpoint, we conducted a sensitivity analysis to identify the source of heterogeneity by excluding each of the included references one by one. All statistical analyses were performed using the Review Manager (version 5.4) and Stata (version 15.0).

3 Results

3.1 Baseline characteristics of the included studies

We initially searched 630 studies, of which 277 were excluded because of duplication and 255 were excluded because they did not meet the inclusion criteria. Finally, a total of 22 RCTs were included, with 2 439 individuals in our meta-analysis [16-37] (Figure 1). All studies were published between 2007 and 2022, and enrolled patients with ICM comorbid with HF. One study recruited participants with ICM comorbid with HF and atrial fibrillation (AF). The follow-up period ranged from 14 days to 6 months. The baseline characteristics of the 22 studies are summarized in Table 1.

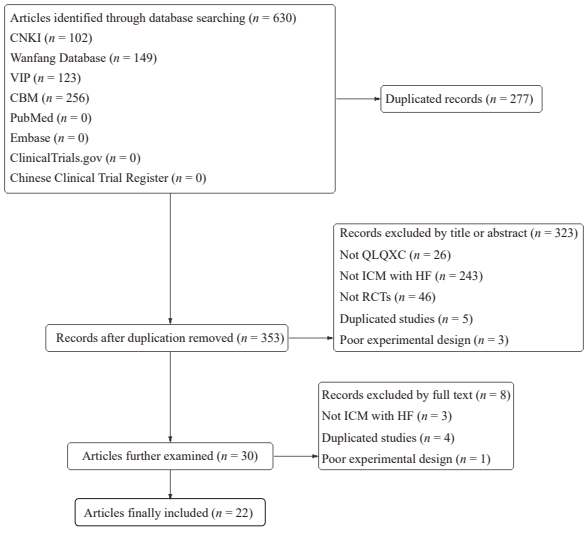

Figure 1 Flow diagram of studies selection

3.2 Risk of bias and quality assessment

All 22 trials mentioned randomization, but only 7 trials recorded the specific randomization methods [16, 19, 20, 22, 24, 29, 31], and 3 used the wrong method (randomization according to the sequence of patients' visits) [33-35]. No trials mentioned whether the allocation concealment and blinding were carried out; hence, unclear risks remained. Two studies compared injection therapy with QLQXC [18, 28], which did not allow the blinding of participants, indicating a high risk. No data loss, selective reporting, or other biases were reported in all studies, which indicated a low risk. The results of publication bias are depicted in Figure 2. The quality of the included RCTs was poor, ranging from 0 – 3 points. The modified Jadad score for each study is shown in Table 2.

3.3 ORR

A total of 17 trials [16, 18, 19, 21-28, 31-36] including 1 986 participants reported the endpoint of ORR. The random-effects model was applied according to high heterogeneity (I^2 = 52%). Compared with conventional therapy, the

Table 1 Baseline characteristics of the 22 RCTs in this meta-analysis

No.	Study	Disease	Age (year)	Case (*n*)		Intervention		Period	Endpoint
				T	C	T	C		
1	BAI CB, 2019 [16]	ICM + HF	60.25 ± 10.50	40	40	CT + Trimetazidine + QLQXC	CT + Trimetazidine	1 month	①③⑤⑦
2	CHEN XH, 2014 [17]	ICM + HF	62.50 ± 10.50	30	30	CT + QLQXC	CT	3 months	②③⑤⑨
3	CHEN XF, 2015 [18]	ICM + HF	70.80 ± 12.37	78	78	CT + Levocarnitine + QLQXC	CT	2 weeks	①②
4	CHEN XD, 2015 [19]	ICM + HF	68.63 ± 8.24	55	55	CT + Trimetazidine + QLQXC	CT + Trimetazidine	3 months	①②⑤
5	CHEN C, 2016 [20]	ICM + HF	70.80 ± 12.61	29	30	CT + QLQXC	CT	12 weeks	②③⑥⑦⑨⑩
6	CHEN Y, 2018 [21]	ICM + HF	70.75 ± 6.60	48	48	CT + Levosimendan + QLQXC	CT + Levosimendan	3 months	①②③④⑤⑧
7	CHEN YX, 2021 [22]	ICM + HF	57.80 ± 6.83	116	116	CT + QLQXC	CT	3 months	①②③④
8	DUAN Y, 2017 [23]	ICM + HF	68.13 ± 16.17	45	42	CT + Trimetazidine + QLQXC	CT + Trimetazidine	3 months	①②③⑤⑧
9	GAO YZ, 2016 [24]	ICM + HF	64.13 ± 7.76	45	45	CT + QLQXC	CT + Trimetazidine	3 months	①②③⑤
10	GUO P, 2014 [25]	ICM + HF	71.40 ± 5.20	46	44	CT + QLQXC	CT	3 months	①②③④⑦⑨
11	LI LC, 2013 [26]	ICM + HF	63.00 ± 12.00	55	55	CT + QLQXC	CT + Irbesartan + Trimetazidine	4 weeks	①⑧
12	LI J, 2014 [27]	ICM + HF	58.50 ± 14.50	54	54	CT + QLQXC	CT	24 weeks	①②⑤⑥⑦⑨⑩
13	LI H, 2015 [28]	ICM + HF	65.05 ± 5.50	78	78	CT + QLQXC	CT + Levocarnitine	14 days	①②
14	LI S, 2017 [29]	ICM + HF	67.35 ± 7.25	38	38	CT + QLQXC	CT	3 months	②④⑤⑦
15	LIU WJ, 2007 [30]	ICM + HF	65.50 ± 10.50	30	30	CT + QLQXC	CT	4 months	⑥⑦
16	LV JG, 2020 [31]	ICM + HF	61.50 ± 12.00	44	44	CT + Irbesartan + QLQXC	CT + Irbesartan	1 month	①②③⑦⑧
17	TAO L, 2015 [32]	ICM + HF	74.95 ± 4.35	30	30	CT + QLQXC	CT	3 months	①②⑤
18	WANG YR, 2014 [33]	ICM + HF	56.50 ± 10.60	96	96	CT + QLQXC	CT	8 weeks	①
19	WANG SP, 2015 [34]	ICM + HF	58.70 ± 10.85	60	60	CT + QLQXC	CT	6 months	①②③⑤⑥⑦⑧
20	WEN X, 2022 [35]	ICM + HF	70.20 ± 2.80	63	62	CT + ARNI + QLQXC	CT + ARNI	3 months	①②④
21	YU J, 2013 [36]	ICM + HF	62.30 ± 14.30	43	43	CT + QLQXC	CT	3 months	①②③⑧
22	ZHANG AJ, 2012 [37]	ICM + HF + AF	65.00 ± 11.00	98	100	CT + QLQXC	CT + Digoxin	6 months	②⑧

ICM, ischemic cardiomyopathy. HF, heart failure. QLQXC, Qili Qiangxin Capsule. CT, conventional therapy. ARNI, angiotensin receptor-neprilysin inhibitor. T, treatment group. C, control group. ① ORR; ② LVEF; ③ LVEDD; ④ LVESD; ⑤ pro-BNP; ⑥ MLHFQ; ⑦ 6MWD; ⑧ AEs; ⑨ Rehospitalization; ⑩ Death.

combination therapy could significantly increase the ORR for patients with ICM comorbid with HF (RR = 1.19, 95% CI: 1.13 to 1.26, $P < 0.000\ 01$; Figure 3). In light of the well-symmetrical funnel plot (Supplementary Figure S2A) and the results of Egger's test (Supplementary Figure S3A), no significant publication bias was found ($P = 0.555$). Based on the sensitivity analysis, the overall estimate of ORR was dependent on a single trial. With the elimination of data from a previous study [27], the results of I^2 decreased markedly ($I^2 = 18\%$) (Supplementary Figure S4).

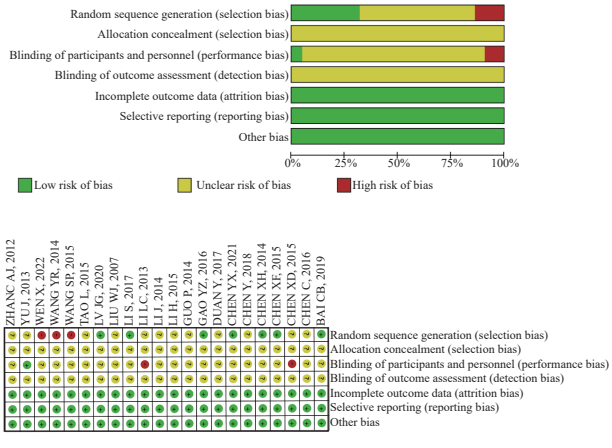

Figure 2 Risk of bias across all included studies

3.4 LVEF

A total of 18 trials [17-25, 27-29, 31-34, 36, 37] including 1 997 participants reported the endpoint of LVEF. The random-effects model was applied according to a high heterogeneity ($I^2 = 91\%$). Compared with conventional therapy, the combination therapy could significantly increase the LVEF for patients with ICM comorbid with HF (MD = 7.40, 95% CI: 5.72 to 9.09, $P < 0.000\ 01$; Figure 4). According to the well-symmetrical funnel plot (Supplementary Figure S2B) and the result of Egger's test (Supplementary Figure S3B), no significant publication bias was detected ($P = 0.436$).

Table 2 The modified Jadad score for each study

Study	Randomization			Allocation concealment			Blinding			With-drawal	Total score
	Adequate	Unclear	Inadequate	Adequate	Unclear	Inadequate	Adequate	Unclear	Inadequate or unused		
BAI CB, 2019 [16]	2	0	0	0	1	0	0	0	0	0	3
CHEN XH, 2014 [17]	0	1	0	0	1	0	0	0	0	0	2
CHEN XF, 2015 [18]	0	1	0	0	1	0	0	0	0	0	2
CHEN XD, 2015 [19]	2	0	0	0	1	0	0	0	0	0	3
CHEN C, 2016 [20]	2	0	0	0	1	0	0	0	0	0	3
CHEN Y, 2018 [21]	0	1	0	0	1	0	0	0	0	0	2
CHEN YX, 2021 [22]	2	0	0	0	1	0	0	0	0	0	3
DUAN Y, 2017 [23]	0	1	0	0	1	0	0	0	0	0	2
GAO YZ, 2016 [24]	2	0	0	0	1	0	0	0	0	0	3
GUO P, 2014 [25]	0	1	0	0	1	0	0	0	0	0	2
LI LC, 2013 [26]	0	1	0	0	1	0	0	0	0	0	2
LI J, 2014 [27]	0	1	0	0	1	0	0	0	0	0	2
LI H, 2015 [28]	0	1	0	0	1	0	0	0	0	0	2
LI S, 2017 [29]	2	0	0	0	1	0	0	0	0	0	3
LIU WJ, 2007 [30]	0	1	0	0	1	0	0	0	0	0	2
LV JG, 2020 [31]	2	0	0	0	1	0	0	0	0	0	3
TAO L, 2015 [32]	0	1	0	0	1	0	0	0	0	0	2
WANG YR, 2014 [33]	0	0	0	0	0	0	0	0	0	0	0
WANG SP, 2015 [34]	0	0	0	0	0	0	0	0	0	0	0
WEN X, 2022 [35]	0	0	0	0	1	0	0	0	0	0	1
YU J, 2013 [36]	0	1	0	0	1	0	2	0	0	0	2
ZHANG AJ, 2012 [37]	0	1	0	0	1	0	0	0	0	0	2

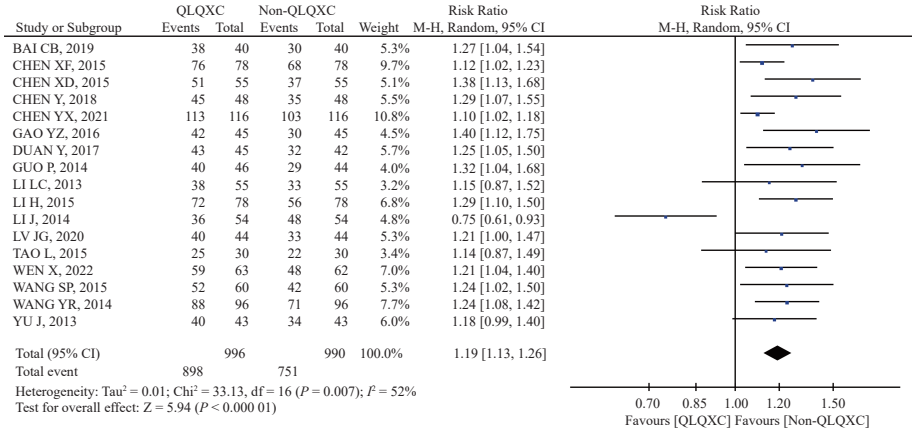

Figure 3 Forest plot of the effect of the adjuvant therapy with QLQXC on ORR

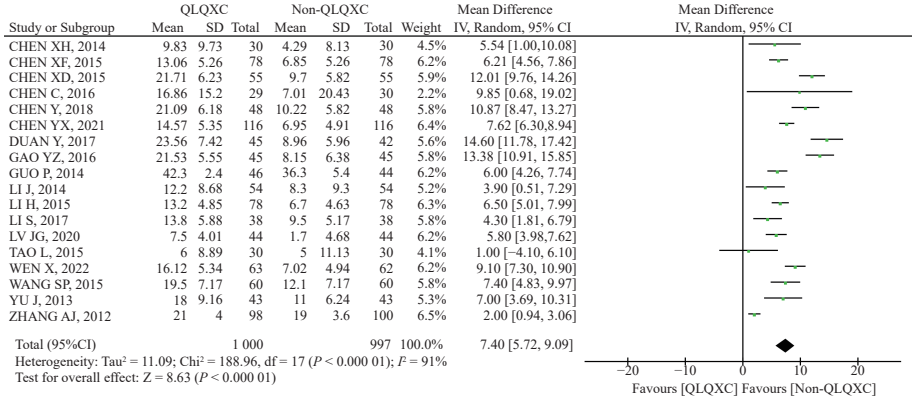

Figure 4 Forest plot of the effect of the adjuvant therapy with QLQXC on LVEF

3.5 LVEDD

Overall, 11 trials [16, 17, 20-25, 31, 34, 36] including 1 088 participants reported the endpoint of LVEDD. The random-effects model was applied according to high heterogeneity (I^2 = 89%). Compared with conventional therapy alone, the combination therapy could significantly reduce LVEDD for patients with ICM comorbid with HF (MD = – 4.76, 95% CI: – 6.72 to – 2.79, P < 0.000 01; Figure 5). In light of the well-symmetrical funnel plot (Supplementary Figure S2C) and the result of Egger's test (Supplementary Figure S3C), no significant publication bias was observed (P = 0.958).

3.6 LVESD

In total, five trials [21, 22, 25, 29, 33] including 619 participants reported the endpoint of LVESD. The random-effects model was applied according to high heterogeneity (I^2 = 96%). Compared with conventional therapy alone, the combination therapy could significantly reduce LVESD for patients with ICM comorbid with HF (MD = – 3.36, 95% CI: – 6.38 to – 0.35, P = 0.03; Figure 6).

3.7 pro-BNP

A total of 10 trials [16, 17, 19, 21, 23, 24, 27, 29, 32, 34] including 896 participants reported the endpoint of pro-BNP. The fixed-effects model was applied according to a significant homogeneity (I^2 = 7%). Compared with conventional therapy alone, the combination therapy could significantly reduce the level of pro-BNP for patients with ICM comorbid with HF (MD = – 57.76, 95% CI: – 70.61 to – 44.90, P < 0.000 01; Figure 7). In light of the well-symmetrical funnel plot (Supplementary Figure S2D) and the result of Egger's test (Supplementary Figure S3D), no significant publication bias was found (P = 0.222).

3.8 MLHFQ

A total of four trials [20, 27, 30, 34] including 347 participants reported the endpoint of the MLHFQ. The random-effects model was applied according to high heterogeneity (I^2 = 54%). Compared with conventional therapy, the combination therapy could significantly increase the score of MLHFQ for patients with ICM comorbid with HF (MD = – 8.28, 95% CI: – 12.66 to – 3.91, P = 0.000 2; Figure 8).

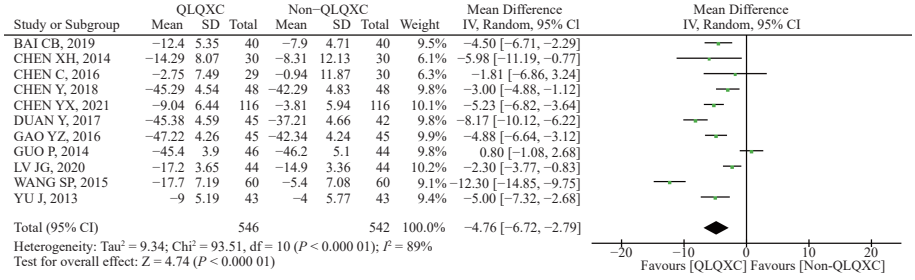

Figure 5 Forest plot of the effect of the adjuvant therapy with QLQXC on LVEDD

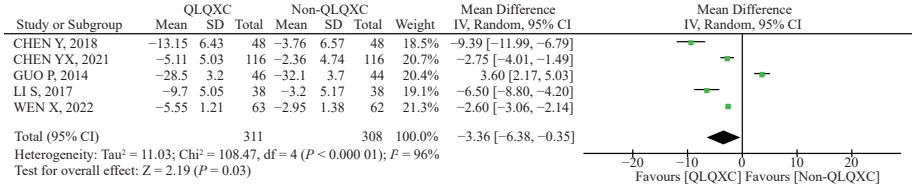

Figure 6 Forest plot of the effect of the adjuvant therapy with QLQXC on LVESD

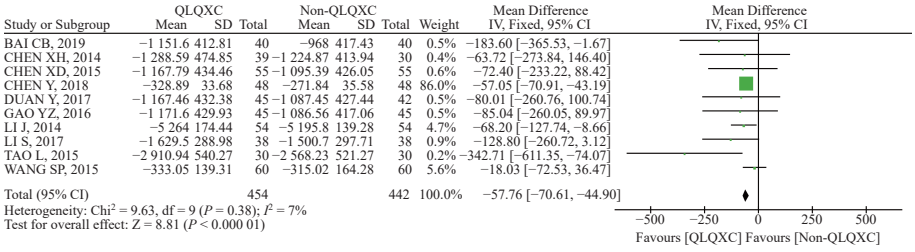

Figure 7 Forest plot of the effect of the adjuvant therapy with QLQXC on pro-BNP

3.9 6MWD

In total, eight trials [16, 20, 25, 27, 29-31, 34] including 681 participants reported the endpoint of 6MWD. The random-effects model was applied according to high heterogeneity (I^2 = 92%). Compared with conventional therapy, the combination therapy could significantly increase 6MWD for patients with ICM comorbid with HF (MD = 45.68, 95% CI: 28.77 to 62.58, P < 0.000 01; Figure 9).

3.10 AEs

Overall, seven trials [21, 23, 26, 31, 34, 36, 37] including 785 participants reported the endpoint of AEs. The fixed-effects model was applied according to a significant homogeneity (I^2 = 38%). Compared with conventional therapy, the combination therapy could significantly reduce the incidence of AEs for patients with ICM comorbid with HF (RR = 0.44, 95% CI: 0.27 to 0.71; P = 0.000 6; Figure 10).

3.11 Rehospitalization

A total of four trials [17, 20, 25, 27] including 317 participants reported the endpoint of rehospitalization. The fixed-effect model was applied according to a significant homogeneity (I^2 = 0%). Compared with conventional therapy, the combination therapy could significantly reduce the incidence of rehospitalization for patients with ICM comorbid with HF (RR = 0.50, 95% CI: 0.35 to 0.73, P = 0.000 3; Figure 11).

3.12 Mortality

A total of two trials [20, 27] including 167 participants reported the endpoint of mortality. The fixed-effects model was applied according to a significant homogeneity (I^2 = 17%). Compared with conventional therapy, the combination therapy could not significantly reduce the incidence of mortality for patients with ICM comorbid with HF (RR = 0.46, 95% CI: 0.11 to 2.02, P = 0.30; Figure 12).

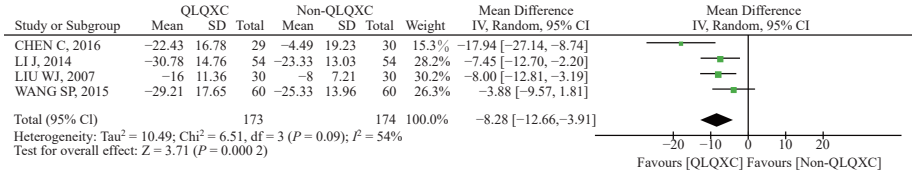

Figure 8 Forest plot of the effect of the adjuvant therapy with QLQXC on MLHFQ

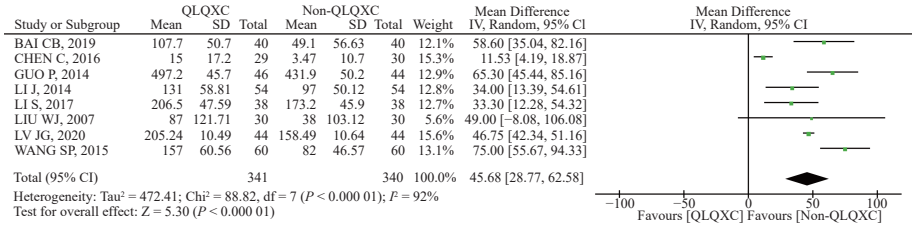

Figure 9 Forest plot of the effect of the adjuvant therapy with QLQXC on 6MWD

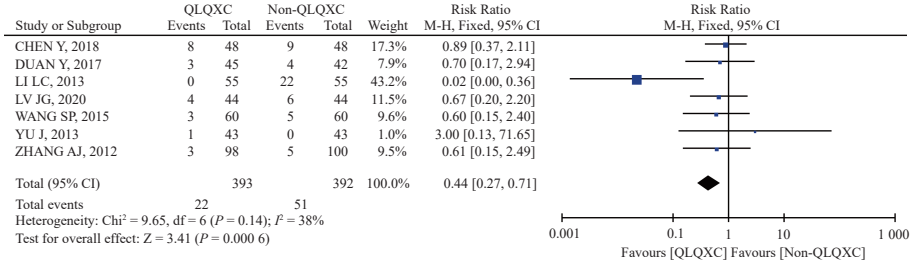

Figure 10 Forest plot of the effect of the adjuvant therapy with QLQXC on AEs

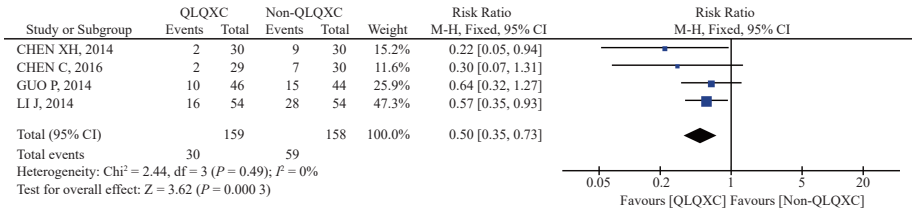

Figure 11 Forest plot of the effect of the adjuvant therapy with QLQXC on rehospitalization

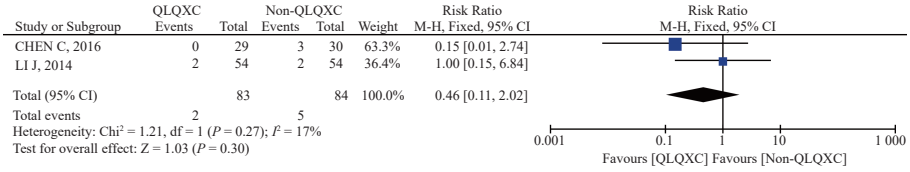

Figure 12 Forest plot of the effect of the adjuvant therapy with QLQXC on mortality

3.13 Results of subgroup analyses

3.13.1 ORR The heterogeneity decreased significantly when stratified by the mean age of participants (I^2 = 1%), follow-up period (I^2 = 16%), publication date (I^2 = 31%), and therapy methods (I^2 = 0%). Additionally, the ORR was increased significantly by the adjuvant QLQXC therapy in the subgroup published after the year of 2014 (RR = 1.21, 95% CI: 1.14 to 1.27, P < 0.000 01), the subgroups with a mean age more than 65 years old (RR = 1.21, 95% CI: 1.14 to 1.28, P < 0.000 01), and the subgroup combined with trimetazidine (RR = 1.30, 95% CI: 1.16 to 1.45, P < 0.000 01) (Supplementary Figure S5).

3.13.2 LVEF The heterogeneity did not differ significantly when stratified by the mean age of participants, follow-up period, publication date, and therapy methods. Additionally, the LVEF was increased significantly by the adjuvant QLQXC therapy in the subgroup published after the year of 2014 (MD = 8.42, 95% CI: 6.75 to 10.08, P < 0.000 01), the subgroup with a mean age over 65 (MD = 8.11, 95% CI: 6.08 to 10.13, P < 0.000 01), the subgroup with a follow-up period under 3 months (MD = 8.07, 95% CI: 6.55 to 9.60, P < 0.000 01), and the subgroup combined with trimetazidine (MD = 13.16, 95% CI: 10.64 to 15.68, P < 0.000 01) (Supplementary Figure S6).

3.13.3 LVEDD The heterogeneity did not differ significantly when stratified by the mean age of participants, publication date, and therapy methods. Additionally, the LVEDD was decreased significantly by the adjuvant QLQXC therapy in the subgroup published after the year of 2014 (MD = 5.36, 95% CI: – 7.46 to – 3.26, P < 0.000 01), the subgroup with a mean age under 65 (MD = – 5.62, 95% CI: – 7.79 to – 3.45, P < 0.000 01), and the subgroup combined with trimetazidine (MD = – 6.37, 95% CI: – 9.97 to – 2.78, P = 0.000 5) (Supplementary Figure S7).

3.13.4 MLHFQ The heterogeneity of the subgroup published before the year of 2014 and that with a mean age under 65 decreased significantly when stratified by the publication date (I^2 = 0%) and the mean age of participants (I^2 = 0%). Additionally, the MLHFQ was decreased significantly by the adjuvant QLQXC therapy in the subgroup with a mean age over 65 (MD = – 12.17, 95% CI: – 21.78 to – 2.55, P = 0.01) (Supplementary Figure S8).

3.13.5 6MWD The heterogeneity did not differ significantly when stratified by the mean age of participants, follow-up period, publication date, and therapy methods. Additionally, the 6MWD was increased significantly by the adjuvant QLQXC therapy in the subgroup published before the year of 2014 (MD = 49.72, 95% CI: 25.91 to 73.53, P < 0.000 1), the subgroup with a mean age under 65 (MD = 52.72, 95% CI: 37.92 to 67.51, P < 0.000 01, and the subgroup with a follow-up period over 3 months (MD = 53.63, 95% CI: 21.87 to 85.40, P < 0.000 1) (Supplementary Figure S9).

4 Discussion

As a famous Chinese patent medicine, QLQXC is composed of Renshen (Ginseng Radix et Rhizoma), Danshen (Salviae Miltiorrhizae Radix et Rhizoma), Tinglizi (Descurainiae Semen Lepidii Semen), Zexie (Alismatis Rhizoma), Honghua (Carthami Flos), Yuzhu (Polygonati Odorati Rhizoma), and Zhiqiao (Aurantii Fructus), which have been widely used to treat chronic HF in China. A large number of studies have clarified that the pathological mechanism of the QLQXC improving cardiac function is multifactorial: (i) increasing the ion level in myocardial cells [38]; (ii) alleviating apoptosis and autophagy [39-41]; (iii) protecting cardiac microvascular endothelial cells [42, 43]; (iv) reducing myocardial fibrosis and inhibiting cardiac remodeling [44, 45]; (v) improving myocardial energy metabolism [46, 47]; (vi) potentiating mitochondrial function and alleviating mitochondrial damage [48, 49]. The specific information from the previous studies is summarized in Table 3.

This meta-analysis is the first evidence-based study focusing on patients with ICM comorbid with HF. Moreover, subgroup and sensitivity analyses were conducted to explore the source of high heterogeneity. We finally included 22 trials with a total of 2 439 patients. ORR, LVEF, LVEDD, LVESD, and pro-BNP were considered as primary outcomes, and AEs, mortality, rehospitalization, and 6MWD as secondary outcomes. We found that the combination therapy of QLQXC with conventional western medicine could improve the endpoint of ORR, LVEF, LVEDD, LVESD, pro-BNP, 6MWD, MLHFQ, and AEs significantly, compared with conventional therapy alone. Surprisingly, this combination therapy could also reduce the risk of rehospitalization significantly. However, the trials we included did not report the exact reason for patients' rehospitalization, and hence, it was uncertain whether the QLQXC reduced the recurrence of HF in

Table 3 The mechanism of QLQXC in regulating cardiac function

Mechanism	Study	Specific pathway of the regulating mechanism
Increasing the ion level in myocardial cells	LI Y, 2022 [38]	Modulating the calcium transients and calcium sparks in cardiomyocytes of human
Alleviating apoptosis and autophagy	FAN CL, 2022 [39]	Inhibiting the ROS/AMPK/mTOR pathway in H/R-induced myocardial injury model
	QIN Y, 2022 [40]	Mediating the PI3K/AKT/mTOR pathway in DOX-induced rat model
	LI F, 2021 [41]	Mediating the ErbB2-AKT-FoxO3a axis
Protecting cardiac microvascular endothelial cells	WANG Y, 2021 [42]	Activating miR-21 and HIF-1α/VEGF pathway
	WANG Y, 2018 [43]	Regulating the prolyl hydroxylases 3 and AMPK/mTOR/HIF-1α pathway
Reducing myocardial fibrosis and inhibiting cardiac remodeling	SUN X, 2020 [44]	Reducing myocardial fibrosis, promoting TGF-β3/Smad7 pathway
	LU Y, 2022 [45]	Modulating the gut microbiota and NLRP3 inflammasome
Improving myocardial energy metabolism	CHENG W, 2020 [46]	Enhancing the cardiac 18F-fluorodeoxyglucose and translocation of GLUT4 in the border area
	WANG Y, 2020 [47]	Regulating glucose uptake, FFA uptake, and key enzymes of energy metabolism
Improving mitochondrial function and alleviating mitochondrial damage	ZHOU J, 2020 [48]	Increasing the expression of PINK1 and Parkin in cardiomyocytes
	LU Y, 2020 [49]	Downregulating the PINK1/Parkin 2 pathway and reversing mitochondrial related metabolic shift

ROS, reative oxygen species. AMPK, AMP-activated protein kinase. mTOR, mechanistic target of rapamycin. H/R, hypoxia-reoxygenation. PI3K, phosphatidylinositide 3-kinases. AKT, protein kinase B. DOX, doxorubicin ErbB2, Receptor tyrosine-protein kinase erbB-2. FoxO3a, Forkhead box protein O3 a miR-21, microRNA-21. HIF-1α, hypoxia-inducible factor 1 alpha. VEGF, vascular endothelial growth factor. TGF-β3, Transforming growth factor beta 3. GLUT4, glucose transporter type 4. FFA, free fatty acid. PINK1, PTEN induced putative kinase 1.

patients with ICM. Additionally, the current study revealed that the combination treatment did not decrease the incidence of death events, which was different from previous studies. We suspect that this phenomenon is related to the specific myocardial damage caused by ICM and will verify the safety of the QLQXC for ICM in future studies.

In order to find the source of high heterogeneity, we conducted subgroup and sensitivity analyses on the endpoints with high heterogeneity. Markedly, high heterogeneity could not be eliminated when subgroup analysis was conducted according to the average age of patients, follow-up period, publication date, and the methods of therapy. Therefore, we speculated that heterogeneity originates from many aspects, and the diversity of clinical treatment and research methods might produce high heterogeneity. Notably, the subgroup analysis put forth the following phenomena. First, the adjuvant effect of QLQXC was age-related. The improvement in ORR, LVEF, MLHFQ, and 6MWD was pronounced with the QLQXC in patients with an average age of 65 years. Second, the adjuvant effect of the QLQXC was related to the follow-up period. The improvement in ORR and LVEF was more significant in the subgroup with a follow-up period of less than three months, while the improvement in 6MWD was more significant in the subgroup whose follow-up period was more than three months. Whether the effect of the QLQXC on ICM is related to the patient's age and intervention duration will also be a research direction in the future. Third, the year of publication might also impact the effectiveness of the QLQXC. Interestingly, the effectiveness of QLQXC in studies published after 2014 was superior to that published before 2014. A large-scale RCT published in 2013 demonstrated that the QLQXC significantly reduced the level of pro-BNP in patients with HF [9]. Subsequently, QLQXC was included in the Chinese Guidelines for the Diagnosis and Treatment of Chronic Heart Failure 2014 and recommended for HF patients with heart-Yang deficiency syndrome [50]. We are curious to explore whether this would have any influence on subsequent clinical studies that would create biases.

Nevertheless, the present study had some limitations. First, some of the included trials were of low quality. Only seven studies reported specific randomization methods, and almost none reported the method of blinding and allocation concealment. Second, the follow-up period of all trials was not long enough; thus, we could not confirm the long-term effects of the QLQXC. Last but not least, the sample size of RCTs we included was unavoidably insufficient, which might cause deviations between the results of our research and the actual situation. So, we look forward to more clinical studies with large sample size to evaluate the effectiveness of adjuvant therapy with QLQXC.

5 Conclusion

In conclusion, the combination therapy of QLQXC with conventional western medicine promotes cardiac function and improves quality of life in patients with ICM

comorbid with HF. Our study provides a new clinical strategy for the treatment of ICM; however, rigorous large-scale RCTs of high quality are needed to verify the efficacy and safety of the combination therapy for patients with ICM with HF.

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Competing interests

The authors declare no conflict of interest.

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芪芪强心胶囊辅助治疗缺血性心肌病心力衰竭的有效性和安全性：一项系统评价和 meta 分析

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【摘要】目的 本研究旨在评估芪芪强心胶囊（QLQXC）联合西药对缺血性心肌病（ICM）合并心力衰竭（HF）患者的有效性和安全性。**方法** 我们在国内数据库中国知网（CNKI）、维普（VIP）、万方和中国生物医学文献数据库（CBM），以及国外数据库 PubMed 和 Embase 数据库检索了相关文献，时间为自数据库创建至 2023 年 1 月 8 日，无语言限制。本研究进行了亚组分析和敏感性分析等，所有统计分析均采用 Review Manager 5.4 和 Stata 15.0 进行。**结果** 与常规西药治疗相比，QLQXC 联合西药明显提升了 ICM 患者的总有效率（ORR）（$P < 0.000\ 01$）、左室射血分数（LVEF）（$P < 0.000\ 01$）、明尼苏达州心力衰竭生存问卷（MLHFQ）分数（$P = 0.000\ 2$）和 6 分钟步行距离（6MWD）（$P < 0.000\ 01$），减少了左室舒张末期内径（LVEDD）（$P < 0.000\ 01$）、左室收缩末期内径（LVESD）（$P = 0.03$）和脑钠肽前体（pro-BNP）（$P < 0.000\ 01$），同时降低了再住院事件发生率（$P = 0.000\ 3$）和不良事件（AEs）发生率（$P = 0.000\ 6$）。对于死亡率结局，QLQXC 联合西药组与常规西药组间无明显差异（$P = 0.30$）。**结论** QLQXC 联合常规西药可以显著改善 ICM 合并 HF 患者的心功能和生活质量。

【关键词】芪芪强心胶囊；缺血性心肌病；心力衰竭；meta 分析；中成药；左室射血分数；左室舒张末期内径