Heliyon 9 (2023) e16012

Contents lists available at ScienceDirect

Heliyon

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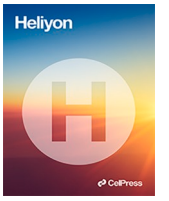

Review article

Effect of Traditional Chinese Medicine Cutaneous Regions Therapy as adjuvant treatment of chronic heart failure: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Chronic heart failure
Traditional Chinese medicine cutaneous regions therapy
Acupuncture
Acupoint application
Moxibustion
Meta-analysis

ABSTRACT

Objective: To systematically evaluate the effectiveness of Traditional Chinese Medicine Cutaneous Regions Therapy (TCMCRT) as an adjunctive treatment for chronic heart failure.
Methods: China National Knowledge Infrastructure (CNKI), Wanfang database, China Science and Technology Journal Database (VIP), Chinese BioMedical Literature Database (CBM), Cochrane Library, PubMed, Web of Science, and EMBASE database were searched to screen randomized controlled trials (RCTs) of TCMCRT for chronic heart failure versus conventional western treatment for chronic heart failure. The Cochrane Risk of Bias Collaboration tool was used to assess the risk of bias in RCTs. Meta-analysis was performed using RevMan 5.3 software to systematically evaluate the effects of conventional western treatment combined with TCMCRT on the cardiac function efficacy, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), 6-min walk test (6MWT), Minnesota Heart Failure Quality of Life Scale (MLHFQ) and Adverse effects, as well as to evaluate the safety of this treatment modality.
Results: 18 RCT studies were finally included, with a total of 1388 patients, including 695 in the experimental group and 693 in the control group. The results of the Meta-analysis showed that the efficacy of improved cardiac function was better in the experimental group than in the control group [RR = 1.24, 95%CI (1.16, 1.32), $P < 0.00001$]. Improvement of LVEF in the experimental group was better than the control group [MD = 0.04, 95%CI (0.02, 0.05), $P < 0.00001$]. LVEDD were better in the experimental group than in the control group after treatment [MD = −3.63, 95% CI (−6.14, −1.12), $P = 0.005$]. The experimental group improved NT-proBNP better than the control group [MD = −586.26, 95%CI (−857.83, −314.68), $P < 0.0001$]. The experimental group improved 6MWT better than the control group [MD = 38.76, 95%CI (20.77, 56.75), $P < 0.0001$]. The experimental group improved MLHFQ values better than the control group [MD = −5.93, 95%CI (−7.70, −4.16), $P < 0.00001$]. Nine of the included studies mentioned the occurrence of adverse reactions, but none reported serious adverse reactions.

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https://doi.org/10.1016/j.heliyon.2023.e16012
Received 31 July 2022; Received in revised form 26 April 2023; Accepted 28 April 2023
Available online 2 May 2023

Conclusion: The available evidence suggests that TCMCRT has good efficacy in the adjuvant treatment of chronic heart failure. However, due to the limitations of this study, more high-quality studies are needed to further validate this conclusion.

Abbreviations

TCM	Traditional Chinese medicine
TCMCRT	Traditional Chinese Medicine Cutaneous Regions Therapy
CHF	Chronic heart failure
RCTs	Randomized controlled trials
ACEI	Angiotensin-converting enzyme inhibitors
ARB	angiotensin receptor antagonists
SGLT-2	sodium-glucose cotransporter protein-2
ARNI	angiotensin receptor neprilysin inhibitor
NYHA	New York Heart Association
LVEF	left ventricular ejection fraction
LVEDD	left ventricular end-diastolic internal diameter
NT-proBNP	*N*-terminal pro-B-type natriuretic peptide
6MWT	6-min walk test
MLHFQ	Minnesota Heart Failure Quality of Life Scale
EBM	Evidence-based medicine

1. Introduction

Chronic heart failure (CHF) has become one of the most important cardiovascular diseases of the 21st century due to its high incidence and mortality rates [1]. Heart failure is a complex clinical syndrome caused by structural or functional damage to the heart, insufficient ventricular filling, or reduced ejection capacity. It is a highly prevalent progressive disease associated with considerable morbidity and mortality [2–4]. CHF is the final stage of various cardiovascular diseases, and despite the development and improvement of treatment strategies, the persistently high rates of morbidity, mortality, and readmissions resulting from this disease remain a major socioeconomic burden [5–8]. Studies have shown that there are approximately 5.1 million patients with heart failure in the United States and the prevalence continues to increase [9]. China also has 4.5 million patients with heart failure, with a population prevalence of 0.9% (men:0.7%,women:1.0%); about 500,000 new cases of heart failure occur each year, with an incidence of 0.7‰–0.9‰ [10,11]. The long-term goal of treatment of this disease should be to prolong life by slowing, stopping, or reversing progressive left ventricular dysfunction [12]. Currently, the focus of CHF treatment is to inhibit myocardial remodeling and restore cardiac function [13]. Conventional western treatment such as diuretics, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor antagonists (ARB), and β-blockers, which are widely used clinically for the treatment of CHF [2,14,15], can stabilize the disease faster, but the prognosis improvement for most patients is still not satisfactory [6]. A few new drugs have made some progress in current treatment, such as sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors, angiotensin receptor neprilysin inhibitor (ARNI), and levosimendan, but there is a lack of evidence-based medical evidence to confirm that they can replace traditional drugs [3,16–18].

Traditional Chinese Medicine Cutaneous Regions Therapy (TCMCRT) is very common in economic undeveloped region, in areas where Traditional Chinese medicine (TCM) treatment is prevalent, and in TCM hospitals at all levels, where it is often used in combination with conventional western treatment during hospitalization [19]. TCMCRT has a long history, from more than 5000 years ago when the current treatment method took shape [20], and has definite efficacy in the treatment of different diseases. TCMCRT easy to operate, easily accepted by the middle-aged and elderly population, and easy to use in primary care units. The adjuvant treatment of CHF with TCMCRT (including acupuncture, acupuncture point application, moxibustion, etc.) can bring into play the characteristics of TCM's holistic view and evidence-based treatment. TCMCRT is relatively simple to operate, inexpensive, easy to promote, and has unique efficacy advantages.

TCMCRT is to apply different manipulation at the body surface acupuncture points, using acupuncture, drug retention (acupoint application), drug heat action (moxibustion), etc., to play the effect of TCM to invigorate the blood and benefit the "qi", communicate with the surface and smooth the blood vessels, to achieve the therapeutic effect of restoring heart function and improving symptoms. Therefore, it is meaningful to study the effect of TCMCRT in the treatment of heart failure. However, most of the existing clinical studies are small sample studies, and there is a lack of large samples and high-quality clinical studies. This study systematically evaluates the efficacy and safety of TCMCRT as an adjuvant treatment for CHF, with the goal of providing an evidence-based foundation for clinical application.

2. Methods

This study has been registered on the PROSPERO platform under the registration number: CRD42022374971.

2.1. Literature search

A total of eight databases were searched by computer, including China National Knowledge Infrastructure (CNKI), Wanfang database, China Science and Technology Journal Database (VIP), Chinese BioMedical Literature Database (CBM), Cochrane Library, PubMed, Web of Science and EMBASE database. The search time of each database is built until September 2022. The English search terms included "chronic heart failure" "acupuncture" "moxibustion" "ear-acupuncture" "acupoint application" "Traditional Chinese Medicine" "randomized controlled trial", etc. The specific search strategy for PubMed, for example, is shown below. The search strategies of other databases were adjusted according to the corresponding search rules.

#1 chronic heart failure [MeSH Terms].
#2 chronic heart failure [Title/Abstract].
#3 #1 OR #2.
#4 traditional Chinese medicine [MeSH Terms].
#5 traditional Chinese medicine [Title/Abstract].
#6 #4 OR #5.
#7 acupuncture [MeSH Terms].
#8 acupuncture [Title/Abstract].
#9 moxibustion [MeSH Terms].
#10 moxibustion [Title/Abstract].
#11 ear-acupuncture [MeSH Terms].
#12 ear-acupuncture [Title/Abstract]#13 acupoint application [MeSH Terms].
#14 acupoint application [Title/Abstract].
#15 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14.
#16 Randomized Controlled Trial [Publication Type].
#17 Controlled Clinical Trial [Publication Type].
#18 random [All Fields].
#19 #16 OR #17 OR #18.
#20 #3AND #6 AND #15 AND #19.

2.2. Inclusion criteria

(1) Study type: Randomized Controlled Trials (RCTs), blindness, language unlimited; (2) Study subjects:(i) patients were diagnosed with CHF according to Framingham criteria [21], and their cardiac function was graded as class II to IV according to American Heart Association criteria [22]; (ii) patients were not limited in gender, age, or duration of disease; (3) interventions: the control group was given diuretics, ACEI, β-blockers, salt corticosteroid receptor antagonists, digoxin and other conventional western treatment [23]; the experimental group was treated with a combination of a single TCMCRT on the basis of the control group, including: acupuncture treatment (using milli-needle piercing and leaving the needle for a certain period of time, including QinZhen acupuncture, FuZhen Acupuncture, Back-Shu Points Acupuncture, etc.), TCM acupoint application (including QiangXin Acupoint Application, Cong Bai Tong Yang Acupoint Application, etc.), moxibustion (including other medication moxibustion), ear-acupuncture, etc. (4)Main outcome indicators: Cardiac function efficacy: refer to the treatment response assessed by the New York Heart Association (NYHA) standard [22] and the Guidelines for Clinical Research on New Drugs in Chinese Medicine [24], significant effect: symptoms and signs basically disappeared, and the New York Heart Association (NYHA) of the United States cardiac function classification improved $\geq$2; effective: symptoms and signs improved, NYHA cardiac function classification improved $\geq$1 and less than 2; ineffective: symptoms and signs did not improve, NYHA cardiac function classification did not change; deterioration: symptoms and signs worsened, NYHA cardiac function classification deteriorated $\geq$1; Evaluation of cardiac function efficacy by counting the number of people who produced a positive effect (significant effect and effective); Secondary outcome indicators: ①left ventricular ejection fraction (LVEF); ②left ventricular end-diastolic diameter (LVEDD); ③NT-proBNP; ④6-min walk test (6MWT); ⑤Minnesota Heart Failure Quality of Life Scale (MLHFQ); ⑥Adverse effects.

2.3. Exclusion criteria

Addition of therapies other than the above treatment measures in the experimental group, such as the addition of other TCM therapies; self-controlled trials, animal experiments, reviews, thought studies, literature studies; descriptive studies; duplicate published literature; no description of the intervention time; no clear outcome indicators and efficacy evaluation criteria, etc. were excluded.

2.4. Data extraction

After retrieving the entire literature, 2 researchers independently screened the literature and extracted the primary data according to the criteria above. After completion, they were summarized and verified, and third-researcher arbitration was requested in case of disagreement. The main elements were: authors of the literature, year of publication, specific way the trial was conducted, mean age of patients included, treatment method, duration of treatment and cardiac function efficacy, LVEF, LVEDD, NT-proBNP, 6MWT, MLHFQ and adverse effects in the treatment and experimental group.

2.5. Quality evaluation

Included studies were independently evaluated for methodological quality according to the Cochrane 5.1.0 systematic reviewer's handbook [25] risk of bias evaluation criteria for controlled trials, including: (1) randomization methods; (2) subject blinding; (3) allocation concealment; (4) reporting bias; (5) data integrity; (6) blinding for outcome evaluation; and (7) other. Each study was judged as "low risk", "high risk", or "inconclusive". When the answer to any item was "high risk", we ultimately judged the overall high risk of study-level bias, and when the answer to all items was "low risk", the overall low risk of study-level bias; the remaining results were judged to be at an overall moderate risk of study-level bias. Bias was evaluated by two persons, and third-researcher arbitration was requested in case of disagreement.

2.6. Statistical analysis

Meta-analysis was performed using RevMan 5.3 software. Count data were expressed as relative risk (RR), and measurement data were expressed as weighted mean difference (WMD), both with 95% confidence intervals (CI) calculated. Heterogeneity among studies was analyzed by P-value and I^2-value statistics tests, and Meta-analysis was performed with a random-effects model when $P < 0.1$ and $I^2 > 50\%$, in parallel with subgroup analysis and sensitivity analysis; when $P \geq 0.1$ and $I^2 \leq 50\%$, fixed-effects model analysis was used. Funnel plots and Egger tests were used to assess publication bias when $\geq$10 included papers for the ending index.

3. Results

3.1. Literature search results

A preliminary search yielded 3957 relevant literature, which were screened strictly according to the inclusion and exclusion criteria and finally included 18 [26–43] studies, all in Chinese. The literature screening process is shown in Fig. 1.

3.2. Basic characteristics of the included studies

A total of 18 studies were included [26–43], with a total of 1388 patients, including 695 in the experimental group and 693 in the

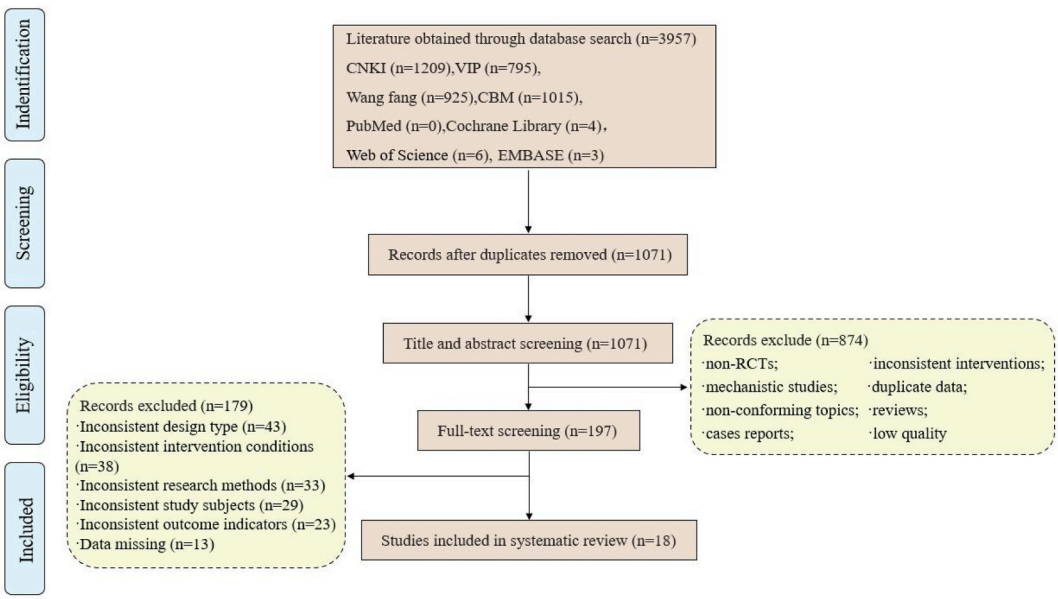

Fig. 1. Flowchart of study selection.

Table 1
Characteristics of included studies.

Author	Sample (E/C)	Male (E/C)		Age (year)		Intervention		Time	Outcomes
		E	C	E	C	E	C		
Jiang 2016 [26]	30/30	17/13	18/12	69.57 ± 12.632	70.93 ± 14.149	QinZhen acupuncture therapy +Conventional treatment	Conventional treatment	Reserved for two days, one day apart , Lasting 3 months	②; ④;⑤; ⑥; ⑦
Liu 2018 [27]	34/33	18/16	16/17	38–75	40–75	Acupuncture +Conventional treatment	Conventional treatment	Once per day, Lasting 4 weeks	①; ②;③; ⑦
He 2021 [28]	35/34	17/18	18/16	69.26 ± 7.85	70.12 ± 7.16	Acupuncture +Conventional treatment	Comfort treatment + Conventional treatment	Once every other day, Lasting 1 months	①; ②;④; ⑦
Zhang 2020 [29]	50/50	26/24	23/27	43–83	40–82	Back-Shu Points Acupuncture +Conventional treatment	Conventional treatment	Once per day, Lasting 4 weeks	②; ⑤
Chen 2020 [30]	31/32	18/13	19/13	56.90 ± 5.78	58.16 ± 5.40	FuZhen Acupuncture +Conventional treatment	Conventional treatment	Once per day, Lasting 15 days	①; ④;⑥; ⑦
Wang 2021 [31]	30/30	16/14	15/15	54.70 ± 1.723	57.27 ± 1647	FuZhen Acupuncture +Conventional treatment	Conventional treatment	Once every other day, Lasting 20 days	①; ⑥;⑦
Wu 2020 [32]	30/30	20/10	19/11	60.5± 6.4	61.4± 5.4	Acupuncture +Conventional treatment	Conventional treatment	Once per day, 2 days rest after 5 consecutive days of treatment, Lasting 28 days	①; ②;⑥
Huang 2019 [33]	63/64	32/31	35/29	62.36 ± 6.56	61.88 ± 7.78	Acupoint Application +Conventional treatment	Conventional treatment	Once per day, Lasting 14 days	②; ③;⑤; ⑥
Zhao 2016 [34]	48/47	25/23	23/24	57.7 ± 11.2	58.7± 10.5	Qiang Xin Acupoint Application +Conventional treatment	Conventional treatment	Once every other day, Lasting 90 days	②; ③
Huang 2018 [35]	55/55	39/16	30/25	60.2± 6.25	61.1± 4.36	Cong Bai Tong Yang Acupoint Application +Conventional treatment	Conventional treatment	Twice a day, Lasting 28 days	①; ④
Zhao 2017 [36]	30/30	15/15	14/16	51.8± 6.6	51.0± 6.5	Acupoint Application +Conventional treatment	Conventional treatment	Once every other day, Lasting 4 weeks	①; ④;⑤; ⑥
Wu J 2020 [37]	30/30	16/14	13/17	64.5± 16.7	62.7± 15.4	Acupoint Application +Conventional treatment	Conventional treatment	Once every other day, Lasting 14 days	①; ②;④; ⑤; ⑦
Deng 2017 [38]	40/40	17/23	16/24	62.75 ± 9.18	63.38 ± 9.45	Acupoint Application +Conventional treatment	Conventional treatment	Once per day, Lasting 12 weeks	①; ②;③; ⑤;⑥
Zhao 2014 [39]	40/38	21/19	19/19	57.4± 9.9	59.6± 9.7	QiangXin Acupoint Application +Conventional treatment	Conventional treatment	Once every other day, Lasting 90 days	①; ②;③; ⑤
Fu 2021 [40]	60/60	34/26	33/27	53.76 ± 6.3	53.91 ± 5.29	Acupoint Application +Conventional treatment	Conventional treatment	Once per day, Lasting 2 weeks	①; ②;③; ⑤;⑦
Wang 2012 [41]	30/30	12/18	13/17	65.0	66.0	Moxibustion +Conventional treatment	Conventional treatment	Once per day, Lasting 4 weeks	①; ②
Chen 2016 [42]	30/30	16/14	13/17	63.03 ± 6.61	63.30 ± 6.85	Moxibustion +Conventional treatment	Conventional treatment	Once per day, 2 days rest after 5 consecutive days of treatment, Lasting 3 weeks	①; ②;③; ④ ⑤; ⑥;⑦
Wang 2016 [43]	29/30	16/13	18/12	61.86 ± 10.07	62.73 ± 10.13	Acupuncture +Conventional treatment	Conventional treatment	Once per day, Lasting 20 days	①; ⑥

*E, experimental group; C, control group.①Cardiac function efficacy; ②LVEF:left ventricular ejection fraction; ③LVEDD:left ventricular end-diastolic internal diameter; ④NT-proBNP; ⑤6MWT:6-min walk test; ⑥MLHFQ:Minnesota Heart Failure Quality of Life Scale; ⑦Adverse events.

control group. Three types of TCMCRTs were involved in the included studies: acupuncture, acupoint application, and moxibustion. Table 1 for details.

3.3. Quality evaluation of included studies

A detailed assessment of the risk of bias for the 18 RCTs [26–43] is shown in Fig. 2. 1) Selective bias (random sequence generation and allocation concealment): 12 studies [26–30,32,33,36–38,40,41] were randomized by random number table; 2 studies [31,43] by computerized randomization; 2 study [35,42] used randomized grouping by order of admission, 1 study [28] referred to allocation concealment. Therefore, the risk of selection bias for the above-mentioned studies was considered to be low. 2) Performance bias (blinding of the participants and personnel): 1 study [28] referred to a blinded implementation, which was considered low risk. Other studies did not provide information on blinding, so the performance bias was evaluated as unclear risk. 3) Detection bias: All studies did not provide enough information to evaluate its risk level; therefore, the risk is unclear. 4) Attrition bias:None of the included RCTs had incomplete data, so the risk of attrition bias was considered "low". 5) Reporting bias: Considering that complete implementation protocols were not available for all studies, the risk of reporting bias was considered "unclear". 6) Other bias: The risk of this bias was considered "low", because no other obvious bias was observed in all studies.

3.4. Meta-analysis results

3.4.1. Comparison of the efficacy of cardiac function

A total of 14 [27,28,30–32,40–43] studies in the included literature reported Cardiac function efficacy in a total of 1006 patients, including 504 in the experimental group and 502 in the control group. There was no significant heterogeneity among the studies ($I^2 =$ 47%), so the data were combined using a fixed-effects model; the results of the Meta-analysis showed statistically significant differences in cardiac function efficacy between the groups [RR = 1.24, 95%CI (1.16, 1.32), $P < 0.00001$] suggesting that the experimental group improved cardiac function efficacy better than the control group. See Fig. 3 for details.

3.4.2. Sensitivity analysis and heterogeneity analysis

The 14 included studies [27,28,30–32,40–43] were excluded one by one and then Meta-analysis was performed. The study by Huang Wei [35] was found to have a relatively large effect on heterogeneity, and after removal, heterogeneity test was performed, and the results showed that there was no significant heterogeneity among the studies ($I^2 = 0\%$), so the fixed-effects model was chosen to combine the data, and the difference between the groups was statistically significant [MD = 1.27, 95%CI (1.18,-1.37), $P < 0.00001$], suggesting that the efficacy of the experimental group on the improvement of cardiac function was better than that of the control group, as detailed in Fig. 4. Analysis of the original article (Huang Wei [35])revealed that the NT-proBNP values of the patients included in this study were significantly greater than those of the remaining studies, suggesting that the condition corresponding to NT-proBNP values may be a source of heterogeneity.

3.4.3. Comparison of post-treatment LVEF values

13 [26–29,32–34,37–42] studies reported post-treatment LVEF in a total of 1036 patients, including 520 in the experimental group and 516 in the control group. There was a large heterogeneity among the studies ($I^2 = 86\%$), so a random-effects model was used to combine the data. The results showed a statistically significant difference in LVEF between the groups [MD = 0.04, 95%CI (0.02, 0.05), $P < 0.00001$], suggesting that the experimental group was superior to the control group in improving post-treatment LVEF. See Fig. 5 for details.

3.4.4. Comparison of post-treatment LVEDD values

7 [27,33,34,38–40,42] studies reported post-treatment LVEDD in a total of 627 patients, 315 in the experimental group and 312 in the control group. There was a large heterogeneity among the studies ($I^2 = 91\%$), so a random-effects model was used to combine the

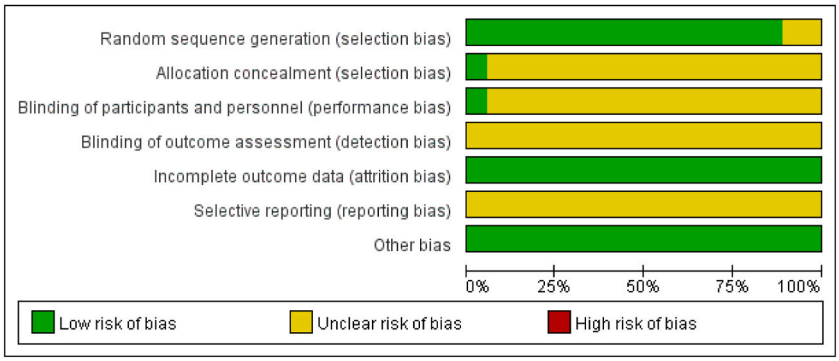

Fig. 2. Inclusion of study risk of bias evaluation chart.

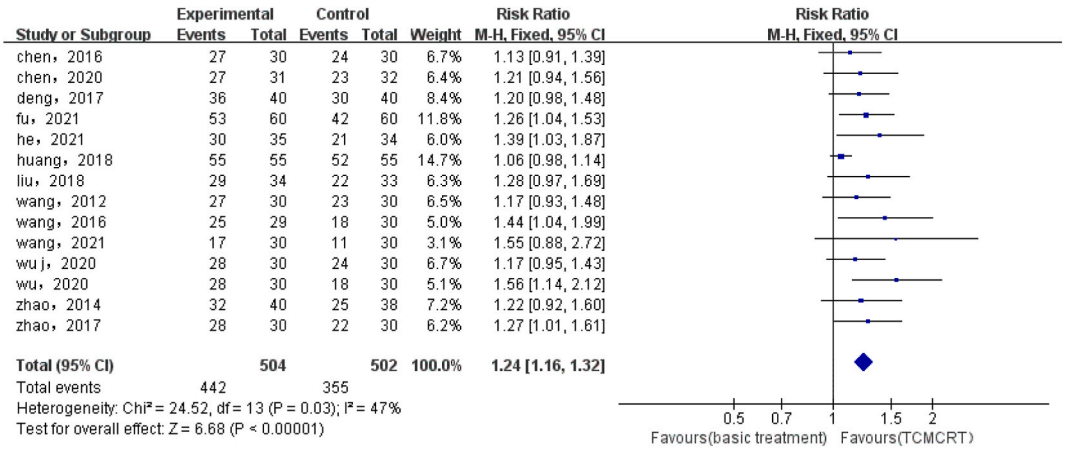

Fig. 3. Forest plot comparing the efficacy of cardiac function in two groups.

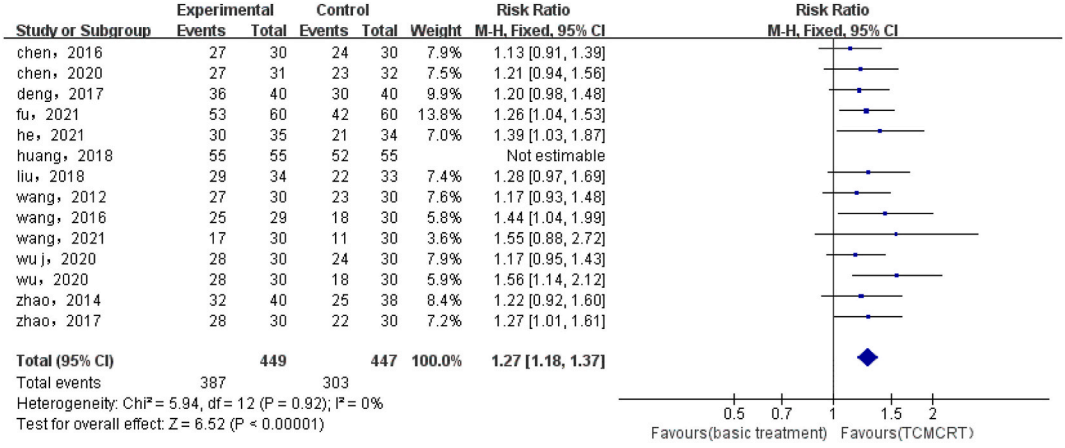

Fig. 4. Sensitivity analysis forest plot comparing the efficacy of cardiac function after treatment in two groups.

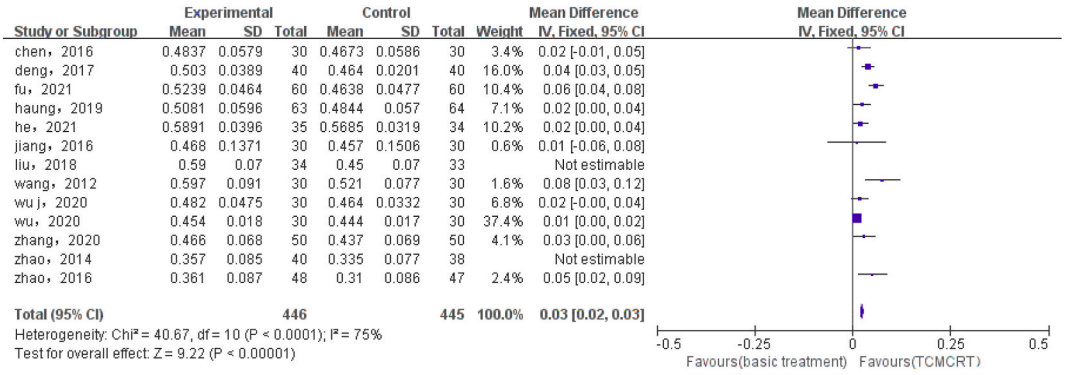

Fig. 5. Forest plot comparing LVEF values after treatment in two groups.

data, and the results showed a statistically significant difference in LVEDD between the groups [MD = −3.63, 95%CI (−6.14, −1.12), $P = 0.005$], suggesting that the experimental group was superior to the control group in improving post-treatment LVEDD values. See Fig. 6 for details.

3.4.5. Comparison of post-treatment NT-proBNP values

7 [26,28,30,35–37,42] studies reported post-treatment NT-proBNP values in a total of 482 patients, including 241 in the experimental group and 241 in the control group. There was a large heterogeneity between studies ($I^2 = 98\%$), so a random-effects model was

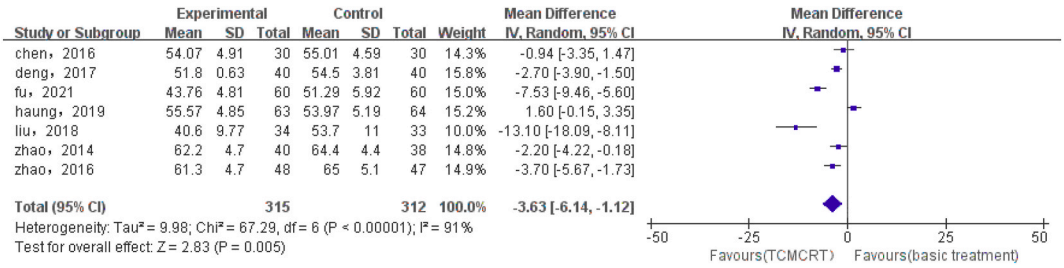

Fig. 6. Forest plot comparing LVEDD values after treatment in two groups.

used to combine the data. The results showed a statistically significant difference in NT-proBNP values between the groups [MD = −586.26, 95%CI (−857.83, −314.68), $P < 0.0001$], suggesting that the experimental group was superior to the control group in improving NT-proBNP values. See Fig. 7 for details.

3.4.6. Comparison of post-treatment 6MWT

9 [26,29,33,36–40,42] studies reported post-treatment 6MWT values in a total of 745 patients, including 373 in the experimental group and 372 in the control group. There was a large heterogeneity among the studies ($I^2 = 95\%$), so a random-effects model was used to combine the data, and the results showed a statistically significant difference in 6MWT values between the groups [MD = 38.76, 95%CI (20.77, 56.75), $P < 0.0001$]. It was suggested that the test group was superior to the control group in improving the post-treatment 6MWT values. See Fig. 8 for details.

3.4.7. Comparison of post-treatment MLHFQ values

8 [26,30–33,38,42,43] studies reported post-treatment MLHFQ values in a total of 569 patients, including 283 in the experimental group and 286 in the control group. There was a large heterogeneity among the studies ($I^2 = 78\%$), so a random-effects model was used to combine the data. The results showed a statistically significant difference in MLHFQ values between the groups [MD = −5.93, 95% CI (−7.70, −4.16), $P < 0.00001$], suggesting that the experimental group was superior to the control group in improving post-treatment MLHFQ values. See Fig. 9 for details.

3.5. Subgroup analysis

Subgroup analysis was performed for LVEF, LVEDD, NT-proBNP, 6MWT, and MLHFQ by intervention time (<4weeks or = 4weeks or >4weeks). The results showed that the results of subgroup analysis were consistent with the overall results without directional changes, but the heterogeneity of the heterogeneity of MLHFQ disappeared at treatment duration <4weeks ($I^2 = 0$) and the heterogeneity of NT-proBNP was significantly reduced ($I^2 = 22\%$), suggesting that treatment duration differences may be the source of heterogeneity of LVEF, LVEDD, NT-proBNP, and MLHFQ. (Table 2).

3.6. Sensitivity analysis

13 studies [26–29,32–34,37–42] included in LVEF, 7 studies [27,33,34,38–40,42] included in LVEDD, 9 studies [26,29,33,36–40,42] included in 6MWT and 8 studies [26,30–33,38,42,43] included in MLHFQ were included using a case-by-case exclusion of individual studies for sensitivity analysis. None of the results changed significantly, suggesting that the results of Meta-analysis involving LVEF, LVEDD, 6MWT, and MLHFQ were more stable. Sensitivity analysis of 8 studies [26,28,30,31,35–37,42] involving NT-proBNP was performed by excluding each study one by one, and the results of the Meta-analysis were significantly changed when studies [26,30,31,35,37,42] were excluded respectively. It was suggested that the experimental group was superior to the control group in terms of improving post-treatment NT-proBNP values when the 6 studies mentioned above were excluded separately.

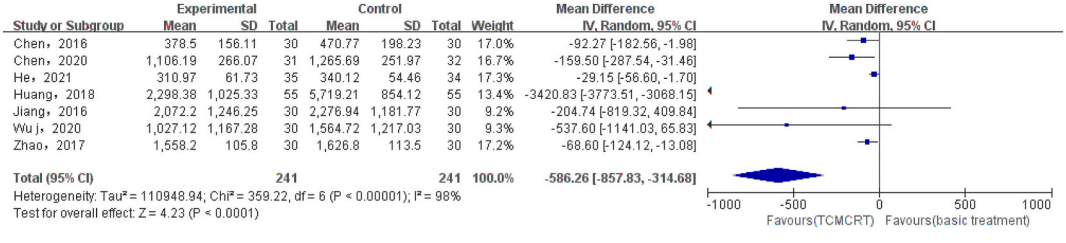

Fig. 7. Forest plot comparing NT-proBNP values after treatment in both groups.

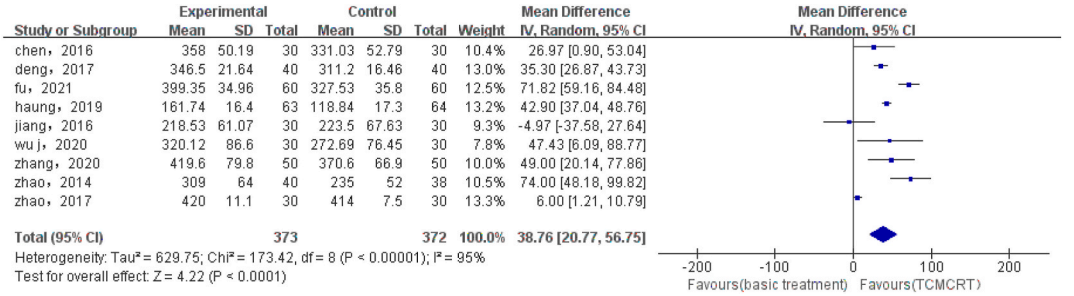

Fig. 8. Forest plot comparing 6MWT values after treatment in both groups.

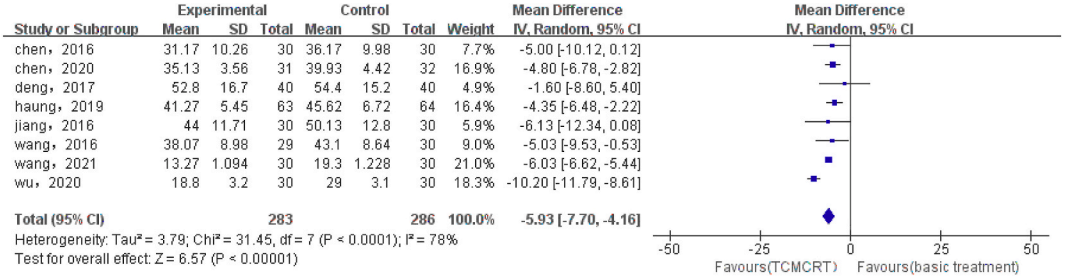

Fig. 9. Forest plot comparing MLHFQ values after treatment in two groups.

Table 2
Results of subgroup analysis of Meta-analysis.

Subgroup	Number of included studies	Heterogeneity test results		Effect model	Meta-analysis results	
		I^2	*P*		95%CI	*P*
LVEF						
Intervention time<4weeks	4 [33,37,40,42]	78%	0.003	Random	0.03 [0.01,0.05]	0.008
Intervention time = 4weeks	5 [27–29,32,41]	93%	<0.00001	Random	0.05 [0.02,0.09]	0.005
Intervention time>4weeks	4 [26,34,38,39]	0%	0.61	Random	0.04 [0.03,0.05]	<0.00001
LVEDD						
Intervention time≤4weeks	4 [27,33,40,42]	95%	<0.00001	Random	−4.68 [-10.24,0.88]	0.10
Intervention time>4weeks	3 [34,38,39]	0%	0.56	Random	−2.81 [-3.72,-1.90]	<0.00001
NT-proBNP						
Intervention time<4weeks	3 [30,37,42]	22%	0.28	Random	−128.48 [-222.20,-34.76]	0.007
Intervention time≥4weeks	4 [26,28,35,36]	99%	<0.00001	Random	764.57 [322.87,1206.27]	0.0007
MLHFQ						
Intervention time<4weeks	5 [30,31,33,42,43]	0%	0.47	Random	−5.81 [-6.34,-5.27]	<0.00001
Intervention time≥4weeks	3 [26,32,38]	70%	0.03	Random	−6.84 [-12.02,-1.66]	0.010

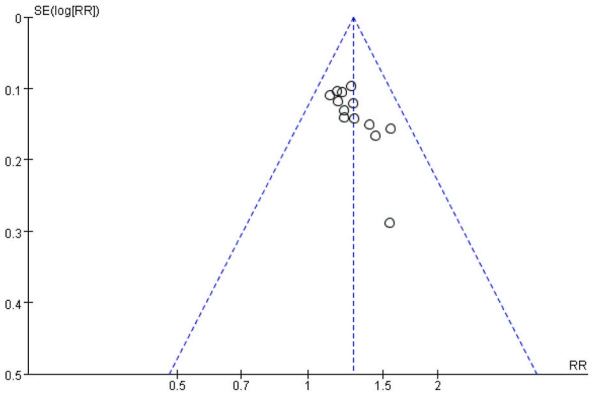

Fig. 10. Funnel plot of cardiac function efficacy of TCMCRT adjuvant treatment of chronic heart failure.

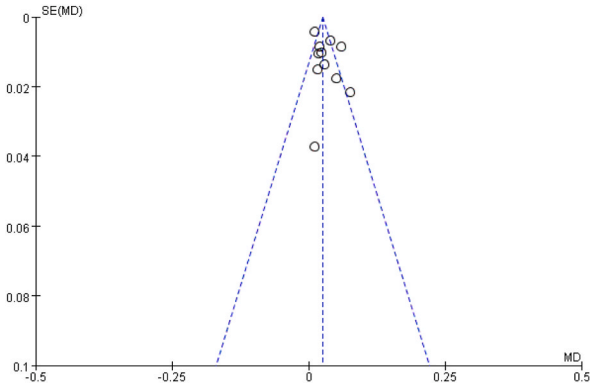

Fig. 11. Funnel plot of LVEF in chronic heart failure treated with the aid of TCMCRT.

3.7. Risk of publication bias assessment

The funnel plots (Figs. 10 and 11) show a more symmetrical distribution of effect sizes for cardiac efficacy and LVEF, which was confirmed by the Egger test ($P = 0.213$; $P = 0.066$, respectively), indicating that there was no significant publication bias for these results. Less than 10 studies assessing LVEDD, NT-proBNP, 6MWT, and MLHFQ6 were included in the study literature; therefore, no test for publication bias was performed for these outcomes.

3.8. Safety analysis

9 studies [26–28,30,31,36,37,40,42] reported adverse reactions, of which four studies [28,36,40,42] reported the type and number of cases of adverse reactions. One study [26] reported one patient who switched from ACEI to ARB because of dry cough, but it did not affect the trial results. The remaining four studies [27,30,31,37] only mentioned that no adverse reactions were found during treatment in 2 groups of patients, as shown in Table 3. Meta-analysis was not performed because of the differences in both the type and degree of adverse reactions.

4. Discussion

TCM complementary therapies, including TCMCRT, have been extensively utilized in China across a broad range of disease areas, including cardiovascular disease. TCMCRT is based on TCM theory, through various measures to give stimulation in the corresponding skin treatment area, thus affecting the corresponding Meridians and Viscera, and play a role in treating diseases. There are two categories according to the mode of stimulation: dermal drug therapy (stimulating the skin with simple drugs to treat the disease) and dermal non-drug therapy (stimulating the skin with certain techniques such as acupuncture, moxibustion, cupping or acupoint application to treat the disease) [44].

Studies have demonstrated that electroacupuncture pretreatment of acupuncture points can reduce the expression of NF-κBp65 protein and serum IL-6 content in the myocardial tissue of MIRI rats, promote the release of IL-10, regulate the dynamic balance between inflammatory factors [45], and slow down the pathogenesis of CHF. Electroacupuncture can inhibit the production of mitochondrial reactive oxygen species, thus reducing the levels of apoptotic factors such as Cyt-C, caspase-9, and caspase-3 [46], which serves to protect cardiomyocytes. Acupuncture at the “Neiguan” point can protect myocardial cells, enhance myocardial blood microcirculation, reduce ATP consumption, improve the electrical instability of ventricular muscle, avoid the aggravation of ultrastructural damage in myocardial cells, and play a protective role in cardiac function [47,48].

Moxibustion can improve cardiac function and myocardial injury in CHF rats, and can reduce LC3-II/I and elevate p62 protein expression levels in cardiomyocytes, exerting an autophagy-inhibiting effect similar to that of 3-MA, inhibiting excessive autophagy and reducing myocardial injury in cardiomyocytes [49,50]. Inhibition of the expression of myocardial pro-apoptosis-related proteins Bax, Fas, and FasL and upregulation of the expression level of the anti-apoptotic protein Bcl-2 reduce myocardial injury and thus improve the state of heart failure caused by myocardial injury [51].

In the included literature, three main types of interventions were mentioned: acupuncture, acupoint application, and moxibustion. In terms of acupuncture therapy, three specific types of acupuncture therapy were included: QinZhen acupuncture therapy, FuZhen Acupuncture, Back-Shu Points Acupuncture. QinZhen acupuncture therapy, or micro acupuncture needles, is a special method of acupuncture treatment that improves clinical symptoms and achieves 24-h continuous therapeutic effects by embedding needles in superficial tissue points. Back-Shu Points Acupuncture, which refers to the implementation of acupuncture treatment in specific locations on the back to achieve therapeutic purposes [52]. FuZhen Acupuncture is a new type of acupuncture therapy (microneedle), which regulates the pathological state and restores physiological functions by acupuncture abdominal points to achieve the purpose of local treatment to save the whole body; it has the advantages of convenient acupuncture points, safety, quick and can produce more comfortable benign stimulation, and so on [53].

Table 3
Occurrence of adverse reactions in the adjuvant treatment of chronic heart failure with TCMCRT.

Inclusion in the literature	Adverse reactions	
	E	C
He2021 [28]	1 halo needle	1 subcutaneous hematoma
Zhao 2017 [36]	1 skin reaction	
Fu2021 [40]	4 dizziness、3 elevated aminotransferase、1 vomiting、1 skin rash	4 elevated aminotransferase、3 dizziness、1 vomiting
Chen 2016 [42]	1 skin blisters	

Acupoint application involves the use of Chinese herbal medicine specific to a disease, which is made into a paste and applied onto an intermediary material that can be adhered to the skin, and then applied to specific acupuncture points. Since it is not absorbed by the gastrointestinal tract and metabolized by the liver, it can avoid damage to liver and kidney function and the destruction of the active ingredients by digestive enzymes, thus improving the utilization rate of the drug and compliance with the drug [54]. In the included literature, there are two special acupoint applications: the QiangXin Acupoint Application, consisting of *Cinnamomi Ramulus, Carthami Flos, Ginsen Radix Et Rhizoma Rubra, Alisma Orientale (Sam.) Juz., cartialgenous, Asari Radix Et Rhizoma,* and *Sinapis alba* L.; and the CongBaiTongYang Acupoint Application, consisting of *Allii Fistulost Bulbus* and *Ricinus communis* L..

This Meta-analysis found that the addition of TCMCRT for the treatment of CHF had significant advantages over the application of conventional treatment alone. Patients included in the study in the experimental group showed a significant improvement in cardiac efficacy after treatment, with a significant increase in LVEF levels, a decrease in LVEDD values, a significant improvement in NT-proBNP, a significant increase in 6-min walk distance, and an improvement in MLHFQ score results. A subgroup analysis revealed high heterogeneity in LVEF, LVEDD, NT-proBNP, and MLHFQ between studies, which may be related to differences in the treatment process.

In particular, in the subgroup analysis with a treatment duration of 4 weeks, a significant decrease in the heterogeneity of cardiac ultrasound indices LVEF and LVEDD was found when the treatment duration was less than 4 weeks. This may be related to the longer time required for alteration of cardiac ultrasound indices [55–57] Longer follow-up periods are necessary to detect significant differences in cardiac ultrasound index changes between therapies. Therefore, future pilot studies observing cardiac ultrasound indices should have extended follow-up periods to ensure significant results can be detected. It has been shown that different TCM evidence type (TCM theory-guided generalizations of pathological attributes at a certain stage of disease development, which can guide treatment) can have an impact on cardiac ultrasound index results. For example, LVEF values were significantly higher in patients with heart-lung "qi" deficiency evidence than in other evidence types [58]. However, the specific TCM evidence types were not highlighted in the literature included in this study; therefore, the relationship between the TCM evidence types affecting cardiac ultrasound indices and differences in the course of treatment needs to be further explored.

The remaining outcome indicators showed a more pronounced heterogeneity, and the analysis of the sources of heterogeneity could be mainly the following.

(1) Different interventions: 18 articles were included in this analysis, including 8 articles on acupuncture therapy (QinZhen acupuncture therapy 1, Back-Shu Points Acupuncture 1, FuZhen Acupuncture 1), 8 articles of acupoint application therapy (QiangXin Acupoint Application 3, CongBaiTongYang Acupoint Application 1), moxibustion therapy 2.
(2) The duration of treatment varied: of the 18 articles included in this analysis, the duration of treatment ranged from 14 days to 4 months, which was generally short. The impact on outcome indicators will vary depending on the duration of treatment, with most external treatments requiring a long course of therapy to provide significant improvement in cardiac function, which may also lead to higher heterogeneity of outcomes.
(3) In addition to the above-mentioned reasons, the different testing instruments, different methods used for testing may make the test results may have a certain degree of error, which can lead to high heterogeneity of results.

Regarding the safety of the interventions, the adjuvant treatment of CHF with TCMCRT had fewer adverse effects (only one [39] of the 18 included studies had more serious adverse effects), indicating a fair safety profile.

Evidence-based medicine (EBM) has improved the quality of evidence for clinical research in acupuncture [59]. With the promotion and use of EBM, more and more high-quality clinical studies have been published in top medical journals [60], and acupuncture therapy has gradually been widely recognized worldwide. Other long-established TCMCRTs have likewise evolved in an objective and quantifiable direction. Currently, the worldwide literature is aware of TCM dermal therapies [61,62], which are used in the treatment of the nervous system, digestive system, respiratory system, and musculoskeletal system, and are also widely used for prevention and health care [63]. In the future, more rigorous adherence to international clinical research protocols will lead to more high-quality research results, which will hopefully be formally used as complementary therapies in other countries.

5. Conclusion

Conventional western treatment combined with TCMCRT is superior to the application of Conventional western treatment alone for the treatment of CHF. The addition of TCMCRT as an adjunct to the treatment of CHF can significantly improve the efficacy of cardiac function, significantly increase LVEF levels, decrease LVEDD levels, improve NT-proBNP, significantly increase 6MWT, improve

MLHFQ score results, and have good safety outcomes. In considering the duration of intervention and cardiac improvement, the differences in changes in cardiac function by therapy are reflected when the duration of treatment is longer. It is recommended that future studies on this subject should try to extend the duration of the experiment to ensure that significant results can be observed.

Summarize the above, the effects that TCMCRT can have on cardiac function in patients with CHF can be summarized in two aspects. At the microscopic level, it regulates the dynamic balance between inflammatory factors and slows down the pathogenesis of CHF. Reducing the content of apoptotic factors and up-regulating the expression level of anti-apoptotic proteins play a role in protecting cardiomyocytes. It protects cardiomyocytes, enhances myocardial blood microcirculation, reduces ATP consumption, and provides protection to cardiac function. Inhibit excessive autophagy of cardiomyocytes and reduce myocardial injury. In turn, it improves the state of heart failure caused by myocardial injury. At the macroscopic level, it improves cardiac output, increases peripheral vascular resistance and means blood pressure, effectively promotes urinary excretion in patients, and reduces body weight and cardiac load.

However, the risk of bias in the included studies was generally moderately high, and the accuracy of some results was affected by heterogeneity. Higher-quality RCTs with large samples and long-term follow-up observational studies should be conducted in the future to verify the efficacy and safety of TCMCRT as an adjunct to the treatment of CHF.

Author contribution statement

LMX and LHD designed the study, developed the search strategy, performed the data analysis, and drafted the manuscript. LXL and LHD conducted the search, assessed the risk of bias, and SJJ provided key methodological advice, and revised the protocol. XWL and LMX screened the articles, LMX collected the data, and revised the manuscript. LHX and SJJ conceived and designed the study, performed the final manuscript revisions, and acted as guarantors. LMX and LHD are co-first authors of this paper. SJJ is the corresponding author of this paper (e-mail:shangjuju@bjzhongyi.com).

Funding statement

This work was supported by the Young Talent Training Program of Beijing Hospital Management Center (No. QML20221014) and the National Natural Science Foundation of China (No. 81274315).

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

All authors declare that there is no conflict of interest.

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