Moxibustion as an Adjuvant Therapy for Heart Failure: A Systematic Review and Meta-Analysis of a Randomized Controlled Trial

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Research Article

Received: 30-Aug-2024, Manuscript No. JPPS-24-146895; **Editor assigned:** 02-Sep-2024, PreQC No. JPPS-24-146895 (PQ); **Reviewed:** 16-Sep-2024, QC No. JPPS-24-146895; **Revised:** 23-Sep-2024, Manuscript No. JPPS-24-146895 (R); **Published:** 30-Sep-2024, DOI: 10.4172/2320-1215.13.3.004

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Citation: Gao B, et al. Moxibustion as an Adjuvant Therapy for Heart Failure: A Systematic Review and Meta-Analysis of a Randomized Controlled Trial. RRJ Pharm Pharm Sci. 2024;13:004

ABSTRACT

Background: Moxibustion as an adjuvant therapy shows clinical efficacy in the treatment of Heart Failure (HF). However, there has been a lack of overall evaluation of the efficacy of moxibustion.

Objective: To evaluate the efficacy and safety of moxibustion combined with conventional drug therapy and the quality of evidence regarding its use for preventing ventricular remodeling, improving cardiac function and improving the prognosis of patients with HF.

Methods: Research the keywords moxibustion therapy and HF from 7 databases. EndNote X8 software was used for literature management. RevMan 5.4.1 software was used to summarize data and Grading of Recommendation, Assessment, Development and Evaluation (GRADE) was used to evaluate the quality of research.

Results: A total of 910 patients were included from 11 studies. Meta-analysis showed that compared with the control groups, patients treated with moxibustion had significantly improved 6-min walk experiment (6-MWD) scores (Mean Difference (MD)=57.39, 95% Confidence Interval (CI) (39.49 to 75.30), p<0.01) and Left Ventricular Ejection Fraction (LVEF) scores (MD =4.93, 95% CI (3.12 to 6.74) for patients with HF, p<0.01), according to GRADE, those using LVEF, Lee's HF score and Brain Natriuretic Peptide (BNP) were “moderate quality” and others were “low quality” or “very low quality”.

Conclusion: Studies suggest that moxibustion is a safe adjuvant treatment that can improve the cardiac function and prognosis of patients with HF. However, owing to the small sample sizes used in previous studies and the low quality of evidence, these results need to be further verified.

Keywords: Moxibustion; Heart failure; Meta-analysis; GRADE

INTRODUCTION

Heart Failure (HF) is the final stage of cardiovascular disease. Its characteristic symptoms include dyspnea, ankle swelling and fatigue [1]. A recent epidemiological studies in China show that the prevalence of HF in adults is 0.90%, the incidence rate of HF increases with age [2]. At present, diuretics, β-receptor antagonists, anticoagulants and other drugs are used in the clinical treatment of HF [3]. Despite recent progress in treatment, the morbidity, mortality and economic burden among HF patients remain high [4]. About 50% of heart failure patients die within 5 years after diagnosis and about 20% die within 1 year after diagnosis and the survival rate of heart failure patients is low [5]. Therefore, adjuvant therapies with outstanding curative effects, such as moxibustion, have attracted research attention. Moxibustion therapy has the properties of warming the body and eliminating cold when used as a burning herbal preparation containing mugwort (Artemisia). Accumulating evidence suggests that moxibustion has a positive regulatory effect on HF. Jin et al., selected RN17, BL15, BL13 and BL17 to treat HF by moxibustion [6]. Similarly, Ji et al., demonstrated that moxibustion can reduce High-Sensitivity C-Reactive Protein (hs-CRP) and N-Terminal Precursor Brain Natriuretic Peptide (NT-proBNP) levels in patients with Chronic Heart Failure (CHF) and improve the clinical symptoms and cardiac function [7]. The research of our research group also confirmed that moxibustion has a benign regulatory effect on heart and neuroendocrine function of CHF rats [8-10]. However, more evidence is needed to elucidate how moxibustion can improve the symptoms of patients with HF by regulating the neuroendocrine system [11]. Previous studies have shown that acupuncture, as an adjuvant therapy for the treatment of HF, is a promising intervention. Nonetheless, the mechanisms of action of acupuncture and moxibustion are not wholly consistent [12]. Acupuncture is a hot spot in research; consequently, the effects of moxibustion may have been missed in previous studies. Furthermore, there has been no systematic appraisal of risk of bias or evidence quality in previous studies; this will be necessary to draw confident conclusions. Therefore, we conducted a meta-analysis of Randomized Controlled Trials (RCTs) of moxibustion in the adjuvant treatment of heart failure to evaluate its efficacy and safety and the quality of evidence regarding its role in preventing ventricular remodeling and improving clinical symptoms in patients.

MATERIALS AND METHODS

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13]. The protocol for this meta-analysis is available in PROSPERO (no. CRD42021292818).

Literature search

Search strategies: Seven Chinese and English databases were independently searched by two researchers (Yue-Cheng and Heng-Wang), comprising PubMed/MEDLINE (PubMed.gov), the Cochrane Library (cochranelibrary.com), EMBASE (embase.com), Web of Science (videos.webofsciencegroup.com), Wanfang data (wanfangdata.com), China national

Knowledge Infrastructure (CNKI.net) and Chongqing VIP (cqvip.com). The databases were searched within a time range from the earliest index to October 03rd, 2021.

Inclusion criteria: This study followed the Pressured-Controlled Intermittent Coronary Sinus Occlusion (PICSO) principle to establish the following inclusion criteria based on factors including participants, interventions, comparisons, results and research design. (1) Patients with a diagnosis of HF, either CHF or acute HF, were eligible. There were no restrictions on gender, race, ejection fraction, systolic/diastolic HF; (2) Studies need to include a control group treated with conventional therapy. The treatment group included moxibustion intervention measure (3) In addition, the intervention type was moxibustion plus conventional drug therapy *vs.* conventional drug therapy. All patients who used Traditional Chinese Medicine (TCM) were included in the treatment group and patients who only used conventional medicine were included in the control group; (4) The main outcome measures were cardiac function and curative effect, including the 6-Min Walk Test (6-MWT), Left Ventricular Ejection Fraction (LVEF) and NT-proBNP. Secondary outcome measures included Lee's HF Score (Leehfs), BNP and adverse events and (5) The studies included were RCTs (blinded or non-blinded or placebo).

Exclusion criteria: (1) Studies involving HF caused by pregnancy, chemotherapy, congenital disabilities, or surgery were excluded; (2) Studies of TCM treatment methods other than moxibustion were excluded, as were studies with; (3) Incorrect, incomplete, or unavailable outcome data.

Study selection and data extraction: The research used Endnote X8 to manage all the retrieved literature. First, a preliminary screening was performed, in which we removed duplicate studies and each title and abstract was checked for relevance; studies that did not meet the inclusion criteria were excluded. If the title or abstract was confusing, we reviewed the whole article in the secondary screening. If necessary, we contacted the person who performed the trial for more precise information. Two independent researchers (Ning Cheng and Heng-Wang) recorded details of the articles to be included in the study in a predefined excel format, including author, year, country, sample size, disease, moxibustion method, intervention measures, frequency, duration, outcome indicators (i.e., 6-MWT, LVEF, NT-proBNP, Leehfs, BNP) and adverse events. In case of disagreement, it will be resolved independently by the third researcher (Zhu Wang).

Assessment of risk of bias: Researchers (Ning Cheng and Heng-Wang) used Cochrane manual 5.1.0 to assess the quality of the included literature [14]. The RCT literature quality evaluation (risk bias assessment tool) included by Cochrane is as follows: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data; (6) Selective reporting and (7) Other biases. Considering the characteristics of moxibustion therapy, other biases include the details of moxibustion (such as the quality specification of moxa velvet, the thickness of moxa sticks and the distance between the ignition point and the skin). The risk of bias includes three options: High risk, low risk or unclear risk.

GRADE: We used the GRADE evidence quality grading and recommendation strength system to evaluate the quality of the main results [15]. According to the GRADE approach, the quality of the evidence group is divided into four categories: High, medium, low and very low. The GRADE approach includes 5 reasons that may reduce the quality of evidence and 3 possible reasons for improving the quality. The quality of evidence and the intensity of recommendation are clearly defined. It is one of the most authoritative scoring methods currently formulated by a widely representative group of international guidelines [16,17].

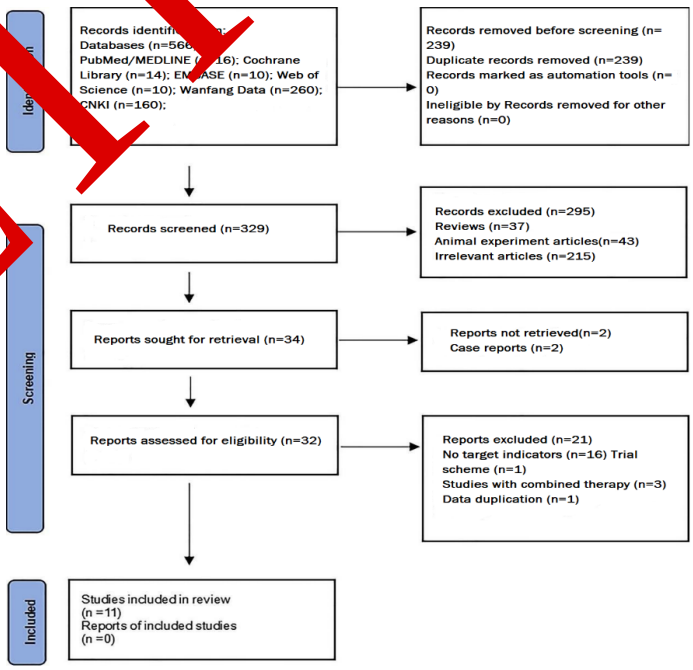
Statistical analysis: The study used Revman 5.4.1 (Nordic Cochrane Centre, Cochrane collaboration, Copenhagen, Denmark) to analyze the included literature. The inverse-variance method in RevMan was adopted. Dichotomous data were computed using the Mantel–Haenszel (MH) statistical method, Fixed Effect (FE) analysis model, Random Effect (RE) analysis model, Odds Ratio (OR) effect measure and 95% Confidence Interval (CI). Continuity variables were expressed as Mean Difference (MD) (95% CI) and different outcome scales were combined using Standardized Mean Deviation (SMD), selecting the inverse variance statistical method, FE analysis model, RE analysis model and MD effect measure to process the data. The included studies quantitatively judged the size of heterogeneity thr... I^2. If there is no statistical heterogeneity among the research results, FE analysis model is used fo... eta-analysis; i... there is statistical heterogeneity among the research results, the source of heterogeneity will be fu... r analyzed. After excluding the influence of obvious clinical heterogeneity, the RE analysis model will b... used for me... nalysis. We performed a sensitivity analysis by removing single or multiple studies to determin... he sour... es of hetero... eity and consistency. If an investigation was deleted from one or more studies and the het... eity was ... ignificantly reduced as a result, this study was considered to be the primary source of heterogeneity ... d furt... r read and evaluated.

RESULTS

Literature search and study selection

Using the search strategy described in section 2.1.1, a total o... 566 literatures ... ere retrieved. First, 239 duplicates were excluded and then a further 295 papers were removed ... cluding 37 ... views, 43 animal studies and 215 irrelevant articles). Among the remaining 32 clini... l papers on m... ... ti... in the treatment of HF, there were two case reports, 16 articles with no target indicators, one ... scheme, three studies involving combined therapy and one duplicate article. Finally, this systematic review and ... eta-a... ysis analyzed 11 RCT articles on moxibustion in the treatment of HF (Figure 1).

Figure 1. Flow chart for selecti... n of stu... es. **Note:** C... KI: China National Knowledge Infrastructure Database; Wanfang: Wanfang Data Journal D... base; ... Chongqing VIP.



Characteristics of the included studies

Eleven RCTs met the inclusion criteria: All studies were conducted in China [18-20]. Nine studies focused on CHF and two studies considered acute HF or CHF [20-26]. A total of 920 patients were included in 11 studies and patients recruited in a single study ranged from 60 to 108; 460 patients in the treatment groups received moxibustion treatment, compared with the control groups receiving general treatment [26-28]. These studies were published online in Chinese or English from 2015 to 2021. The degree of HF was assessed by the cardiac function evaluation scale of the New York Heart Association (NYHA). Only one trial included patients with grade IV HF and other trials recruited patients with grade II-III HF. Most subjects had a disease course of more than 3 years and two studies did not explain the subject's disease course [19,25]. The included study showed that the treatment was indirect moxibustion. Four studies used Gewu moxibustion (in which the burning end of a moxa stick is separated by Chinese herbal medicine), six studies used moxa sticks, of which one used Leihuo moxibustion (with moxa sticks containing other traditional Chinese medicines) [24]. In addition, one study used a moxibustion instrument for treatment. Moxibustion tools were used in seven studies [18-22,25-27]. The research method was to add moxibustion to routine drug treatment and compare the curative effects of the two groups. All interventions lasted for 5 min-60 min. Treatment time ranged from 1 week to 12 weeks. Three physiological indexes (6-MWT, LVEF and NT-proBNP) were the main outcomes. Furthermore, five studies reported Leehfs and three studies reported BNP [18,23,]. These measurements are used as secondary results in the study of heart function. Three studies reported adverse reactions; in two of these, the patient had a small blister [18,19,26]. The characteristics of the 11 studies are shown in Table 1.

Table 1. Characteristics of the included literatu

Author	Sample size (T/C)	Disease	Moxa method	Intervention		Frequency	Outcome	Adverse event
				Treatment group	Control group			
Zeng et al. [18]	46/46	CHF/AHF	Moxa box	Moxa (RN4, RN6, RN9, RN8, RN12) plus med	med	7d, 1/d	BNP, Lee HFS	None
Dong et al. [19]	32/32	CHF/AHF	Moxa tube	Moxa (BL15, BL13, BL20, BL23, RN4) plus med	med	7d, 1/d	NT-probnp, Lee HFS	Blister (T:1)
Wang et al. [20]	45/45	CHF	Moxa box plus aconite cake	Moxa (RN4, RN6, ST36, PC6) plus med	med	22d, 1/d	LEVF, NT-probnp	NR
et al. [21]	31/31	CHF	Moxa box	Moxa (BL15, RN17) plus med	med	4w, 1/2d	NT-probnp	NR
Gao et al. [22]	61/61	CHF	Moxa plus CHM cake	Moxa (BL44, DU11) plus med	med	12w, 1/d	6-MWT, LEVF, NT-probnp, Lee HFS LVEDd	NR
Xia et al. [23]	40/40	CHF	Long snake Moxa	Moxa (DuMai from GV14 to GV2) plus med	med	12w, 1/w	6-MWT, LEVF, BNP, LVEDd	NR
Li et al. [24]	46/46	CHF	Leihuo moxa stick plus Moxa box	Moxa (LI1, SP1, DU9, DU10, DU11, DU4) plus med	med	6w, 1/d	6-MWT, LEVF, NT-probnp, LeeHFS, LVEDd	NR

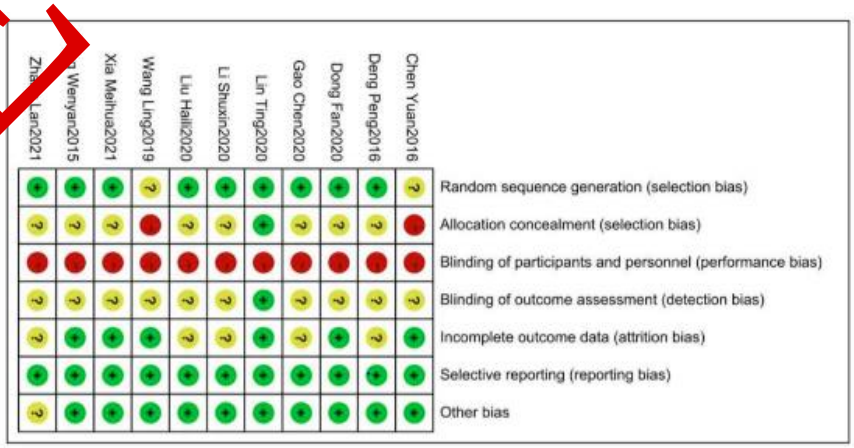
Zhang et al. [25]	30/30	CHF	Moxa box	Moxa (RN12, RN8, RN4, ST36, ST40) plus med	med	10d, 1/d	6-MWT, LEVF	NR
Chen et al. [26]	30/30	CHF	Moxa apparatus	Moxa (BL15, BL13, BL14, PC4, PC6) plus med	med	3w, 5/w	6-MWT, LEVF, NT-probnp, LVEDd	Blister (T:1)
Deng et al. [27]	40/40	CHF	Moxa	Moxa (BL15, DU9, RN17) plus med	med	8w, 1/d	6-MWT, LEVF, BNP, LVEDd	NR
Liu et al. [28]	54/54	CHF	Moxa plus CHM cake	Moxa (BL44, DU11) plus med	med	12w, 1/d	6-MWT, LEVF, NT-probnp, Lee HFS, LVEDd	NR

Note: CHF: Chronic Heart Failure; AHF: Acute Heart Failure; Moxa: Moxibustion; CHM: Chinese Herbal Medicine; med: Medicine; 3 moxa 'snakes': Moxibustion Takes Three Times; Lee HFS: Lee Heart Failure Score; T: Treatment Group; C: Control Group; NR: No Reporting.

Assessment of risk of bias

Eight studies reported and used a random number table [18,19,21,28]. In one study, a computer was used to randomly generate numbers; therefore, this study was evaluated as low risk in terms of bias [21]. Two studies mentioned randomization but did not specify the method of randomization; these studies belong to the risk of unclear bias [20,26]. One study assigned patients to the study group by using a sealed opaque envelope; this was rated as low risk [21]. Two studies where patients were assigned according to their order of admission were ranked as high risk [20,26]. Eight of the studies did not explain how allocation was concealed; the risk of bias in these studies was unclear [22-25]. Owing to the characteristics of moxibustion therapy, none of the studies used blinding. Most trials did not report the use of blinded outcome assessments and were therefore judged to have an unclear risk of bias. However, one study emphasized that researchers were prohibited from influencing patients to ensure the objectivity of the results; this study was therefore judged to have low risk of bias [21]. Six studies had a low risk of bias for incomplete outcome data, the drop-out rate of participants was slightly less than 10%. Other studies did not clearly describe the drop-out of patients, so the risk was assessed as unclear [18-21,23,26]. Finally, regarding selective criteria; there may also have been other biases as shown in Figure 2.

Figure 2. Assessment of risk of bias.



Outcomes

6-MWT score: Seven studies (n=612) examined the effects of moxibustion on scores on the 6-MWT [22-28]. There was pronounced heterogeneity between the trials (MD=57.39, 95% CI (39.49 to 75.30), p<0.01, I^2=79%, Figure 3); hence, an Reverse Emitter (RE) model was used for statistical analysis. Sensitivity analysis was used to assess the stability of the results. When we only observe the study of the combination of moxibustion and Chinese herbal medicine (as in Gewu moxibustion and LeiHuo moxibustion), results did not change (p<0.01) but heterogeneity decreased (I^2=0%, Table 2), suggesting that the results were relatively stable. Therefore, the results show that addition of moxibustion to conventional treatment could improve 6-MWT scores.

Figure 3. Forest plot of the 6-WMT assessment. **Note:** 6-WMT: 6-Minute Walk Experiment

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95%
Chen et al. [26]	358	50.19	35	331.03	52.79	35	14.0%	26.97 (-0.84, 54.78)
Deng et al. [27]	345.55	32.56	40	313.28	27.35	40	17.1%	32.27 (19.09, 45.45)
Gao et al. [22]	449.88	81.57	61	360.59	66.74	61	13.3%	89.29 (62.84, 115.74)
Li et al. [24]	451.85	82.84	46	369.97	65.94	46	12.1%	81.88 (51.28, 112.48)
Liu et al. [28]	451.87	82.57	54	369.79	65.94	54	12.8%	82.08 (53.90, 110.26)
Xia et al. [23]	406.26	37.69	40	356.49	52.02	40	15.3%	49.77 (29.86, 69.68)
Zhang et al. [25]	485.5	36.36	30	432.54	41.75	30	13.6%	52.96 (33.15, 72.77)
Total (95% CI)	-	-	306	-	-	306	100.0%	57.39 (33.49, 81.30)
Heterogeneity: Tau²=443.48; Chi²=28.16, df=6 (p<0.0001); I²=79%								
Test for overall effect: Z=6.28 (p<0.00001)								

Mean difference IV. Random, 95% CI

-100 -50 0 50 100

Favours [control] Favours [treatment]

LVEF score: Eight RCTs enrolled 702 patients and observed the Ventricular Ejection Function of patients with HF based on LVEF indicators. As apparent heterogeneity existed among studies (MD=4.93, 95% CI (3.12 to 6.74), p<0.01, I^2=68%, Figure 4), an RE model was used [19-20,22-28]. The results of the sensitivity analysis showed that when we analyzed Gewu moxibustion, LeiHuo moxibustion and long snake moxibustion, the results did not change (p<0.01) but the heterogeneity was reduced (I^2=40%, Table 2). The remaining heterogeneity may have been caused by the mode of intervention.

Figure 4. Forest plot of the LEVF assessment. **Note:** LEVF: Left Ventricular Ejection Fraction.

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV. Random, 95% CI
Chen et al. [26]	48.37	5.[illegible]	35	46.73	5.86	35	13.2%	1.64 (-1.09, 4.37)
Deng et al. [27]	47.45	8.19	40	46.4	6.54	40	11.7%	1.05 (-2.20, 4.30)
Gao et al. [22]	40.31	7.21	61	40.22	6.91	61	13.8%	8.09 (5.58, 10.60)
Li et al. [24]	47.65	7.3	46	40.74	6.94	46	12.6%	6.91 (4.00, 9.82)
Liu et al. [28]	47.0[illegible]	7.19	54	40.76	6.97	54	13.3%	6.89 (4.22, 9.56)
Wu et al. [20]	53.42	5.93	45	49.44	4.75	45	14.7%	3.98 (1.76, 6.20)
Xia et al. [23]	61	9.41	40	55.81	7.03	40	10.7%	5.59 (1.95, 9.23)
Zhang et al. [25]	5[illegible].23	7.23	30	50.22	8.24	30	10.0%	5.01 (1.09, 8.93)
Total (95% CI)	-	-	351	-	-	306	100.0%	4.93 (3.12, 6.74)
Heterogeneity: Tau²=[illegible].54; Chi²=21.83, df=7 (p<0.0003); I²=68%								
Test for overall effect: Z=5.34 (p<0.00001)								

Mean difference IV. Random, 95% CI

-20 -10 0 10 20

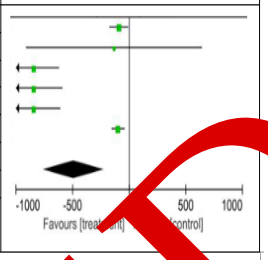
Favours [control] Favours [treatment]

NT-proBNP score: Six RCT studies used NT-proBNP to detect therapeutic effects in HF patients (The data of Lin et al., are expressed in interval form and could not be merged with other studies. The author of this study did not respond to my email inquiry. Finally, this meta-analysis was included in six studies) [19-20,21,24,26,28]. We used an RE model because of the obvious heterogeneity (MD=-490.65, 95% CI (-760.16 to -221.13), p<0.01, I^2=95%, Figure 5). Sensitivity analysis showed that when we analyze all studies that received less than 30 treatments, the results changed little (p<0.01) and the heterogeneity was reduced (I^2=0%, Table 2), suggesting that the results were relatively stable.

Figure 5. Forest plot of the NT-proBNP assessment. **Note:** NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide.

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV. Random, 95% CI
Chen et al. [26]	378.5	156.11	35	470.77	198.23	35	19.9%	-92.27 (-175.86, -8,68)
Dong et al. [19]	1,778.4	1,643.47	32	1,913.34	1,527.45	32	7.5%	-134 (-912.32, 642.44)
Gao et al. [22]	2,359.69	610.43	61	3,200.85	634.79	61	17.8%	-841.16 (-1062.16, -620.16)
Li et al. [24]	2,356.85	609.3	46	3,199.65	633.2	46	17.2%	-842.80 (-1096.74, -588.86)
Liu et al. [28]	2,356.64	609.53	54	3,199.75	633.73	54	17.6%	-843.11 (-1077.63, -608.59)
Wang et al. [20]	581.09	115.74	45	678.67	163.47	45	20.1%	-97.58 (-156.10, -39.06)
Total (95% CI)	-	-	273	-	-	273	100.0%	-490.65 (-760.16, -221.13)

Heterogeneity: Tau²=93389.28; Chi²=103.12, df=5 (p<0.00001); I²=95%
Test for overall effect: Z=3.57 (p<0.0004)

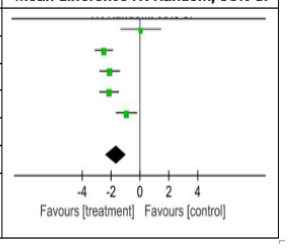


Leehfs: Five RCT studies included 478 patients and used Leehfs to study the prognosis of patients with HF [18,19,22,24,28]. These pooled studies were analyzed by RE models because of the marked heterogeneity (MD=-490.65, 95% CI (-760.16 to -221.13), p<0.01, I²=95%, Figure 6). Moxibustion treatment was significantly correlated with Leehfs; however, the results were reversed after the sensitivity analysis (p=0.17, I²=32%, Table 2), indicating that this finding was unreliable.

Figure 6. Forest plot of the Leehfs assessment. **Note:** Leehfs: Lee Heart Failure Score

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV. Random, 95% CI
Dong et al. [19]	4.72	3.27	32	4.66	2.44	32	13.5	0.06 (-1.35, 1.47)
Gao et al. [22]	5.59	1.64	61	8.09	1.93	61	22.3%	-2.50 (-3.14, -1.8
Li et al. [24]	5.62	1.62	46	7.71	1.88	46	21.4%	(-2.81, -1.37)
Liu et al. [28]	5.65	1.66	54	7.78	1	54	21.8%	-2.13 (-2.81, -1.45)
Zeng et al. [18]	3.89	1.68	46	4.91	1.9	46	21.0%	-0.93 (-1.68, -0.18)
Total (95% CI)	-	-	239	-	-	239		-1.66 (-2.39, -0.92)

Heterogeneity: Tau²=0.53; Chi²=17.96, df=4 (p<0.001); I²=78%
Test for overall effect: Z=4.40 (p<0.0001)

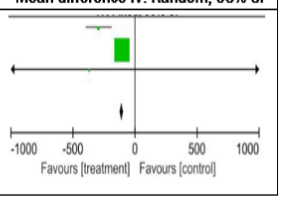


BNP score: Three RCTs (n=252) used BNP to assess the prognosis of patients with HF [18,23,27]. Meta-analysis showed that moxibustion combined with routine treatment. There was significant heterogeneity in the included studies (p<0.01, I²=84%, Figure 7); therefore, a RE model was applied. In this sensitivity analysis, when study of Xia et al. was excluded, the heterogeneity among studies was significantly reduced (I²=0%, p=0.94, Table 2) [23]. Meta-analysis results using a fixed effect model also showed that moxibustion combined with standard treatment improved BNP compared with standard treatment alone (p<0.01).

Figure 7. Forest plot of the BNP assessment. **Note:** BNP: Brain Natriuretic Peptide.

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV. Random, 95% CI
Deng et al. [27]	383.38	178.22	40	676.46	285.36	40	1.6%	-293.08 (-397.34, -188.82)
Xia et al. [23]	251.33	26.92	40	356.09	32.64	40	98.4%	-104.76 (-117.87, -91.65)
[illegible] [18]	380.54	491.223	46	751.56	6.946	46	0.0%	-371.03 (-2383.30, 1641.25)
Total (95% CI)	-	-	126	-	-	126	100.0%	-107.70 (-120.71, -94.69)

Heterogeneity: Chi²=12.40, df=2 (p=0.002); I²=84%
Test for overall effect: Z=16.23 (p<0.00001)



Adverse events: Two studies reported adverse reactions; other studies did not find any adverse reactions [19,26]. Overall, all reported adverse reactions were mild. One case of adverse response (small skin blisters caused by the heat of moxibustion) was reported in the treatment group of each of the two studies [19,26]. Owing to the characteristics of moxibustion treatment, it can easily generate blisters due to heat irritating the skin.

Sensitivity analysis: By eliminating individual studies one by one for sensitivity analysis, the results show that the direction of meta-analysis results has changed and only the results of LVEF score are consistent, indicating that the stability of the results is poor. Table 2 describes the results of sensitivity analysis of various indicators in detail. See 3.4.1.-3.4.5. for the analysis of indicators.

Table 2. Sensitivity analysis of various indicators.

Outcome	Studies	Heterogeneity test		Effect model	Meta-analysis results	
		p-value	I^2 value		MD (95% CI)	p-value
6-WMT	3 [22,24,28]	0.91	0%	Random	84.77 (68.45, 101.08)	<0.00001
LVEF	5 [20,22-24,28]	0.16	40%	Random	6.25 (4.68, 7.82)	<0.00001
NT-proBNP	3 [19,20,26]	0.99	0%	Random	-95.98 (-143.83, -48.13)	<0.0001
LeehfS	2 [18,19]	0.22	32%	Random	-0.62 (-1.52, 0.27)	0.17
BNP	2 [18,27]	0.94	0%	Random	-293.29 (-397.39, -189.19)	<0.00001

Note: CI: Confidence Interval; 6-WMT: 6-Minute Walk Experiment; LEVF: Left Ventricular Ejection Fraction; NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide; Leehfs: Lee Heart Failure Score; BNP: Brain Natriuretic Peptide.

GRADE assessment: According to the GRADE principles, we evaluated the quality of the evidence provided based on 6-WMT, NT-proBNP, LVEF, Leehfs and BNP. Table 3 shows the GRADE method's evaluation of the quality of each index included in the literature. Studies using 6-WMT were classified as "low quality" those using LVEF, Leehfs and BNP were categorized as "moderate quality" and those using NT-proBNP were classified as "very low quality."

Table 3. GRADE evaluation of evidence quality.

Outcome	Certainty assessment							Number of patients		Effect absolute (95% CI)	Certainty	Importance
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	Treatment group	Control group	Relative (95% CI)		
6-MWD	7 [22-28]	Randomized trial	Serious	Serious[a]	Not serious	Not serious	None	306	306	-	MD 57.39 higher (39.49 higher to 75.3 higher)	⊕⊕◯◯ C (Low)	Important
LVEF	8 [20,22-28]	Randomized trial	Not serious	Serious[b]	Not serious	Not serious	None	351	351	-	MD 4.93 higher (3.12 higher to 6.74 higher)	⊕⊕⊕◯ B (Moderate)	Critical
NT-pro BNP	6 [19,20,21,24,26,28]	Randomized trial	Not serious	Serious[c]	Very serious	Not serious	None	273	273	-	MD 490.65 lower (760.16 lower to 221.13 lower)	⊕◯◯◯ D (Very Low)	Critical
LeehfS	5 [18,19,22,23,27]	Randomized trial	Not serious	Serious[d]	Not serious	Not serious	None	239	239	-	MD 1.66 lower (2.39 lower to 0.92 lower)	⊕⊕⊕◯ B (Moderate)	Important
BNP	2 [18,23,27]	Randomized trial	Not serious	Serious[f]	Not serious	Not serious	None	126	126	-	MD 107.70 lower (120.71 lower to 94.69 lower)	⊕⊕⊕◯ B (Moderate)	Critical

Note: CI: Confidence Interval; MD: Mean Difference; [a]: I^2=79%; [b]: I^2=68%; [c]: I^2=95%; [d]: I^2 =78%; [e]: I^2=84%; 6-WMT: 6-Minute Walk Experiment; LEVF: Left Ventricular Ejection Fraction; NT-proBNP: N-Terminal Pro-B-Natriuretic Peptide; Leehfs: Lee Heart Failure Score; BNP: Brain Natriuretic Peptide; GRADE: Grades of Recommendation, Assessment, Development and Evaluation.

DISCUSSION

This systematic review is the first to investigate the potential relationships between moxibustion prescription parameters (moxibustion equipment, moxibustion materials, frequency and duration) in TCM therapy and clinical efficacy in HF patients. Previous reviews combined moxibustion prescriptions but did not examine each parameter separately [29]. In particular, the relationships of moxibustion materials and/or duration with clinical efficacy and changes in prognosis following TCM treatment had not been previously investigated.

Moxibustion is an effective method for prevention and treatment of HF and is a commonly used adjuvant therapy in clinical practice. Moxibustion has functions such as warming meridians, dispersing cold and promoting blood circulation and qi circulation. Previous studies have demonstrated the therapeutic role of moxibustion using volatile oil of wormwood leaves (which includes platyclone, eucalyptus oil essence, β-caryophyllene and 39 other compounds) and infrared resonance radiation of acupoints under pathological conditions [30,31]. In addition, this treatment has the potential to improve cardiac function and regulate neuroendocrine reactions [32]. Clinical research has suggested that TCM therapy (e.g. moxibustion) can effectively alleviate symptoms and improve the quality of life of patients with CHF [33].

Although previous systematic evaluations and meta-analyses indicate that acupuncture and moxibustion are inseparable, they both act on acupoints and meridians. However, the primary mode of action of moxibustion involves a photo thermal effect, whereas acupuncture involves mechanical stimulation. In addition, acupuncture is mainly used to dispel the causes of disease, so it is mostly used in excess heat syndrome, whereas moxibustion is mainly used to nourish the body and is mostly used in deficiency cold syndrome. Because the theory of TCM believes that the disease nature of HF is mainly deficiency cold, moxibustion is more suitable for the treatment of HF than acupuncture.

None of the 11 studies included were placebo-controlled. In fact, in China, the blinding of acupuncture and moxibustion, clinical trials rarely include sham acupuncture groups. Thousands of years of clinical experience and curative effects have proved the effectiveness of acupuncture and moxibustion. Moreover, traditional Chinese medicine includes both physiological and psychological interventions.

Regulating the mind is an essential purpose of acupuncture and moxibustion treatment. The so-called placebo effect is closely related to psychological suggestion. Through our meta-analysis, we found that the material, treatment time, and times of wormwood leaves may affect the curative effect of moxibustion. Through further research, we found that in most cases, the materials of moxibustion included wormwood leaves and/or other Chinese herbal medicines such as aconite and ginger. The average retention time of moxibustion is about 25 min (excluding long snake moxibustion). Most studies were conducted over a 12 weeks, three to seven times a week.

This meta-analysis showed that compared with conventional therapy, moxibustion therapy could significantly improve the 6-MWD and LVEF scores of patients with HF and reduce their NT-proBNP scores. In addition, the evidence was assessed as medium and low quality, respectively. 6-MWT can be used for efficacy detection, cardiac function evaluation and prognostic evaluation in cardiovascular diseases [34,35]. Studies of patients with CHF have shown that a 6-MWT walking distance of less than 300 m is associated with a 1-year mortality as high as 50%. In patients with a walking distance greater than 450 m, mortality is significantly reduced [36]. In the current study, we found that moxibustion could improve the 6-MWT scores of patients. Sensitivity analysis showed that when similar moxibustion materials were used, the statistical heterogeneity disappeared, indicating that the use of different moxibustion materials affect the heterogeneity. Finally, the included literature was of low quality. More reliable evidence is needed to demonstrate that moxibustion improves cardiac function in patients with HF.

Cardiac ultrasound has a vital role in hemorheology and examination of cardiac structural changes in patients with HF. LVEF is an important index that is used to judge cardiac ejection function [37]. According to this meta-analysis, moxibustion could improve LVEF scores. Sensitivity analysis showed that the use of different materials of moxibustion may have led to high heterogeneity. The occurrence and development of HF are closely related to changes in various humoral factors. In particular, NT-proBNP has high specificity and sensitivity for the detection of ventricular function

[38]. As well as indicating early changes in ventricular function, it can reflect the severity of CHF and is a significant predictor of cardiac system death and events. According to this meta-analysis, moxibustion could reduce NT-proBNP scores. Sensitivity analysis showed that differences in the number of moxibustion treatments may have been the reason for the heterogeneity among studies. In addition, two studies were of medium quality and thus represent important references for evaluating the efficacy of moxibustion.

Leehfs is a scoring system that was formulated by Lee et al., in 1982, based on clinical manifestations and changes in patient X-rays. It has been widely recognized as a relatively objective standard that can be used to evaluate the curative effects of HF treatments. Leehfs can comprehensively reflect the therapeutic effects of moxibustion on HF [39]. During the onset of HF, the rise of ventricular wall pressure and ventricular endocrine BNP leads to increased BNP levels in the blood. Some studies have shown that detection of BNP is helpful for early diagnosis of CHF [40]. These two indexes demonstrate the superiority of moxibustion combined with conventional treatment.

The advantages of this review include the following. (1) Acupuncture, traditional Chinese medicine decoction, heaven moxibustion and other therapies with essentially different effects from moxibustion were excluded, to ensure the consistency of the therapies received by patients with HF; (2) The moxibustion materials, treatment frequency and the duration of each individual treatment of moxibustion were analyzed in two indexes to demonstrate the superiority of moxibustion combined with conventional treatment.

This paper provides some insight for future research. First, moxibustion materials, single treatment time and total treatment times have different effects on the improvement in cardiac function. Their relevance can be further clarified later. Second, previous studies have lacked long-term follow-up, so it is necessary to evaluate the efficacy of moxibustion therapy further to determine whether it can reduce the hospitalization rate and mortality. Third, to further determine the optimal frequency and amount of moxibustion for the treatment of HF and promote this therapy, a strict, standardized and high-quality RCT design is required to provide high-quality evidence.

CONCLUSION

This meta-analysis shows that moxibustion can improve cardiac function and clinical symptoms in patients with heart failure. As the quality of the literature included in this meta-analysis was moderate, low, or very low, more high-quality research is needed to provide high-quality evidence in further support of the efficacy of moxibustion. Owing to a lack of follow-up, it is uncertain whether moxibustion can prolong the survival time of patients with HF. There is the low or very low certainty of evidence that the use of moxibustion combined with conventional drug is associated the short-term improvement of cardiac function and clinical symptoms compared to conventional drug therapy alone in patients with HF. In short, we look forward to the implementation of multi center large-scale research to provide more high-quality evidence for moxibustion as an adjuvant therapy for HF in the future.

LIMITATIONS

This study also had some limitations. (1) Owing to the differences in moxibustion implementation methods, moxibustion materials, treatment frequency and treatment time, some heterogeneity of results was evident; (2) There were some differences between acute HF and CHF; (3) Most studies did not specifically describe the process of randomization, allocation concealment and blinding, resulting in low overall quality and high risk of bias and (4) Most studies did not describe their ethical review status and there is the possibility that experimental ethics were violated.

FINANCIAL SUPPORT

The present review was funded by the National Natural Science Foundation of China (81574084); Key Research and Development Plan Project of Anhui Province, China (No. 202004j0702045); and Open Fund Project of the Key Laboratory of Ministry of Education of Xin'an Medicine (2020xayx07); 2021 natural science research project of colleges and universities in Anhui Province, China (kj2021a0570).

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Bing Gao: Conceptualization, Data curation, Writing-original draft, Writing-review and Editing, Visualization. Ruonan Ma: Formal analysis. Qingling Li: Investigation. Zhu Wang: Methodology. Heng Wang: Methodology. Yue Cheng: Writing-Review and Editing. Qiang Ma: Validation. Zhuocao Qi: Writing-Review and Editing. Wei Wang: Methodology, Data curation. Yonglei Zeng: Writing-Review and Editing. Jing Wang: Conceptualization, Resources, Writing-Review and Editing.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no conflicts of interest. No author is a member of the editorial board of this journal.

ACKNOWLEDGMENTS

The authors would like to thank the Key Laboratory of Xin'an Medicine, Ministry of Education and Anhui University of traditional Chinese medicine for their efforts to complete this study.

REFERENCES

1. Donagh TAM, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24:4-131.
2. Li SJ. Research progress on epidemiology, pathophysiology and prognosis of senile heart failure. Chinese Journal of Senile Cardiovascular and Cerebrovascular Diseases. 2021;23:318-320.
3. Kane SF. Heart failure: Heart failure with preserved ejection fraction. FP Essentials. 2021;506:11-19.
4. Sivaratnam JP, et al. Atrial fibrillation and heart failure: Epidemiology, pathophysiology, prognosis and management. Card Electrophysiol Clin. 2021;13:47-62.
5. Huang [illegible] et al. Atrial fibrillation: Current understanding and treatment suggestions-2018. Chinese Journal of Cardiac Pacing and Electrophysiology. 2018;32:315-368.
6. [illegible] Z, et al. Effects of moxibustion on cardiac function, BNP and CA125 in patients with heart failure of qi deficiency and blood stasis type. J Tradit Chin Med. 2021;56:134-135.
7. Li LF, et al. Xinmailong injection combined with moxibustion in the treatment of coronary heart disease and heart failure. Chin J Integr Med. 2018;27:865-867.
8. Li QL, et al. Effect of moxibustion on cardiac function and expression of autophagy-related proteins of cardiomyocytes in chronic heart failure rats. J Acupunct Res. 2020;45:259-263+274.
9. Liu NN, et al. Effect of moxibustion on autophagy function of cardiomyocytes in rats with chronic heart failure. J Acupunct Res. 2019;44:25-30.

10. Li D, et al. Effects of moxibustion on ventricular mass index and myocardial apoptosis related protein expression in rats with chronic heart failure. J Acupunct Res. 2018;43:80-85.
11. Li Q, et al. Moxibustion improves chronic heart failure by inhibiting autophagy and inflammation *via* upregulation of mTOR expression. eCAM. 2021;(2021):6635876.
12. Tu M, et al. Acupuncture for treating chronic stable angina pectoris-associated anxiety and depression: A protocol for systematic review and meta-analysis. Medicine. 2020;99:e21583.
13. Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;339:b2535.
14. Higgins JPT, et al. Cochrane handbook for systematic reviews of interventions version 5.1.0. 2011.
15. Atkins D, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMJ. 2004;328:1490.
16. Balshem H, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401-406.
17. Guyatt GH, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64:1311-1316.
18. Zeng WY. Clinical observation of moxibustion on congestive heart failure with Yang deficiency syndrome. GUCM. 2015.
19. Dong F. Clinical study on baixiao moxibustion in the treatment of acute decompensation of Yang deficiency water generalized chronic heart failure. FJTCM. 2020.
20. Wang L. Clinical observation of aconite cake separated moxibustion in the treatment of chronic heart failure with deficiency of heart and kidney yang. CJTCM. 2019.
21. Lin T. Clinical observation of moxibustion combined with medicine in the treatment of heart failure with deficiency of heart and kidney yang. FJTCM. 2020.
22. Gao C, et al. Shendao baxian point medicine separated moxibustion combined with western medicine in the treatment of heart lung qi deficiency syndrome of chronic heart failure. Shanghai Journal of Acupuncture and Moxibustion. 2020;39:1089-1093.
23. Xia MH, et al. Clinical study of long snake moxibustion combined with western medicine in the treatment of chronic heart failure with deficiency of heart and kidney yang. J Acupunct Tuina Sci. 2021;19:284-290.
24. Li SX, et al. Observation on the efficacy of thunder fire moxibustion at ghost eye point and Du Mai group point in the treatment of chronic heart failure complicated with depression. J Tradit Chin Med. 2020;37:1304-1309.
25. Zhang L, et al. Moxibustion technology of heat sensitive group for the treatment of chronic heart failure. Journal of Changchun University of Traditional Chinese Medicine. 2021;37:571-573.
26. Chen Y. Clinical observation of moxibustion combined with western medicine in the treatment of chronic heart failure with heart yang deficiency. Heilongjiang University of Traditional Chinese medicine. 2016.
27. Deng P, et al. Study on the clinical efficacy of heat sensitive moxibustion on chronic heart failure. Bulletin of Traditional Chinese medicine. 2016;15:37-39.
28. Liu HL, et al. Shendao baxian point medicine separated moxibustion combined with western medicine in the treatment of chronic heart failure with qi deficiency and blood stasis. Shanghai Journal of Acupuncture and Moxibustion. 2020;39:269-273.
29. Liang B, et al. The effect of acupuncture and moxibustion on heart function in heart failure patients: A systematic review and meta-analysis. eCAM. 2019;6074967.

30. Deng HP, et al. Infrared radiation characteristics of moxibustion and meridian points. Chinese Acupuncture. 2004;2:33-35.
31. Chen CJ, et al. Analysis and evaluation of volatile components of AI germplasm resources. Chinese Journal of Traditional Chinese medicine. 2021;46:3814-3823.
32. Song B, et al. Downregulation of ASPP2 in pancreatic cancer cells contributes to increased resistance to gemcitabine through autophagy activation. Mol Cancer. 2015;14:177.
33. Fu YN, et al. Clinical study on self-made Tingli Shengmai Wuling powder acupoint application combined with moxibustion in the treatment of chronic congestive heart failure. World Traditional Chinese Medicine. 2020;15:1778-1782.
34. Santos VB, et al. Accuracy of the defining characteristics of fatigue in patients with heart failure as identified by the 6-minute walking test. Int J Nurs Knowl. 1996;110:325-332.
35. Wang YL, et al. The value of 6-min walking test combined with plasma N-terminal precursor brain natriuretic peptide in evaluating the prognosis of patients with chronic heart failure. Chinese Journal of Geriatrics. 2020;39:1411414.
36. Giannitsi S, et al. 6-minute walking test: A useful tool in the management of heart failure patients. Ther Adv Cardiovasc Dis. 2000;89:72-80.
37. Price S, et al. Expert consensus document: Echocardiography and lung ultrasonography for the assessment and management of acute heart failure. Nat Rev Cardiol. 2017;14:427-440.
38. Sheng Y, et al. Decreased albumin is associated with elevated N-terminal pro-brain natriuretic peptide and poor long-term prognosis in patients with chronic heart failure. Medicine. 2020;99:e23872.
39. Lee DC, et al. Heart failure in outpatients: A randomized trial of digoxin *versus* placebo. NEJM. 1982;306:699-705.
40. Farnsworth CW, et al. Diagnostic concordance between NT-proBNP and BNP for suspected heart failure. Clin Biochem. 2018;59:50-55.