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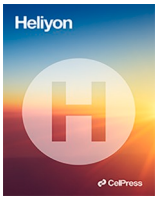

Adjuvant treatment with shenfu injection improve quality of life in chronic heart failure patients: A meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Shenfu Injection (SFI) derived from Shenfu decoction, has been widely used for treating heart failure in China. This meta-analysis aimed to assess the effect of SFI as an adjuvant therapy on quality of life in patients with chronic heart failure (CHF).
Methods: A systematic literature search was conducted in CKNI, VIP, Wanfang, Sinomed, Cochrane Library, PubMed, and Embase database until March 16, 2023. Randomized controlled trials (RCTs) evaluating the effect of SFI plus conventional therapy versus conventional therapy alone for treating CHF were included. Outcome measures were quality of life defineded by the Minnesota Living with Heart Failure questionnaire (MLHFQ), left ventricular ejection fraction (LVEF), 6-min walking distance, and blood brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP) level.
Results: Thirteen RCTs enrolling 1042 CHF patients were included. SFI plus conventional therapy significantly reduced the total MLHFQ score (mean difference [MD] −8.69 points; 95% confidence intervals [CI] −13.46 to −3.91) compared with the conventional therapy alone. Moreover, adjuvant treatment with SFI significantly improved the 6-min walking distance (MD 65.42 m; 95% CI 44.23 to 86.62), LVEF (MD 3.89; 95% CI 1.03 to 6.75), and blood level of BNP/NT-proBNP (SMD -1.73; 95% CI -2.43 to −1.03).
Conclusions: Adjuvant treatment with SFI can achieve additional benefits in improving quality of life and exercise tolerance in patients with CHF. These beneficial effects of SFI may correlate with its improving cardiac function. However, our findings should be interpreted with presence of significant heterogeneity and suboptimal quality of the analyzed trials.

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1. Introduction

Chronic heart failure is a complex clinical syndrome characterized by progressive reduction in cardiac function. The prevalence of chronic heart failure increases with age, affecting approximately more than 10% of individuals aged ≥70 years [1]. Despite advances in medical treatment, chronic heart failure remains the major cause of frequent hospitalization and higher risk of mortality [2]. Patients living with chronic heart failure may experience a moderate to poor quality of life (QoL) [3]. Worse QoL can negatively affect the survival and hospitalization outcomes [4]. Therefore, improving QoL has been identified as an important end point of heart failure therapy [5].

Traditional Chinese Medicine (TCM) has been widely used for the management of heart failure in China [6]. Shenfu Injection (SFI), derived from Shenfu decoction, is a herbal preparation extracting from Panax ginseng C.A. Mey (family Araliaceae) and *Austrosteenisia blackii* var. *blackii* (family Fabaceae). The main active ingredients of SFI are ginseng saponin and aconitum alkaloids. Several clinical trials [7–13] have demonstrated that adjuvant treatment with SFI could improve cardiac function in patients with heart failure. However, the beneficial effect of SFI on QoL remained controversial [7–9,14,15].

Two recent meta-analyses [16,17] have shown that SFI in combination with conventional medicine had additional benefits in terms of improving total clinical response rate, cardiac function, and QoL among heart failure patients. However, the QoL outcome was analyzed in the small number of trials. A systematic review of the update literature for the impact of SFI on QoL remains unavailable in patients with chronic heart failure. Therefore, we conducted this meta-analysis of randomized controlled trials (RCTs) to assess the effect of SFI as an adjuvant therapy on QoL in these patients.

2. Material and methods

2.1. Search strategy

The current study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [18] and registered in the PROSPERO databases (CRD42022408858). Two independent authors systematically searched China National Knowledge Infrastructure (CNKI), VIP, Wanfang, Chinese Biomedical Literature Database (Sinomed), Cochrane Library, PubMed, and Embase database until March 16, 2023. Keywords or items used for the English literature search included: “Shenfu injection” OR “Shen Fu injection” AND “heart failure” OR “cardiac insufficiency” OR “cardiac failure” AND “quality of life”. The following combined keywords used for the Chinese literature search: “Shen Fu Zhu She Ye” AND “Xin Shuai” OR “Xin Li Shuai Jie” OR “Xin Gong Neng Bu Quan” AND “Shen Huo Zhi Liang” AND “Dui Zhao” AND “Sui Ji”. The detailed search strategy is summarized in Supplement text S1. Moreover, the reference lists of related articles were also manually reviewed to identify any additional trials.

2.2. Study selection

Two authors independently read the titles or abstracts, retrieved the potentially eligible full-text articles, and further chose the eligible studies according to our inclusion and exclusion criteria. Trails satisfying all the criteria were considered eligible: 1) type of studies: RCTs publishing in peer-review journal, 2) participants: patients with a diagnosis of chronic heart failure, 3) intervention: SFI plus conventional therapy versus the conventional therapy alone, and 4) outcome measures: quality of life defined by the Minnesota Living with Heart Failure questionnaire (MLHFQ) as the primary endpoint and left ventricular ejection fraction (LVEF), 6-min walking test (6MWT), and blood brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP) level as the secondary endpoints. Conventional therapy includes the diuretics, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, β-blockers, aldosterone receptor antagonist, digoxin, or others recommended by the Chinese guideline for the diagnosis and management of chronic heart failure. Exclusion criteria included:1) trials enrolling patients with acute heart failure, 2) Shenfu decoction as intervention, 3) SFI combined with other therapies as intervention, and 4) duplicate publication.

2.3. Data extraction and risk of bias assessment

Two independent authors collected the following data: name of the first author, year of publication, number of patients in each group, gender distribution, mean age or age range, diagnostic criteria, Chinese medicine syndrome differentiation, baseline LVEF, method of randomization, allocation concealment, blinding methods, assessment of QoL, and interventions (dosage of SFI, duration of treatment, types of conventional treatment). Two authors independently evaluated the study quality using the RevMan 5.1 of the Cochrane Collaboration. This risk bias tool assesses the randomization generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias (whether selection of patients considering TCM syndrome differentiation). Each domain was grouped as “low risk”, “high risk” or “unclear risk”. In case of discrepancy between two authors, the corresponding author did an independent review to settle any disagreements.

2.4. Data analysis

Meta-analyses were performed using the RevMan 5.1 or Stata 12.0 software. Continuous outcomes were summarized by the mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (CI). Statistically significant heterogeneity

between trials was defined by *P*-value <0.1 of the Cochrane Q test and/or I^2 statistic ≥50%. We selected a random effect model when there was significant heterogeneity. Leave-one-out sensitivity analysis was conducted to assess the robustness of the original pooling results. Subgroup analysis was performed according to the baseline LVEF, dosage of SFI, sample sizes, or whether selection of patients considering TCM syndrome.The likelihood of publication bias was evaluated by the Begg's test [19] and Egger's test [20]. A trim-and-fill approach was performed to investigate the potential effect of publication bias. The GRADE analysis was used to summarize the certainty of evidence, which assessed the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

3. Results

3.1. Search results and study characteristics

The initial literature search yielded 203 articles. Of which, 113 articles were obtained to evaluate the titles and abstracts after removing the duplicate records. Fifty-three articles were retrieved for full-text assessment. After applying the inclusion and exclusion criteria, 40 articles were further excluded for various reasons (Supplemental text S2). Finally, 13 trials [7–15,21–24] were included in the meta-analysis (Fig. 1).

Basic characteristics of the included trials are described in Table 1. These trials were published from 2013 to 2021 and performed in China. Sample sizes of the included trials varied between 42 and 150, with a total of 1042 CHF patients. Three trials [13,14,22] selected patients based on the TCM syndrome differentiation. The dosage of SFI ranged from 40 to 100 ml per day and the course of the treatment varied from 5 to 28 days. The methodological quality of each study is shown in Supplemental Fig. S1 and Fig. S2. All the included trials reported to randomly assign patients into different groups; however, only 7 trials [11–15,22,24] clearly provided the detailed method of randomization. Allocation concealment and blinding methods were not reported in the included trials. Overall, the

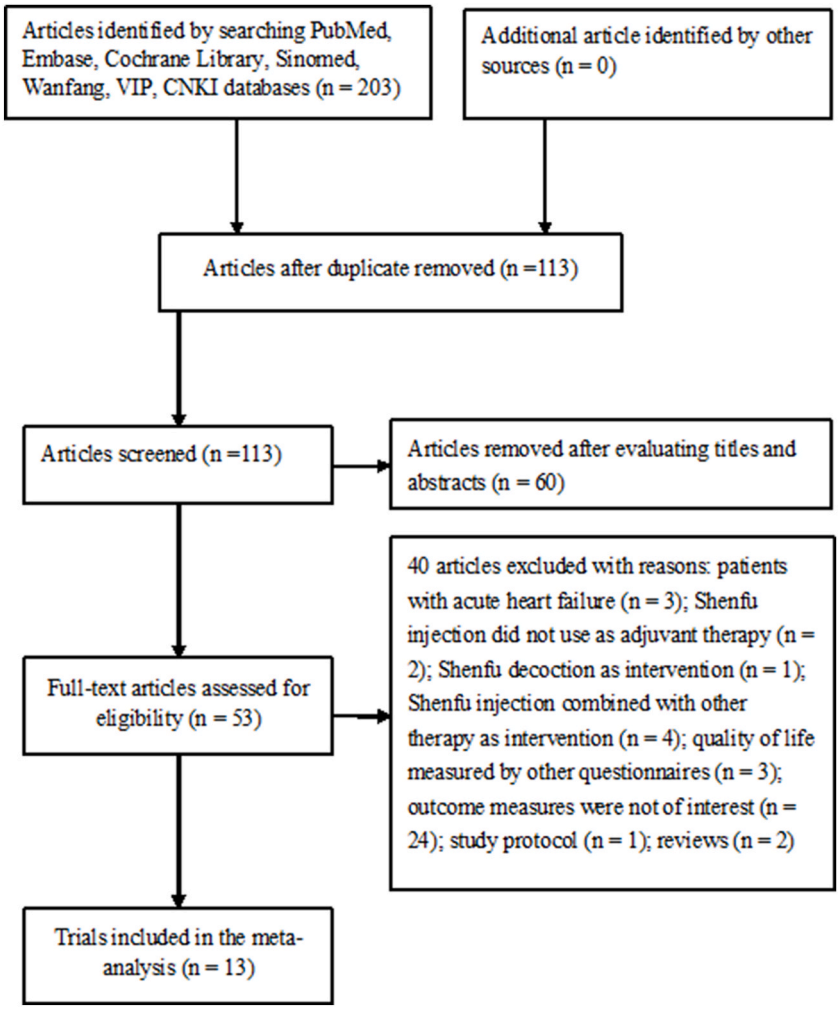

Fig. 1. Flow chart showing trials selection process.

Table 1
Main characteristics of the included clinical trials.

Study	Sample sizes	Men (%)	Age (years)	Baseline LVEF (%)	Main interventions SFI group	Control group	Course of treatment	Outcome measures
Pei Q 2013 [14]	SFI:36 Con: 36	SFI:53 Con: 56	SFI: 63.5 ± 10.2 Con: 63.8 ± 9.39	NR	SFI 1 ml/kg/d + CT	CT	14 days	QoL, 6MWT, NT-proBNP
Wu JB 2013 [8]	SFI:40 Con: 40	SFI:65 Con: 68	SFI: 64.1 ± 5.4 Con: 66.4 ± 7.4	SFI: 31.3 ± 2.88 Con: 30.5 ± 3.25	SFI 40 ml/d + Erythropoietin 2000 IU/week + CT	CT + Erythropoietin 2000 IU/week	14 days	QoL, LVEF, NT-proBNP
Yu M 2013 [7]	SFI:39 Con: 40	51	40 ± 13	SFI: 40.3 ± 3.2 Con: 41.7 ± 2.9	SFI 40 ml/d + Trimetazidine 90 mg/d + CT	CT + Trimetazidine 90 mg/d	14 days	QoL, 6MWT, LVEF, BNP
Zhao W 2014 [15]	SFI:21 Con: 21	SFI:53 Con: 48	SFI: 64.1 ± 8.86 Con: 65.6 ± 16.6	NR	SFI 100 ml/d + CT	CT	5–10 days	QoL, NT-proBNP
Xu LL 2015 [9]	SFI:25 Con: 25	SFI:60 Con: 68	SFI: 64 ± 11 Con: 63 ± 10	SFI: 36.6 ± 3.2 Con: 36.3 ± 3.4	SFI 100 ml/d + CT	CT	7 days	QoL, LVEF, NT-proBNP
Xue Z 2015 [21]	SFI:40 Con:40	49	60.2 ± 5.67	NR	SFI 40 ml/d + CT	CT	14 days	QoL, LVEF, NT-proBNP
Zhang T 2015 [22]	SFI:28 Con: 28	SFI:57 Con: 54	SFI: 69.6 ± 11.2 Con: 70.3 ± 13.8	NR	SFI 80 ml/d + CT	CT	14 days	QoL, NT-proBNP
He YL 2016 [10]	SFI:45 Con: 45	SFI:64 Con: 67	SFI: 61.4 ± 8.3 Con: 62.3 ± 7.8	SFI: 43.2 ± 3.25 Con: 43.2 ± 3.42	SFI 60 ml/d + CT	CT	14 days	QoL, LVEF, BNP
Yao KW 2016 [24]	SFI:51 Con: 51	SFI:45 Con: 41	SFI: 71.7 ± 8.2 Con:71.2 ± 8.2	NR	SFI 60 ml/d + CT	CT	14 days	QoL
Cao XM 2017 [11]	SFI:48 Con:47	SFI:67 Con:70	SFI: 74 ± 4 Con: 72 ± 4	SFI: 31 ± 4 Con: 30 ± 5	SFI 100 ml/d + CT + Levocarnitine 2 g/d	CT + Levocarnitine 2 g/d	14 days	QoL, 6MWT
Sun LX 2018 [12]	SFI:53 Con: 53	SFI:64 Con: 55	SFI: 68.5 ± 6.4 Con: 67.9 ± 6.5	SFI: 33.0 ± 4.0 Con: 33.2 ± 4.5	SFI 100 ml/d + CT + Bisoprolol fumarate	CT + Bisoprolol fumarate	28 days	QoL, 6MWT, LVEF, NT-proBNP
Wang H 2018 [23]	SFI:25 Con: 25	SFI:64 Con: 60	SFI: 54.0 ± 11 Con: 53.6 ± 12	NR	SFI 40 ml/d + CT	CT	7 days	QoL, NT-proBNP
Zhou TT 2021 [13]	SFI:75 Con: 75	SFI:57 Con: 60	NR	SFI: 46 ± 4 Con: 45 ± 6	SFI 40 ml/d + Nosinoxintal + CT	CT + Nosinoxintal	10 days	QoL, 6MWT, LVEF, NT-proBNP

Abbreviations: SFI, Shenfu Injection; Con, control; NR, not reported; CT, conventional therapy; LVEF, left ventricular ejection fraction; QoL, quality of life; HF, heart failure; CHF, chronic heart failure; DCM, dilated cardiomyopathy; 6MWT, 6-min walking test; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide.

included trials were considered as to have unclear risk of bias.

3.2. Quality of life based on the MLHFQ

Eleven RCTs [7–10,12–15,22–24] reported the effect of SFI as adjuvant therapy on the QoL based on defined by the MLHFQ. As shown in Fig. 2, there was significant heterogeneity between trials ($I^2 = 98.0\%$, $p < 0.001$). A random effect model meta-analysis showed that SFI plus conventional therapy significantly reduced the total MLHFQ score (MD -8.69 points; 95% CI -13.46 to −3.91) than the conventional therapy alone. Sensitivity analysis suggested that individual trial did not significantly alter the originally statistical significance. However, the effect of SFI on QoL was not statistically significant in the trials with SFI dosage at 40 ml/day subgroup (Supplemental Table S1). Begg's test ($p = 0.755$) and Egger's test (t = −0.20, 95% CI -11.41891 to 9.601282, p = 0.849) indicated the unlikelihood of publication bias.

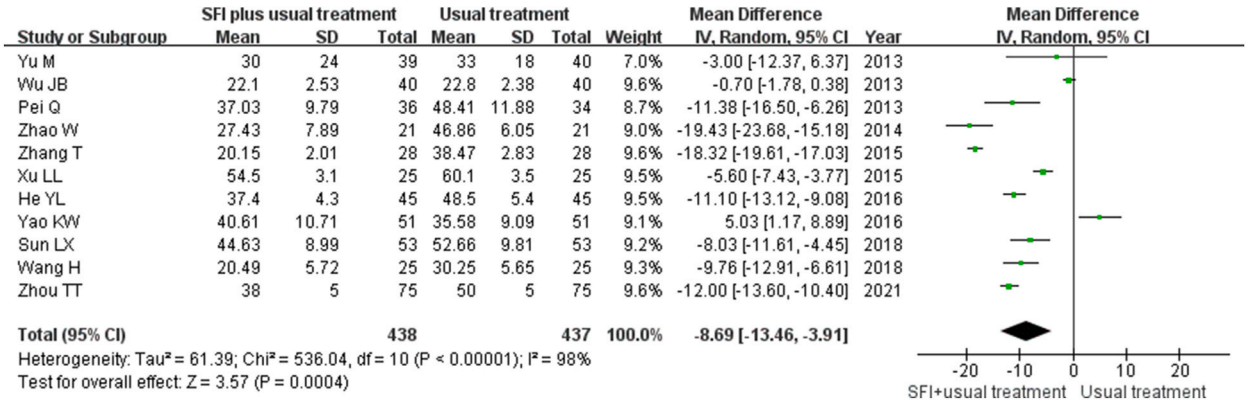

Fig. 2. Forest plots showing the effect of Shenfu injection on quality of life defined by the Minnesota Living with Heart Failure questionnaire.

3.3. Six-minute walking test

Six RCTs [7,11–14,21] reported the effect of SFI as adjuvant therapy on the 6-min walking distance. As shown in Fig. 3, significant heterogeneity ($I^2 = 85.0\%$, $p < 0.001$) was found between the included trials. A random effect model meta-analysis showed that SFI plus conventional therapy significantly improved the 6-min walking distance (MD 65.42 m; 95% CI 44.23 to 86.62) compared with the conventional treatment alone. Sensitivity analysis confirmed the reliability of the original pooling effect size.

3.4. Left ventricular ejection fraction

Seven RCTs [7–13] reported the effect of SFI as adjuvant therapy on the LVEF. As shown in Fig. 4, SFI plus conventional therapy significantly improved the LVEF (MD 3.89; 95% CI 1.03 to 6.75) compared with the conventional therapy alone, with significant heterogeneity ($I^2 = 96.0\%$, $p < 0.001$). Leave-out one trial sensitivity analysis demonstrated the robustness of the original pooling effect size.

3.5. Blood BNP/NT-proBNP level

Eleven RCTs [7–10,12–15,21–23] reported the effect of SFI as adjuvant therapy on the blood BNP/NT-proBNP level. As shown in Fig. 5, significant heterogeneity ($I^2 = 95.0\%$, $p < 0.001$) was observed between these trials. A random effect model meta-analysis indicated that SFI plus conventional therapy significantly reduced the blood BNP/NT-proBNP level (SMD -1.73; 95%CI -2.43 to −1.03) than the conventional therapy alone. In leave-out one trial sensitivity analysis, individual trial did not significantly change the originally statistical significance. Publication bias was not found according to Egger's test (t = −1.97, 95% CI -21.56293 to 1.477725, $p = 0.080$) and Begg's test ($p = 0.436$). Moreover, a trim-and-fill analysis showed that the corrected SMD was −2.02 (95%CI -2.76 to −1.29) after imputing 2 potential missing trials.

3.6. GRADE certainty of evidence

Supplemental Table S2 lists the certainty of evidence. The overall certainty of evidence was low for the QoL, 6MWT, and BNP/NT-proBNP level. LVEF assessment was considered as very low quality.

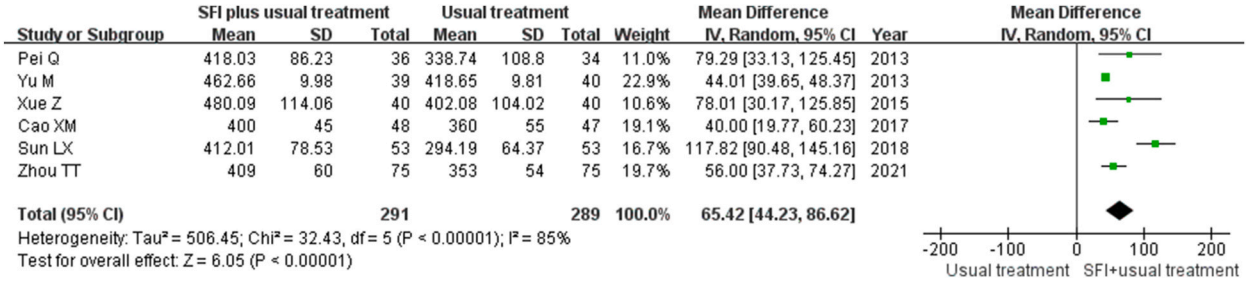

Fig. 3. Forest plots showing the effect of Shenfu injection on 6-min walking test.

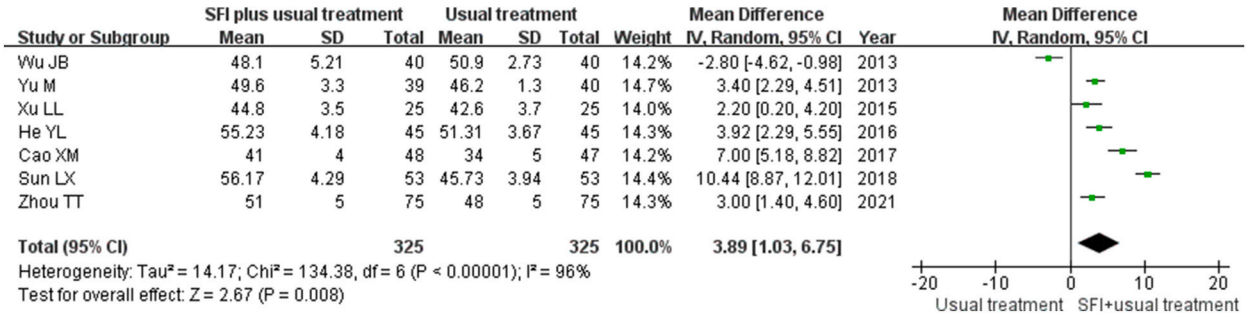

Fig. 4. Forest plots showing the effect of Shenfu injection on left ventricular ejection fraction.

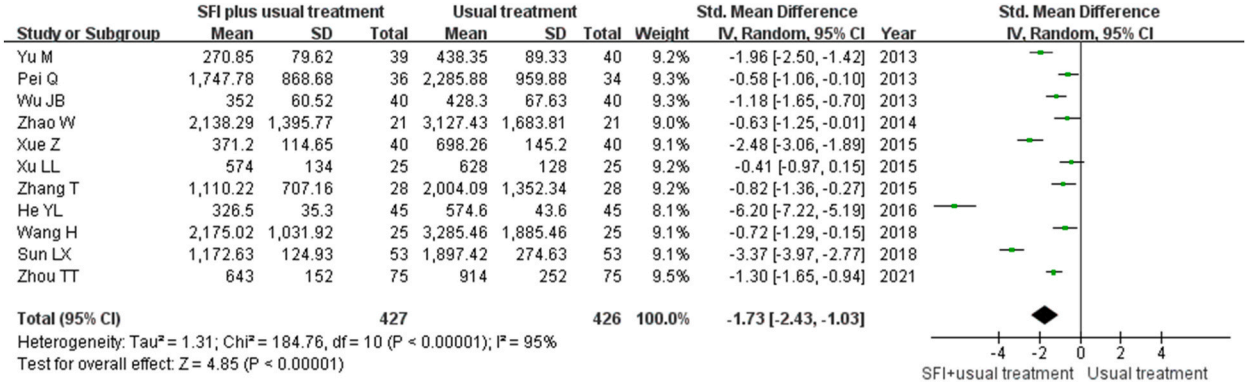

Fig. 5. Forest plots showing the effect of Shenfu injection on blood BNP/NT-proBNP level.

4. Discussion

The current meta-analysis suggested that SFI plus conventional therapy significantly improved the QoL and exercise tolerance compared with conventional therapy alone. Moreover, adjuvant treatment with SFI also significantly increased the LVEF as well as reduced the blood BNP/NT-proBNP level. These findings indicate that SFI as adjuvant therapy may acquire additional benefits in patients with chronic heart failure. However, the overall certainty of evidence regarding the QoL and exercise tolerance was low according to the GRADE assessments.

The MLHFQ is widely used to measure the QoL of heart failure patients. This tool consists of 21 questions focused on patient perceptions concerning a variety of physical and emotional aspects. Higher score of MLHFQ reflects the lower QoL. Apart from the MLHFQ, adjuvant treatment with SFI also improved the QoL defined by the Short Form-36 (SF-36) [25] and the Left Ventricular Dysfunction questionnaire (LVD-36) [26] in patients with heart failure. In a prospective randomized controlled trial, oral administration of Shenfu decoction significantly improved by MLHFQ score (35.27 $\pm$ 10.72 vs. 23.87 $\pm$ 11.96) than the control group in patients with symptomatic chronic heart failure [27]. These findings further supported the beneficial effect of SFI on improving QoL.

Syndrome differentiation is the main feature of TCM [28]. Our subgroup analysis showed that the effect of SFI on the QoL was stronger (−14.14 points *vs*.-6.66 points) in the trials considering the TCM syndrome differentiation than those without. This result suggested that precisely tailoring SFI for patients based on TCM syndrome differentiation can improve its efficacy. Moreover, the dosage of SFI is another factor affecting its effect on the QoL. The dosage of SFI used in the included RCTs ranged from 40 ml to 100 ml per day. Results of our subgroup analysis showed that the effect of SFI on the QoL was not statistically significant in the trials that administrated SFI at the dosage 40 ml/day. To enhance the efficacy of SFI on improving QoL, clinicians should be aware of the following issues: 1) selection of patients should consider the TCM pattern differentiation, and 2) the dosage of SFI should be greater than 40 ml/day.

Regarding safety, a well-designed review [29] summarized that the most commonly reported side effects of SFI included dry mouth, dryness heat, stretching head, palpitation, insomnia, skin itching, facial flushing, dizziness, irritability, and gastrointestinal discomfort. However, the included trials particularly those with high-dose of SFI (100 ml/day) did not report the above mentioned adverse events [11,15] or similar incidence of adverse events between two group [12].

Several limitations should be taken into consideration in our meta-analysis. First, methodological flaw was a major concern of the included trials. Only half of trials reported the method of random sequence generation. Allocation concealment and blinding methods were not mentioned in all the included trials. Therefore, majority of included trials were deemed as to have unclear risk of bias. Second, most of the included RCTs enrolled the patients according to the modern medical diagnosis rather than TCM syndrome differentiation,

which may have led to selection bias. Third, significant heterogeneity between trials was found in pooling the individual outcome. The existed heterogeneity may be correlated with different etiology of heart failure, dosage, or course of SFI treatment, and regimen of conventional treatment. Fourth, we could not determine the long-term effect of SFI treatment because the effects of SFI were evaluated after 5–28 days' treatment. Most of the trials did not mention the follow-up results or the follow-up duration was insufficient to access the long-term effects. Finally, our meta-analysis could not determine the specific aspects of MLHFQ which SFI acted due to insufficient such data.

5. Conclusions

SFI as adjuvant therapy may achieve additional beneficial effects in improving QoL and exercise tolerance in patients with chronic heart failure. The beneficial effects of SFI may correlate with improving cardiac function. However, the current findings should be interpreted with presence of significant heterogeneity and suboptimal quality of the analyzed trials.

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Data availability statement

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

CRediT authorship contribution statement

Junya Zhou: Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – review & editing. **Songge Chen:** Data curation, Formal analysis, Investigation, Methodology, Resources, Validation. **Minghui Xu:** Data curation, Formal analysis, Investigation, Resources, Validation, Visualization. **Yali Guo:** Formal analysis, Methodology, Validation, Visualization, Writing – review & editing. **Xue Xia:** Validation, Data curation, Investigation, Methodology, Writing – review & editing. **Qingzhu Qin:** Conceptualization, Methodology, Supervision, Validation, Writing – original draft. **Hongmei Zhang:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

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

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20594.

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