Original Article

Shenfu injection for heart failure based on the AMSTAR-2, PRISMA, and GRADE tools

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Background: Evidence of the efficacy of Shenfu injection (SFI) in the treatment of heart failure (HF) is inconsistent. This study aimed to strictly evaluate the methodological quality, reporting quality, and evidence quality of systematic reviews (SRs) and meta-analyses (MAs) on the efficacy of SFI.

Methods: From inception to December 2020, using standardized search strategies, we searched for relevant SRs and MAs in the following seven databases: Cochrane library, Embase, PubMed, SinoMed, China National Knowledge Infrastructure (CNKI), Wanfang Database, and VIP Database. The Appraisal Tool for Systematic Reviews of Randomized and Observational Studies 2 (AMSTAR-2) and Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) tools were used to evaluate the methodological and reporting quality of SRs, respectively. The quality of results was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. If necessary, we conducted quantitative synthesis or descriptive analysis of the original data.

Results: There were 12 SRs/MAs involving 302 original randomized controlled trials (RCTs) and more than 22,445 participants (the total number was not mentioned in 1 study). The treatment group was classified as SFI combined with western medicine (WM), while the control group was WM alone. The methodological quality of all the literatures was very low, and the quality of reports was relatively good, with an average PRISMA score of 18.25 points. We evaluated 52 outcomes, of which 3 were moderate quality, 13 were low quality, and the rest were very low quality. Low quality evidences indicated that the clinical efficacy of SFI combined with WM for HF was better than that of WM, which can improve the quality of life and cardiac function of patients.

Conclusions: It appeared that SFI was effective in the treatment of HF. Due to the low quality of methodology and reports in the literature, we cannot be sure of the results. We strongly recommend that more high-level RCTs be carried out in the future. Besides, researchers should strictly comply with the AMSTAR-2, PRISMA, and GRADE guidelines for SRs.

Keywords: Heart failure (HF); Shenfu injection (SFI); quality assessment; overview

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Introduction

Heart failure (HF) is the final stage of cardiovascular disease, which leads to myocardial damage, along with structural and functional problems. The global prevalence of HF is estimated to exceed 37.79 million (1). Although the incidence of HF has remained at a relatively stable level, the rates of rehospitalization and mortality are still high. Globally, 17–45% of hospitalized HF patients die within 1 year after admission, while the majority die within 5 years after admission. The 5-year death rate is similar to that of many cancers (2,3). According to the American Heart Association, the prevalence rate in developed countries is 1–2% in the adult population. In the United States, 5.8 million patients suffered from HF in 2012, which is expected to rise to 8.5 million by 2030, and the medical costs will rise to $70 billion (4-6). According to the report outline of cardiovascular Disease in China [2018], it is estimated that the number of patients with cardiovascular disease is 290 million, including 4.5 million cases of HF (7), and the in-hospital mortality is 5.3% (451/8,516) (8). It has become a major public health problem worldwide.

Currently, the conventional medical treatment for HF includes angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, mineralocorticoid/aldosterone receptor antagonists (MRAs), diuretics, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNI), aldosterone antagonists, digitalis and vasodilators and so on, but the shortcomings of western medicine (WM) are prominent, such as persistent high cost, short-term efficacy, and adverse reactions or side effects (6). Traditional Chinese medicine (TCM) has its own specific characteristics and advantages. Among the treatment methods of TCM, TCM injection is used in the treatment of HF and has shown good efficacy (9). Shenfu injection (SFI) is a TCM injection that is widely used in clinical treatment, and is composed of red ginseng and aconite. It can restore the yang and prevent the adversity, replenish and solidify qi, enhance myocardial contractibility, protect myocardium, improve hemodynamics, and regulate heart rate (10); the safety of SFI is very high, and the incidence of adverse drug reactions (ADRs) is 0.076%, 95% confidence interval (CI): (0.045 to 0.108) (11).

At present, from clinical trials to systematic reviews (SRs), many studies have reported the efficacy of treating HF with either a single or combined conventional drug, but the findings have been inconsistent (12,13). As SRs provide the highest quality of evidence that guides clinical decision-making, it is particularly important to evaluate the quality of SRs. The purpose of this study was to evaluate the methodological quality, quality of the literature report, and to grade the main results, so as to understand the current situation and challenges of SR in SFI treatment of HF, and provide ideas for clinical treatment of HF.

Methods

Search strategy

The deadline for literature publication is up to December 2020, relevant literatures were searched for in the following seven databases: Cochrane library, Embase, PubMed, SinoMed, China National Knowledge Infrastructure (CNKI), Wanfang Database, and VIP Database. The key search words included: “Shenfu injection”, “heart failure”, “heart decompensation”, “cardiac failure”, “myocardial failure”, “heart insufficiency”, “cardiac insufficiency”, “ventricular dysfunction”, “systematic review”, “systematic evaluation”, “meta-analysis”. The search strategy was adjusted according to the characteristics of each database. In addition, we manually searched relevant grey literature, conference articles, and other published literature. The literature retrieval was conducted independently by two reviewers (JTJ and ZML). When differences occurred, they were resolved by discussion between the two reviewers, and any unresolved problems were resolved by a third reviewer (FYZ). The search strategies are shown in *Tables 1-5*.

Eligibility criteria

Inclusion criteria

All articles met the following inclusion criteria: (I) must be a SR/meta-analysis (MA) of HF treated by SFI, and each SR must contain at least two randomized controlled trials (RCTs); (II) all participants were diagnosed with HF, and were included regardless of gender, age, region, race, etiology, disease course, degree, and other factors; (III) the treatment group was treated with SFI or combined with other methods, while the control group could be any other treatment method except SFI; (IV) the efficacy indexes included 1 or more of the following: effect rates, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDd), brain natriuretic peptide (BNP), N-terminal pro-B type natriuretic peptide (NT-proBNP), 6-min walk test (6-MWT), the Minnesota Living

Table 1 Search strategy in the PubMed database

Number	Search items
#1	Heart failure [All fields]
#2	Heart decompensation [All fields]
#3	Cardiac failure [All fields]
#4	Myocardial failure [All fields]
#5	Heart insufficiency [All fields]
#6	Cardia insufficiency [All fields]
#7	Ventricular dysfunction [All fields]
#8	1 or 2–7
#9	Shenfu injection [All fields]
#10	Systematic review [All fields]
#11	Systematic evaluation [All fields]
#12	Meta-analysis [All fields]
#13	10 OR 11–12
#14	8 AND 9 AND 13

Table 2 Search strategy in the Cochrane library database

Number	Search items
#1	(Heart failure):ti,ab,kw
#2	(Heart decompensation):ti,ab,kw
#3	(Cardiac failure):ti,ab,kw
#4	(Myocardial failure):ti,ab,kw
#5	(Heart insufficiency):ti,ab,kw
#6	(Cardia insufficiency):ti,ab,kw
#7	(Ventricular dysfunction):ti,ab,kw
#8	1 or 2–7
#9	(Shenfu injection):ti,ab,kw
#10	(Systematic review):ti,ab,kw
#11	(Systematic evaluation):ti,ab,kw
#12	(Meta-analysis):ti,ab,kw
#13	10 OR 11–12
#14	8 AND 9 AND 13

ti,ab,kw, title, abstract, key word.

Table 3 Search strategy in the Embase database

Number	Search items
#1	Heart failure OR heart decompensation OR cardiac failure OR myocardial failure OR heart insufficiency OR cardia insufficiency OR ventricular dysfunction
#2	Shenfu injection
#3	Systematic review OR systematic evaluation OR meta-analysis
#4	#1 AND #2 AND #3

Table 4 Search strategies for the SinoMed database

Number	Search items
#1	"Heart failure" [Common fields: intelligence] OR "Cardiac insufficiency" [Common fields: intelligence] OR "Cardiac failure" [Common fields: intelligence] OR "Cardiac decompensation" [Common fields: intelligence] OR "Ventricular dysfunction" [Common fields: intelligence]
#2	"Shenfu Injection" [Common fields: intelligence]
#3	"Systematic review" [Common fields: intelligence] OR "Meta-analysis" [Common fields: intelligence]
#4	(#1) AND (#2) AND (#3)

Intelligence retrieval: to realize the extended retrieval of search terms and their synonyms (including subject terms).

Table 5 Search strategies for other databases

Database	Search items
CNKI	SU: (heart failure OR cardiac insufficiency OR myocardial failure OR decompensation OR ventricular insufficiency) AND U: (shenfu injection) AND U: (systematic review OR meta-analysis)
Wanfang	SU: (heart failure or cardiac insufficiency or cardiac failure or cardiac decompensation or ventricular dysfunction) and SU: (shenfu injection) and SU: (systematic review or meta-analysis)
VIP	U: (heart failure OR cardiac insufficiency OR myocardial failure OR decompensation OR ventricular insufficiency) AND U: (shenfu injection) AND U: (systematic review OR meta-analysis)

CNKI, China National Knowledge Infrastructure; U, all fields; SU, subject search.

With Heart Failure Questionnaire (MLHFQ), mortality, and rehospitalization rate.

Exclusion criteria

All the following literatures were excluded: (I) without SFI treatment; (II) not SR literatures, including animal experiments, RCTs, general reviews, conference articles, case reports, expert consensus, and so on; (III) incomplete data and duplicate papers.

Study selection

The two reviewers (SMC and GZ) strictly followed the eligibility criteria and search strategies to conduct literature searches in the above seven databases without language restrictions. Preliminary screening was carried out through reading titles and abstracts, and the literatures were poured into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) to eliminate duplicate documents. Then, all the initial qualified literature titles and were listed and the full text was further read to exclude all non-conforming literature. If there were date defects in the original literature, the original author was contacted. Any dispute was settled between the two reviewers, and any unresolvable differences were settled by a third reviewer (FYZ).

Data extraction

Another two reviewers (JTJ and ZML) extracted data through a unified extraction table, including: general information (title, first author, year of publication, country, language, contact information, funding, conflict of interest, ethical perceptions), research contents (participants, sample size, randomization, allocation concealment, blind, intervention, comparison), research outcomes (risk assessment tools, main outcomes, adverse reactions/events and main conclusions). Any dispute was settled between the two reviewers, and any unresolvable differences were resolved by a third reviewer (FYZ).

Quality assessment

The two reviewers (LYL and SY) independently evaluated all the included SRs according to the requirements of the three evaluation tools [Appraisal Tool for Systematic Reviews of Randomized and Observational Studies 2 (AMSTAR-2) (14-16), Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) (17), and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (18)], and then cross-checked. In the case of inconsistent evaluation results, the two reviewers attempted resolution through discussion, and any unresolved disagreements were settled by a third reviewer (FYZ).

AMSTAR-2

The popular AMSTAR tool was developed in 2007 to rigorously evaluate the methodological quality of SRs. In 2017, AMSTAR-2 was officially published, which can be used to evaluate SRs in randomized or non-randomized trials. AMSTAR-2 retains 10 original items and expands six new items for a total of 16 items. The content of each item is simpler and clearer, and the overall score is based on weaknesses in key areas. Each item requires the reviewers to answer "yes", "no" and "partial yes", and items 2, 4, 7, 9, 11, 13, and 15 are key items. It can seriously affect whether the evaluation result is downgraded or not. The quality of the SR is divided into four levels: (I) high: none or only one non-key item does not meet the requirements; (II) moderate: more than one non-key item does not meet the requirements; (III) low: only 1 key item does not meet and it does not meet with or without non-key items;

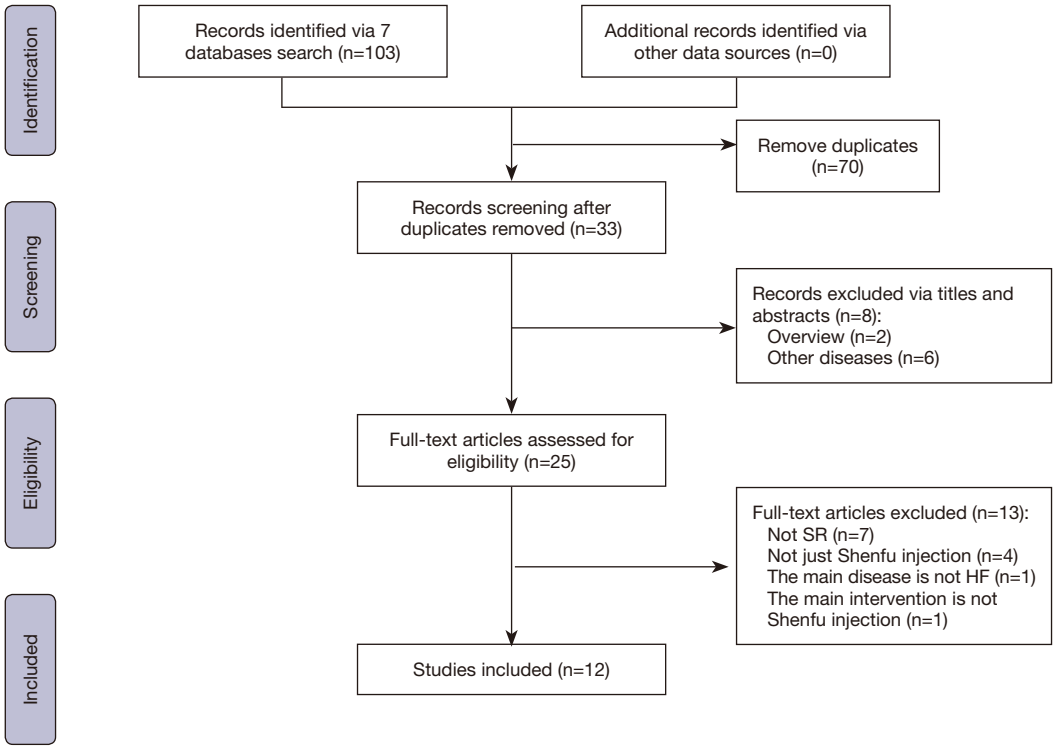

Figure 1 Flowchart of literature selection. SR, systematic review; HF, heart failure.

(IV) very low: more than one key item does not meet the requirements, with or without non-key items does not meet the requirements. The AMSTAR-2 tool is consistent with SRs, which indicates that it is a practical method.

PRISMA

The PRISMA tool is used to evaluate reporting quality. The PRISMA statement covers 27 lists. Each item requires the reviewer to answer "yes", "no", and "partial yes". Both AMSTAR-2 and PRISMA can be expressed as a percentage of items that meet "yes".

GRADE

The GRADE tool is used to grade the quality of evidence of the main outcomes. There may be several reasons for the decrease of evidence, including the study limitations, inconsistency of results, indirectness of evidence, imprecision, or reporting bias. The quality of evidence can be classified into four levels: high, moderate, low, and very low. No degradation equates to high quality, one degradation to moderate quality, two degradation to low quality, and three or more degradation to very low quality.

Statistical analysis

Due to the lack of access to the original data, we could only carry out quantitative synthesis or descriptive analysis of existing data. The kappa index was used to measure reliability between the two reviewers: a kappa index over 0.75 indicated excellent consistency; 0.4–0.75 indicated fair consistency; and less than 0.4 indicated poor consistency.

Results

Search results

According to the search strategy, 103 articles were initially screened from 7 databases, of which 22 were from CNKI, 24 from SinoMed, 25 from Wanfang, 20 from VIP, 8 from Embase, 4 from PubMed, and 0 from Cochrane library. A total of 70 duplicate references were excluded in Endnote X9; further, 8 articles were excluded after reading the titles and abstracts, and then 13 articles were excluded by reading the full text. Finally, a total of 12 articles were included for data analysis (19-30). The process of the literature search and screening is shown in *Figure 1*. The list of excluded

Table 6 Excluded list

Citation	Reason for exclusion
Yu N. Systematic evaluation of shenfu injection in the treatment of heart failure. Chinese Journal of Applied Medicine 2019;14:87-8.	Not SR
Li P, Wang T, Fu S, *et al.* Comparison of clinical effects of shenfu and shenmai injection based on meta-analysis. Chinese Herbal Medicine 2016;47:2949-59.	Not SR
Bai D, Yue G, Wang R, *et al.* Clinical application characteristics of 5 Traditional Chinese medicine injections in the treatment of heart failure based on meta-analysis. Chinese Journal of Traditional Chinese Medicine 2008;43:4152-62.	Not SR
Jiang H, Men P, Li X, *et al.* An evidence-based evaluation of the efficacy and safety of Shengmai Injection in the treatment of chronic heart failure. Journal of Clinical Pharmacotherapy 2020;18:31-4.	Not SR
Li C. Study on the standardized application of Traditional Chinese Medicine Injection. Henan College of Traditional Chinese Medicine 2015.	Not SR
Yuan C. Effects of Shenfu Qiangxin Decoction combined with Shenmai Injection on symptoms and cardiac function of patients with severe heart failure. Henan Medical Research 2019;28:1869-70.	Not SR
Li Q, Zhou T, Guan H, *et al.* Cost-effectiveness analysis of shenfu injection combined with conventional regimens in the treatment of heart failure. Chinese Journal of New Drugs 2017;26:1718-24.	Not SR
Yang F, Zou J, Wang Y, *et al.* Chinese Journal of Traditional Chinese. Medicine 2008;43:1247-53.	Not just SFI
Zhu X, Wang Q, Gan C, *et al.* A Meta-analysis on the efficacy and safety of Yiqi - retaining and demultifying Traditional Chinese medicine injection combined with Levosimendan in the treatment of heart failure. Chinese Journal of Evidence-Based Cardiovascular Medicine 2020;12:664-8.	Not just SFI
Yang FW, Zou JH, Wang Y, *et al.* Network meta-analysis of Chinese medical injections for heart failure. Zhongguo Zhong Yao Za Zhi 2018;43:1247-53.	Not just SFI
Wang KH, Wu JR, Zhang D, *et al.* Comparative efficacy of Chinese herbal injections for treating chronic heart failure: a network meta-analysis. BMC Complement Altern Med 2018;18:41.	Not just SFI
Zhu Y, Shen X, Han Q, *et al.* Meta-analysis of clinical efficacy of Shenfu Injection in the adjuvant treatment of myocardial infarction with heart failure. Chinese Journal of Evidence-Based Cardiovascular Medicine 2012;10:402-6.	The main disease is not HF
Zhang Q, Wu W. Effect of non-invasive positive pressure ventilation combined with Shenfu injection on the treatment of acute left heart failure was analyzed by Mate. Journal of Practical Internal Medicine of Traditional Chinese Medicine 2020;34:137-42.	The main intervention is not SFI

SR, systematic review; SFI, Shenfu injection; HF, heart failure.

articles is shown in *Table 6*.

Characteristics of included reviews

A total of 12 literatures were peer-reviewed articles from 2011 to 2020, 11 of which were published in Chinese journals and 1 in British journals (19). This study involved 302 original RCTs and more than 22,445 participants [1 of which did not mention the total number of participants (29)]. The minimum and maximum sample sizes were 8 RCTs (559 participants) (25) and 97 RCTs (8,202 participants) (19), respectively. The treatment groups were treated with SFI plus WM, and the control groups were treated with WM. The main result was clinical efficacy rate, and the secondary results included LVEF, LVEDd, BNP, NT-proBNP, 6-MWT, MLHFQ, mortality, and rehospitalization rate. All literatures were evaluated by methodology, including 7 by the Jadad scale, and 5 by the Cochrane Handbook. A total of 5 studies reported adverse events (AEs), 1 study reported no adverse reactions (25), and 4 studies delineated specific

adverse reactions (19,23,24,28) (see *Table* 7 for detailed literature features).

Methodological assessment

The methodological quality of the literature was evaluated by AMSTAR-2, among which items 2, 4, 7, 9, 11, 13, and 15 were key items. The literature failed to meet any of the requirements and was rated as very low level. The evaluation results showed that the methodological evaluation level of all literatures was very low. First of all, (I) all literature highlighted research problems and inclusion criteria in accordance with the PICO principle. (II) Most literature listed the screening process [except (21,26,30)]. (III) At least two evaluators extracted data independently [except (21,28)]. (IV) Evaluation tools were used to assess the risk of bias in the included studies and the research data were analyzed comprehensively [except (20,30)]. (V) A total of six studies explained the possible causes of the risk of bias (19,22,23,25-27). (VI) A total of seven studies discussed the impact of risk of bias on the results (19,21,23,26-28,30). However, with regard to its key items, (I) there was no preliminary design plan or registration protocol before the SR in all articles. (II) No reproducible and comprehensive search strategy was provided. (III) No detailed exclusion list and exclusion reasons were listed. (IV) The assessment of the risk of bias was not comprehensive [except (19,23)]. The detailed results are shown in *Figure 2* and *Table 8*. The reliability between the two reviewers was excellent (kappa =0.941).

Reporting quality

Some of the papers were of good quality, with an average score of 18.25 and a completion degree of 13.5–23 points. Among them, the main measures of project title, data synthesis, risk assessment methods, and results of bias were comprehensively reported (100%). Most literatures reported basic principles, qualification criteria, study selection, study characteristics, individual study results, results synthesis, and conclusions (over 75%). There was no pre-registration of literatures, and some of the articles were incomplete or unreported for the remaining entries. Report quality of the studies is shown in *Figure 3* and *Table 9*. The reliability between the two reviewers was excellent (kappa =0.886).

Quality of evidence

The 12 studies contained a total of 52 outcome indicators, of which 3 were moderate quality, 13 were low quality, and the rest were very low quality. The limitations of all results were reduced, followed by publication bias (48 results), imprecision (29 results), inconsistency (24 results), and indirectness (0 results). The relevant results are shown in *Table 10*.

Outcomes

Effective rate

All literatures analyzed the effective rate, including comprehensive curative effect (20,24,27-29), clinical effective rate (19,21,23,25,26,30), and TCM syndrome curative effect (22). The results suggested that SFI combined with WM could significantly improve the clinical efficacy of HF treatment. The results are shown in *Figure 4* and *Table 11*.

Cardiac parameters

We counted the related indicators of cardiac function, including LVEF, EF, LVEDd, BNP, NT-proBNP, and 6-MWT. Xu et al. (25) pointed out that LVEF was not statistically significantly different compared with the control group (P=0.05, 5 trials). It was highlighted in two SRs (19,22) that LVEDd was not statistically significant compared with the control group (respectively, P=0.06, 2 trials and P=0.4, 16 trials). Other results suggested that SFI could improve the cardiac function of patients with HF. A total of 7 SRs analyzed LVEF, 3 analyzed EF, 7 analyzed LVEDd, 4 analyzed NT-probNP, and 5 analyzed 6-MWT. The results are shown in *Figures 5-10* and *Tables 12-17*.

Mortality and rehospitalization rate

A total of two SRs analyzed death and conducted a subgroup analyses. It was shown that SFI can significantly reduce the mortality of HF patients induced by myocardial infarction [relative risk (RR) =0.52, 95% CI: 0.37 to 0.74; P<0.01]. In other subgroups, there was no significant difference between the two groups (RR =0.68, 95% CI: 0.36 to 1.26; P=0.22). However, the overall results of the two subgroups were significantly different (RR =0.56, 95% CI: 0.41 to 0.75; P<0.01, 11 trials) (19). Another study found no significant difference in mortality compared with the control group (OR =0.59, 95% CI: 0.31 to 1.13; P>0.05). At the same time, the researchers analyzed the rehospitalization rate, and the difference was statistically significant (OR =0.42, 95% CI: 0.29 to 0.59; P<0.05, 5 trials) (26).

Table 7 The details of systematic reviews

Author	Year	Language	Condition	Research [participants]	Intervention	Comparison	Primary outcomes	Risk assessment tools	Adverse effects	Main conclusion
Song (19)	2012	English	HF	97 [8,202]	SFI plus WM	WM	①②④⑥⑦⑩	Cochrane Handbook	Dry mouth, dryness heat, fullness of the head, insomnia, dysphoria, skin itching, tachycardia, feverish dysphoria, flushing of face, tidal fever, dizziness due to low blood pressure, gastrointestinal discomfort and palpitation	SFI appear to be effective for treating HF
Luo (20)	2015	Chinese	HF	25 [1,975]	SFI plus WM	WM	①②④⑤	Jadad	N	SFI combined with WM in treating HF was better than that of WM alone
Bin (21)	2010	Chinese	CHF	8 [875]	SFI plus WM	WM	①	Jadad	N	On the basis of WM, SFI was effective in the treatment of CHF and can improve the clinical symptoms
Wu (22)	2018	Chinese	AHF	10 [851]	SFI plus WM	WM	①②④⑤	Cochrane Handbook	N	On the basis of WM, SFI could significantly improve TCM syndrome and cardiac function
Guo (23)	2020	Chinese	AHF	22 [1,753]	SFI plus WM	WM	①②⑤⑥⑧	Cochrane Handbook	Dizziness, rash, cold, complications include hypotension, arrhythmia, infection	SFI combined with WM in the treatment of AHF could improve the clinical efficiency and cardiac function, with good safety
Jia (24)	2018	Chinese	AHF	17 [1,286]	SFI plus WM	WM	①③⑤	Jadad	Hotness, insomnia	On the basis of WM, SFI could improve the clinical effect of AHF compared with WM alone
Xu (25)	2013	Chinese	CHF	8 [559]	SFI plus WM	WM	①②④⑦	Cochrane Handbook	Y	SFI combined with WM could further improve the clinical efficacy of elderly patients with HF, and the safety is good
Ma (26)	2017	Chinese	CHF	19 [1,829]	SFI plus WM	WM	①⑦⑨⑩ ⑪	Jadad	N	Although SFI could not reduce the mortality of CHF, it could significantly improve the quality of life during the survival period
Wen (27)	2017	Chinese	HF	21 [1,630]	SFI plus WM	WM	①②④⑤⑥⑧	Jadad	N	SFI combined with WM in treating HF was better than that of WM alone

Table 7 (*continued*)

Table 7 (*continued*)

Author	Year	Language	Condition	Research [participants]	Intervention	Comparison	Primary outcomes	Risk assessment tools	Adverse effects	Main conclusion
Hou (28)	2011	Chinese	CHF	16 [1,117]	SFI plus WM	WM	①③④⑤	Cochrane Handbook	Irritability	WM with SFI could further improve the clinical efficacy of heart failure
Du (29)	2014	Chinese	HF	31 [unclear]	SFI plus WM	WM	①③④⑤⑥⑦	Jadad	N	SFI could further improve clinical efficacy and cardiac function in the treatment of HF
Huang (30)	2011	Chinese	HF	28 [2,368]	SFI plus WM	WM	①②⑤⑦	Jadad	N	SFI could further improve effective rate and cardiac function in the treatment of HF

① : Effective rate; ② : LVEF; ③ : EF; ④ : LVEDd; ⑤ : BNP; ⑥ : NT-proBNP; ⑦ : 6-MWT; ⑧ : TCM syndrome score; ⑨ : rehospitalization rate; ⑩ : mortality; ⑪: MLHFQ. HF, heart failure; SFI, Shenfu injection, WM, western medicine; CHF, chronic heart failure; TCM, traditional Chinese medicine; AHF, acute heart failure; LVEF, left ventricular ejection fraction; EF, ejection fraction; LVEDd, left ventricular end-diastolic dimension; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-B type natriuretic peptide; 6-MWT, 6-minute walk test.

TCM syndrome score and MLHFQ score

A total of two studies (23,27) showed that SFI combined with WM can significantly improve TCM syndrome scores in patients with HF, but the quality of evidence was poor [OR =2.94, 95% CI: 1.71 to 5.04; P<0.0001, 7 trials and mean difference (MD) =–2.12, 95% CI: –2.93 to 1.31; P<0.00001, 5 trials]. Only one study (26) results showed that MLHFQ score was significantly better in the SFI + WM group than in the control group (MD =–5.57, 95% CI: –8.26 to –2.87); P<0.01, 6 trials).

AEs

A total of five studies reported AEs; one study reported no adverse reactions, and four studies described specific adverse reactions. The AEs specifically included: hotness, insomnia (24); dry mouth, dryness heat, fullness of the head, insomnia, dysphoria, skin itching, tachycardia, feverish dysphoria, flushing of face, tidal fever, dizziness due to low blood pressure, gastrointestinal discomfort, and palpitation (19); irritability (28); dizziness, rash, cold, and complications included hypotension, arrhythmia, and infection (23).

Discussion

Summary of main findings

A total of 12 SRs were reported on in this study, and the results showed that SFI combined with WM was more effective than using WM alone for HF. However, most conclusions emphasized that it was necessary to carry out more high-quality RCTs for verification of findings. The results of SR are considered the highest quality of evidence to guide clinical decision-making. We searched SRs related to the treatment of HF with SFI, and comprehensively evaluated the methodological quality, quality of reports in literature, and quality of evidence of main results by using AMSTAR-2, PRISMA, and GRADE evaluation tools. Unfortunately, the methodological quality and the reporting quality were not high in most SRs involved in this study.

The treatment of HF, especially chronic HF (CHF), is a long process. In the future, when conducting studies on SFI in the treatment of HF, researchers should appropriately increase the follow-up time, strengthen the observation of cardiovascular end points, such as rehospitalization rate and mortality (within 1 or 5 years), and pay more attention to improving the quality of the methodology.

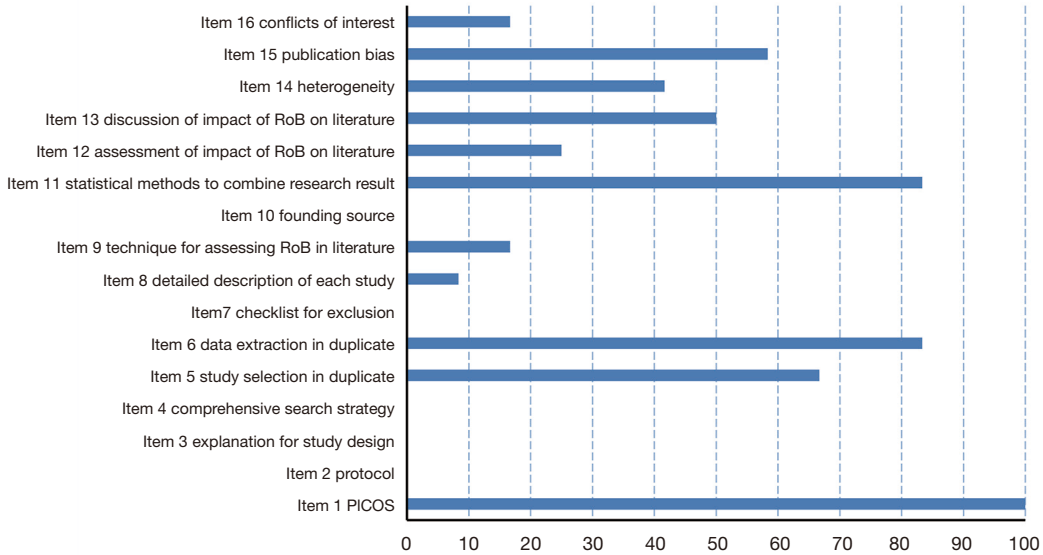

Figure 2 Percentage of studies with "yes" for each AMSTAR-2 item. AMSTAR-2, Appraisal Tool for Systematic Reviews of Randomized and Observational Studies 2.

Table 8 Methodological quality assessment of SRs by AMSTAR-2

AMSTAR-2	Song (19)	Luo (20)	Bin (21)	Wu (22)	Guo (23)	Jia (24)	Xu (25)	Ma (26)	Wen (27)	Hou (28)	Du (29)	Huang (30)	Yes, n (%)
Item 1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12 (100.00)
Item 2	N	N	N	N	N	N	N	N	N	N	N	N	0 (0.00)
Item 3	N	N	N	N	N	N	N	N	N	N	N	N	0 (0.00)
Item 4	PY	PY	N	PY	PY	PY	PY	PY	PY	PY	PY	PY	0 (0.00)
Item 5	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	N	8 (66.67)
Item 6	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	10 (83.33)
Item 7	N	N	N	N	N	N	N	N	N	N	N	N	0 (0.00)
Item 8	Y	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	1 (8.33)
Item 9	Y	PY	PY	PY	Y	PY	PY	PY	PY	PY	PY	PY	2 (16.67)
Item 10	N	N	N	N	N	N	N	N	N	N	N	N	0 (0.00)
Item 11	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10 (83.33)
Item 12	Y	N	N	N	Y	N	N	N	Y	N	N	N	3 (25.00)
Item 13	Y	N	N	Y	Y	N	Y	Y	Y	N	N	N	6 (50.00)
Item 14	Y	N	Y	N	Y	N	N	N	N	Y	Y	N	5 (41.67)
Item 15	Y	N	Y	N	Y	N	N	Y	Y	Y	N	Y	7 (58.33)
Item 16	Y	N	N	N	Y	N	N	N	N	N	N	N	2 (16.67)
Ranking of quality	Very low level	Very low level	Very low level	Very low level	Very low level	Very low level	Very low level	Very low level	Very low level	Very low level	Very low level	Very low level	–

Y, 1 point; PY, 0.5 point; N, 0 point. SRs, systematic reviews; AMSTAR-2, Appraisal Tool for Systematic Reviews of Randomized and Observational Studies 2.

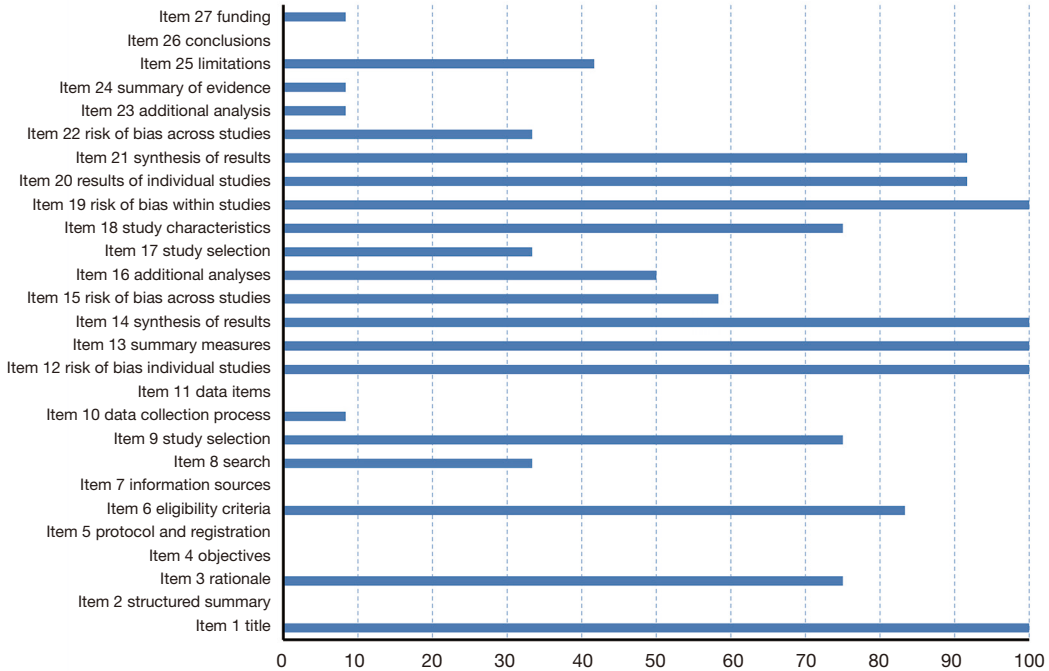

Figure 3 Percentage of studies with "yes" for each PRISMA item. PRISMA, Preferred Reporting Item for Systematic Reviews and Meta-Analyses.

Efficacy and safety of SFI in acute phase of CHF

Evidence has shown that SFI was also used for treatment of CHF during the acute phase, but few standard clinical trials have evaluated its efficacy and safety. In 2009, a randomized, double-blind, multicenter, placebo-controlled trial was the first to evaluate the safety and efficacy of SFI in treating patients with CHF in the acute phase (31). Main outcomes included New York Heart Association (NYHA) classification and TCM syndrome scores. NYHA has been shown to be closely associated with survival and is used to reflect the severity of acute HF (AHF) (32,33). TCM syndrome score is based on TCM symptoms and signs. It is one of the most important and commonly used indexes in TCM efficacy evaluation (34). The major results included the following: (I) The clinical symptoms and cardiac tolerance of the patients were improved; (II) SFI did not induce AEs or ADRs. In fact, it is necessary to further explore the efficacy and safety of SFI for CHF patients with acute phase.

Strengths and limitations

Strengths: (I) as far as we know, this study was the first to evaluate the latest overview of HF-related SR treated with SFI in strict accordance with the assessment requirements of AMSTAR-2, PRISMA, and GRADE. (II) We comprehensively searched seven databases and enumerated clear retrieval strategies one by one, which was reproducible. (III) The data synthesis and composition of the main outcome indicators are helpful to more intuitive analysis of the advantages and disadvantages of the research results.

Limitations: (I) the quality of the RCT-based SR methodology and the quality of the literature report was not shown to be high, which limited our judgment of the results to some extent. (II) A total of seven literatures were published earlier than the launch of AMSTAR-2, and the original authors did not follow the existing rules, which may be one of the reasons for the low quality of methodology. (III) Admittedly, this was the first time we had used the AMSTAR-2, PRISMA, and GRADE tools, and our understanding of some items may have been somewhat skewed, but consistency between the two reviewers was ensured as much as possible.

Factors influencing methodological quality and literature reporting quality

Firstly, AMSTAR-2 (16 items) is used to evaluate the

Table 9 Reporting quality assessment of SRs by PRISMA

PRISMA	Song (19)	Luo (20)	Bin (21)	Wu (22)	Guo (23)	Jia (24)	Xu (25)	Ma (26)	Wen (27)	Hou (28)	Du (29)	Huang (30)	Yes, n (%)
Item 1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12 (100.00)
Item 2	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	0 (0.00)
Item 3	Y	Y	Y	Y	Y	PY	Y	PY	Y	PY	Y	Y	9 (75.00)
Item 4	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	Y	PY	0 (0.00)
Item 5	N	N	N	N	N	N	N	N	N	N	N	N	0 (0.00)
Item 6	Y	PY	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	10 (83.33)
Item 7	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	0 (0.00)
Item 8	N	N	N	N	Y	Y	PY	N	PY	Y	N	Y	4 (33.33)
Item 9	Y	Y	Y	Y	Y	Y	Y	PY	Y	Y	PY	PY	9 (75.00)
Item 10	PY	PY	N	PY	PY	PY	PY	PY	Y	PY	PY	PY	1 (8.33)
Item 11	PY	PY	PY	PY	PY	PY	PY	PY	N	PY	N	PY	0 (0.00)
Item 12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12 (100.00)
Item 13	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12 (100.00)
Item 14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12 (100.00)
Item 15	Y	N	Y	Y	Y	Y	Y	N	N	N	N	Y	7 (58.33)
Item 16	N	N	Y	N	Y	N	Y	Y	Y	N	N	Y	6 (50.00)
Item 17	Y	N	N	PY	Y	PY	PY	Y	Y	PY	PY	PY	4 (33.33)
Item 18	Y	N	Y	Y	Y	Y	Y	Y	PY	Y	N	Y	9 (75.00)
Item 19	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12 (100.00)
Item 20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	11 (91.67)
Item 21	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	11 (91.67)
Item 22	Y	N	Y	N	Y	Y	N	N	N	N	N	N	4 (33.33)
Item 23	N	N	N	N	Y	N	N	N	N	N	N	N	1 (8.33)
Item 24	PY	PY	PY	PY	PY	PY	PY	PY	PY	Y	PY	PY	1 (8.33)
Item 25	PY	Y	Y	Y	Y	Y	PY	PY	PY	PY	N	PY	5 (41.67)
Item 26	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	Y	11 (91.67)
Item 27	Y	PY	N	N	PY	PY	N	N	PY	PY	N	N	1 (8.33)
Total score	19.5	15	18.5	17	22.5	23	20	16.5	18	17.5	13.5	18	–

Y, 1 point; PY, 0.5 point; N, 0 point. SRs, systematic reviews; PRISMA, Preferred Reporting Item for Systematic Reviews and Meta-Analyses.

Table 10 Quality of evidence in the included studies assessed by GRADE

Author	Intervention	Outcomes	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Quality of evidence
Song (19)	SFI plus WM *vs*. WM	Effective rate [97]	–1	0	0	0	–1	Low
		LVEF [61]	–1	–1	0	0	–1	Very low
		LVEDd [16]	–1	–1	0	0	–1	Very low
		NT-proBNP [12]	–1	–1	0	–1	–1	Very low
		Mortality11	–1	0	0	0	–1	Low
		6-MWT [8]	–1	–1	0	–1	–1	Very low
Luo (20)	SFI plus WM *vs*. WM	Effective rate [25]	–1	0	0	0	–1	Low
		LVEF [16]	–1	–1	0	0	–1	Very low
		LVEDd [5]	–1	0	0	–1	–1	Very low
		BNP [8]	–1	–1	0	–1	–1	Very low
Bin (21)	SFI plus WM *vs*. WM	Effective rate [8]	–1	0	0	–1	0	Low
Wu (22)	SFI plus WM *vs*. WM	Effective rate [5]	–1	0	0	–1	–1	Very low
		BNP [6]	–1	–1	0	–1	–1	Very low
		LVEF [4]	–1	0	0	–1	–1	Very low
		LVEDd [2]	–1	0	0	–1	–1	Very low
Guo (23)	SFI plus WM *vs*. WM	Effective rate [17]	–1	0	0	0	0	Moderate
		BNP [10]	–1	–1	0	–1	–1	Very low
		NT-proBNP [7]	–1	–1	0	–1	–1	Very low
		LVEF [16]	–1	–1	0	–1	–1	Very low
		TCM scores [5]	–1	–1	0	–1	–1	Very low
Jia (24)	SFI plus WM *vs*. WM	Effective rate [7]	–1	0	0	0	–1	Low
		EF [10]	–1	–1	0	0	–1	Very low
		BNP [10]	–1	–1	0	–1	–1	Very low
Xu (25)	SFI plus WM *vs*. WM	Effective rate [7]	–1	0	0	0	–1	Low
		LVEDd [4]	–1	0	0	–1	–1	Very low
		LVEF [5]	–1	–1	0	–1	–1	Very low
		6-MWT [4]	–1	–1	0	–1	–1	Very low
Ma (26)	SFI plus WM *vs*. WM	Effective rate [14]	–1	0	0	0	0	Moderate
		MLHFQ [6]	–1	–1	0	–1	–1	Very low
		6-MWT [13]	–1	0	0	0	0	Moderate
		Rehospitalization rate [5]	–1	0	0	–1	–1	Very low
		Mortality [5]	–1	0	0	–1	–1	Very low

Table 10 (*continued*)

Table 10 (*continued*)

Author	Intervention	Outcomes	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Quality of evidence
Wen (27)	SFI plus WM *vs*. WM	Effective rate [20]	–1	0	0	0	–1	Low
		TCM syndrome scores [7]	–1	0	0	0	–1	Low
		LVEF [19]	–1	–1	0	0	–1	Very low
		LVEDd [11]	–1	–1	0	0	–1	Very low
		BNP [12]	–1	–1	0	–1	–1	Very low
		NT-proBNP [5]	–1	–1	0	–1	–1	Very low
Hou (28)	SFI plus WM *vs*. WM	Effective rate [12]	–1	0	0	0	–1	Low
		LVEDd [5]	–1	0	0	–1	–1	Very low
		EF [13]	–1	0	0	0	–1	Low
		BNP [3]	–1	0	0	–1	–1	Very low
Du (29)	SFI plus WM *vs*. WM	Effective rate [24]	–1	0	0	0	–1	Low
		EF [22]	–1	0	0	0	–1	Low
		LVEDd [11]	–1	0	0	0	–1	Low
		BNP [11]	–1	0	0	–1	–1	Very low
		NT-proBNP [4]	–1	0	0	–1	–1	Very low
		6-MWT [3]	–1	0	0	–1	–1	Very low
Huang (30)	SFI plus WM *vs*. WM	Effective rate [23]	–1	–1	0	0	–1	Very low
		LVEF [18]	–1	–1	0	0	–1	Very low
		6-MWT [4]	–1	–1	0	–1	–1	Very low
		BNP [3]	–1	–1	0	–1	–1	Very low

[a], the design of the experiment with a large bias in random, distributive hiding, or blind; [b], the heterogeneity I^2 is large, and the overlap of Cs is small; [c], inability to determine whether it is direct evidence; [d], the sample size is small, and the CI is wide; [e], funnel plot was not symmetrical, or the number of included studies was small and all were positive results. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine; TCM, traditional Chinese medicine; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-B type natriuretic peptide; 6-MWT, 6-minute walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

methodology quality of the system evaluation, five of which are critical, and failure to perform any of them will result in a direct downgrade, including (14-16):

- ❖ Protocol registered before commencement of the review (item 2);
- ❖ Adequacy of the literature search (item 4);
- ❖ Justification for excluding individual studies (item 7);
- ❖ Risk of bias from individual studies being included in the review (item 9);
- ❖ Appropriateness of meta-analytical methods (item 11);
- ❖ Consideration of risk of bias when interpreting the results of the review (item 13);
- ❖ Assessment of presence and likely impact of publication bias (item 15).

In addition, the PRISMA statement consists of a 27-item checklist and a four-phase flow diagram. The checklist includes items deemed essential for transparent reporting of a SR (17). Therefore, whether a reviewer follows the AMSTAR-2 (16 items) and PRISMA (27 items) tools in developing a SR will have a significant impact on methodological quality and literature reporting quality.

Secondly, the quality of the original literature included in the SR/MA, such as RCTs, did not strictly follow the

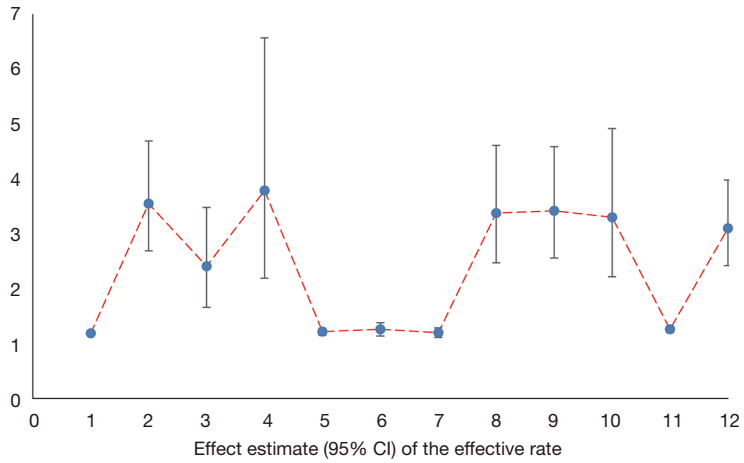

Figure 4 Effect estimate (95% CI) of the effective rate in included SRs. (X-axis: the number of included literatures; Y-axis: CI). CI, confidence interval; SRs, systematic reviews.

Table 11 Details of effective rate in included SRs

Number	Study	Included trials	Intervention		Effect estimate (95% CI)	P value	GRADE rating
			Treatment group	Control group			
1	Song (19)	97	SFI plus WM	WM	1.19 (1.17 to 1.21)	<0.01	Low
2	Luo (20)	25	SFI plus WM	WM	3.55 (2.69 to 4.69)	<0.00001	Low
3	Bin (21)	8	SFI plus WM	WM	2.41 (1.66 to 3.48)	<0.00001	Low
4	Wu (22)	5	SFI plus WM	WM	3.79 (2.19 to 6.57)	<0.00001	Very low
5	Guo (23)	17	SFI plus WM	WM	1.22 (1.15 to 1.28)	<0.0001	Moderate
6	Jia (24)	7	SFI plus WM	WM	1.26 (1.14 to 1.38)	<0.05	Low
7	Xu (25)	7	SFI plus WM	WM	1.2 (1.11 to 1.29)	<0.00001	Low
8	Ma (26)	14	SFI plus WM	WM	3.38 (2.47 to 4.61)	<0.01	Moderate
9	Wen (27)	20	SFI plus WM	WM	3.42 (2.56 to 4.59)	<0.00001	Low
10	Hou (28)	12	SFI plus WM	WM	3.3 (2.22 to 4.92)	<0.0001	Low
11	Du (29)	24	SFI plus WM	WM	1.26 (1.20 to 1.32)	<0.00001	Low
12	Huang (30)	23	SFI plus WM	WM	3.1 (2.42 to 3.98)	<0.01	Very low

SRs, systematic reviews; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine.

Consolidates Standards of Reporting Trials (CONSORT), which was affect the reporting bias of the SR. Therefore, clinical researchers should conduct high-quality studies in strict accordance with the CONSORT standard in order to obtain more scientific, accurate and high-quality clinical evidence. Finally, we must acknowledge that although the AMSTAR-2 and PRISMA tools have outlined specific evaluation criteria, the tools are interpreted differently by different researchers, subjectively affecting the quality of the methodology and the quality of the reporting results.

AMSTAR-2: an update based on AMSTAR

AMSTAR-2 changed the four items in AMSTAR to five

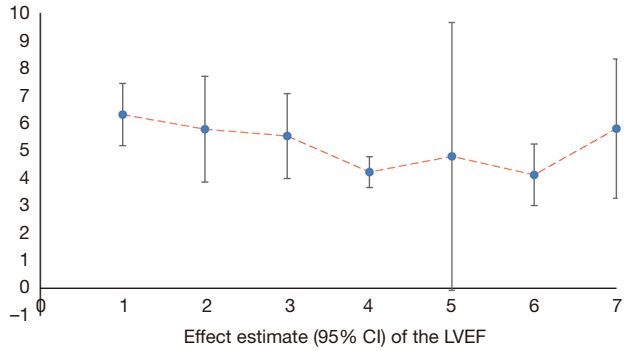

Figure 5 Effect estimate (95% CI) of the LVEF in included SRs. (X-axis: the number of included literatures; Y-axis: CI). CI, confidence interval; LVEF, left ventricular ejection fraction; SRs, systematic reviews.

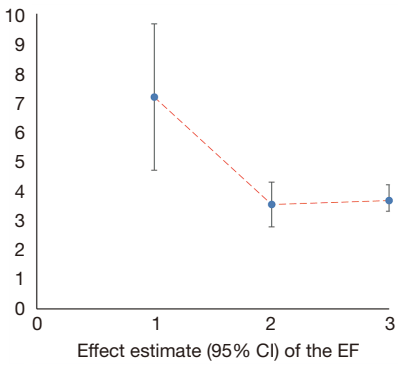

Figure 6 Effect estimate (95% CI) of the EF in included SRs. (X-axis: the number of included literatures; Y-axis: CI). CI, confidence interval; EF, ejection fraction; SRs, systematic reviews.

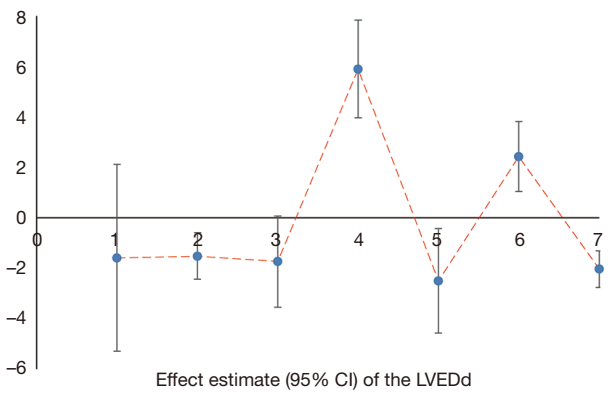

Figure 7 Effect estimate (95% CI) of the LVEDd in included SRs. (X-axis: the number of included literatures; Y-axis: CI). CI, confidence interval; LVEDd, left ventricular end-diastolic dimension; SRs, systematic reviews.

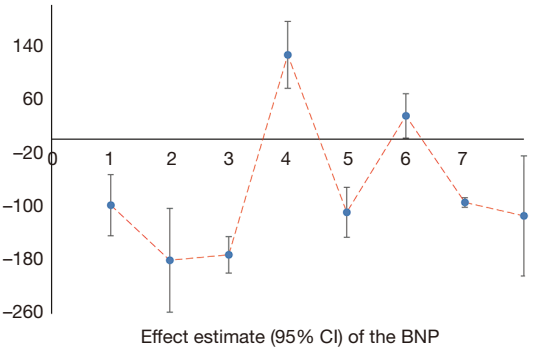

Figure 8 Effect estimate (95% CI) of the BNP in included SRs. (X-axis: the number of included literatures; Y-axis: CI). CI, confidence interval; BNP, brain natriuretic peptide; SRs, systematic reviews.

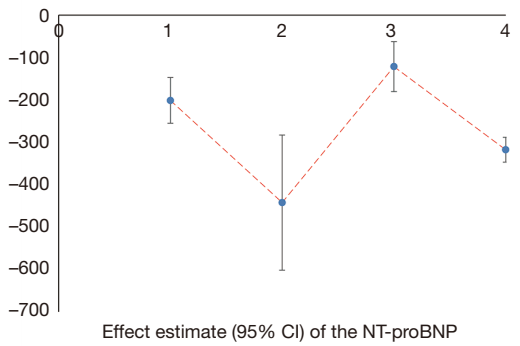

Figure 9 Effect estimate (95% CI) of the NT-proBNP in included SRs. (X-axis: the number of included literatures; Y-axis: CI). CI, confidence interval; NT-proBNP, N-terminal pro-B type natriuretic peptide; SRs, systematic reviews.

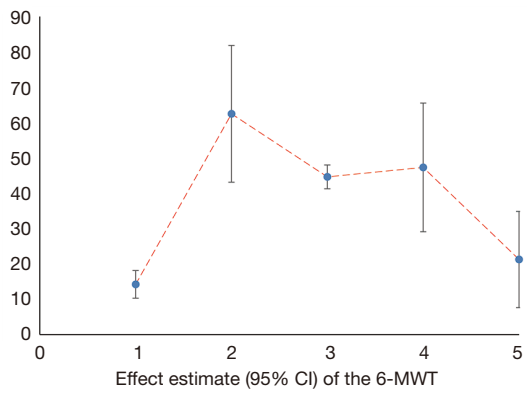

Figure 10 Effect estimate (95% CI) of the 6-MWT in included SRs. (X-axis: the number of included literatures; Y-axis: CI). CI, confidence interval; 6-MWT, 6-minute walking test; SRs, systematic reviews.

Table 12 Details of LVEF in included SRs

Number	Study	Included trials	Intervention		Effect estimate (95% CI)	P value	GRADE rating
			Treatment group	Control group			
1	Song (19)	61	SFI plus WM	WM	6.31 (5.18 to 7.44)	<0.01	Very low
2	Luo (20)	16	SFI plus WM	WM	5.78 (3.86 to 7.70)	<0.01	Very low
3	Wu (22)	4	SFI plus WM	WM	5.53 (3.99 to 7.07)	<0.00001	Very low
4	Guo (23)	16	SFI plus WM	WM	4.22 (3.67 to 4.78)	<0.00001	Very low
5	Xu (25)	5	SFI plus WM	WM	4.79 (–0.07 to 9.65)	0.05	Very low
6	Wen (27)	19	SFI plus WM	WM	4.12 (3.00 to 5.24)	<0.00001	Very low
7	Huang (30)	18	SFI plus WM	WM	5.8 (3.28 to 8.33)	<0.01	Very low

LVEF, left ventricular ejection fraction; SRs, systematic reviews; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine.

Table 13 Details of EF in included SRs

Number	Study	Included trials	Intervention		Effect estimate (95% CI)	P value	GRADE rating
			Treatment group	Control group			
1	Jia (24)	10	SFI plus WM	WM	7.18 (4.70 to 9.66)	<0.05	Very low
2	Hou (28)	13	SFI plus WM	WM	3.54 (2.78 to 4.30)	<0.0001	Low
3	Du (29)	22	SFI plus WM	WM	3.67 (3.31 to 4.21)	<0.00001	Low

EF, ejection fraction; SRs, systematic reviews; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine.

Table 14 Details of LVEDd in included SRs

Number	Study	Included trials	Intervention		Effect estimate (95% CI)	P value	GRADE rating
			Treatment group	Control group			
1	Song (19)	16	SFI plus WM	WM	–1.59 (–5.29 to 2.12)	0.4	Very low
2	Luo (20)	5	SFI plus WM	WM	–1.52 (–2.43 to –0.61)	<0.01	Very low
3	Wu (22)	2	SFI plus WM	WM	–1.73 (–3.54 to 0.07)	0.06	Very low
4	Xu (25)	4	SFI plus WM	WM	5.9 (3.97 to 7.84)	<0.00001	Very low
5	Wen (27)	11	SFI plus WM	WM	–2.5 (–4.57 to –0.43)	0.02	Very low
6	Hou (28)	5	SFI plus WM	WM	2.43 (1.04 to 3.82)	0.0006	Very low
7	Du (29)	11	SFI plus WM	WM	–2.03 (2.76 to –1.31)	<0.00001	Low

LVEDd, left ventricular end-diastolic dimension; SRs, systematic reviews; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine.

Table 15 Details of BNP in included SRs

Number	Study	Included trials	Intervention		Effect estimate (95% CI)	P value	GRADE rating
			Treatment group	Control group			
1	Luo (20)	8	SFI plus WM	WM	–98.3 (–143.81 to –52.78)	<0.00001	Very low
2	Wu (22)	6	SFI plus WM	WM	–180.16 (–257.41 to –102.91)	<0.00001	Very low
3	Guo (23)	10	SFI plus WM	WM	–172.12 (–199.34 to –144.91)	<0.00001	Very low
4	Jia (24)	10	SFI plus WM	WM	125.62 (75.86 to 175.37)	<0.05	Very low
5	Wen (27)	12	SFI plus WM	WM	–108.73 (–145.93 to –71.52)	<0.00001	Very low
6	Hou (28)	3	SFI plus WM	WM	34.69 (1.78 to 67.60)	<0.04	Very low
7	Du (29)	11	SFI plus WM	WM	–94.2 (–101.43 to –86.97)	<0.00001	Very low
8	Huang (30)	3	SFI plus WM	WM	–114.24 (–203.60 to –24.88)	<0.05	Very low

BNP, brain natriuretic peptide; SRs, systematic reviews; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine.

Table 16 Details of NT-proBNP in included SRs

Number	Study	Included trials	Intervention		Effect estimate (95% CI)	P value	GRADE rating
			Treatment group	Control group			
1	Song (19)	12	SFI plus WM	WM	–201.26 (–255.27 to –147.25)	<0.01	Very low
2	Guo (23)	7	SFI plus WM	WM	–442.41 (–601.95 to –282.88)	<0.00001	Very low
3	Wen (27)	5	SFI plus WM	WM	–121.51 (–180.61 to –62.40)	<0.0001	Very low
4	Du (29)	4	SFI plus WM	WM	–317.75 (–347.06 to –288.44)	<0.00001	Very low

NT-proBNP, N-terminal pro-B type natriuretic peptide; SRs, systematic reviews; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine.

Table 17 Details of 6-MWT in included SRs

Number	Study	Included trials	Intervention		Effect estimate (95% CI)	P value	GRADE rating
			Treatment group	Control group			
1	Song (19)	8	SFI plus WM	WM	14.22 (10.31 to 18.13)	<0.01	Very low
2	Xu (25)	4	SFI plus WM	WM	62.48 (43.12 to 81.84)	<0.00001	Very low
3	Ma (26)	13	SFI plus WM	WM	44.65 (41.27 to 48.03)	<0.01	Moderate
4	Du (29)	3	SFI plus WM	WM	47.32 (29.11 to 65.53)	<0.00001	Very low
5	Huang (30)	4	SFI plus WM	WM	21.26 (7.64 to 34.88)	<0.01	Very low

6-MWT, 6-minute walking test; SRs, systematic reviews; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SFI, Shenfu injection; WM, western medicine.

items. Is research selection and data extraction conducted independently by two reviewers? (Item 2 in AMSTAR was split into items 5 and 6). Did the author report the source of funding and any potential conflicts of interest? (Item 11 in AMSTAR was split into items 10 and 16). Whether publication status is adequately considered in inclusion criteria has been removed (item 4).

In total, four items were added. Did the research

questions and inclusion criteria include elements of the PICO (item 1)? Did the author explain why the systematic review was chosen to include the study design type (item 3)? If a meta-analysis was performed, did the authors consider the potential impact of the risk of bias included in the study on the meta-analysis or other integration of evidence (item 12)? Did the author satisfactorily explain or discuss the heterogeneity in the results of the systematic review (item 14)? Finally, AMSTAR-2 removed the "not applicable" and "cannot answer" options in the original AMSTAR instrument, and answered each item with "yes", "no" and "partial yes".

Mechanism of SFI on cardiac function and apoptosis

SFI is an intravenous injection made from the extracts of red ginseng and aconite. Modern pharmacological studies shown that the active ingredient of red ginseng in SFI is ginsenoside, which has positive inotropic effect and can enhance myocardial contractility. It can also enhance the body's ability to resist hypoxia and ischemia, improve the energy metabolism of cardiomyocytes. It also inhibits platelet aggregation to a certain extent. The active ingredient in aconite is normethylaconitine, which is similar to isoproterenol. It can increase the level of cyclic adenosine in cardiomyocytes and enhance atrioventricular conduction and myocardial contractility. At the same time, α-adrenergic receptors can also be excited, which can significantly promote the reduction of coronary cerebral and peripheral vascular resistance by increasing coronary artery and brain blood flow, and improve the situation of myocardial blood and oxygen supply. SFI also had a significant protective effect on myocardial ischemia-reperfusion injury (35). In addition, red ginseng and aconite can also remove oxygen free radicals in blood, inhibit lipid peroxidation, reverse ventricular remodeling and improve heart function (36-38). Caspase 3-mediated apoptosis is related to myocardial injury. Studies have found that SFI could reduce myocardial injury and improve myocardial ultrastructure by inhibiting the expression of Bcl-2, Bax and Caspase 3 proteins, regulate myocardial cell apoptosis, and have a cardiac protective effect (39).

Recommendations for the future based on research outcomes

Based on the results of this study, we found that most SRs were methodological problems. For example, no research plan or registration agreement was provided in any of the literature; it is necessary to make a detailed research plan before the SR, and following this plan may reduce the risk of bias in the process of SR. Therefore, researchers must register agreement on the relevant registration platform [such as PROSPERO (https://www.crd.york.ac.uk/prospero/)] before conducting their SR. Besides, the search strategy was not comprehensive, in addition to the resources obtained in electronic retrieval, gray literature is very important. Researchers should also perform supplementary retrieval, such as professional registries, consultation with experts in related fields, and manual retrieval of other gray literature to fully obtain the research references. At the same time, researchers should make a detailed list of excluded literatures and the reasons for exclusion. Detailed search strategies and exclusion lists are conducive to the repeatability of other studies. Furthermore, the systematic reviewers should use bias risk tools appropriately to comprehensively evaluate the methodological quality of the original literature and evaluate the possible bias caused by confounders, selective bias, exposure and outcome measurement bias, and selective reporting bias; they should then conduct subgroup analysis or regression analysis if necessary. Finally, researchers should clearly explain the source of project funds, the identity of the sponsor, and any conflicts of interest.

Conclusions

The results showed that compared with WM alone, the SFI and WM combined treatment of HF could improve clinical efficacy, quality of life, and cardiac function. However, the methodological and evidence quality of most SRs was poor, so we could not draw a clear conclusion. Judging from the existing results, it is still necessary to explore the efficacy and safety of SFI in the treatment of HF. A high quality SR should be formulated in strict accordance with the items required by the AMSTAR-2 tool, in order to improve the methodological quality, and be explained and elaborated in accordance with the PRISMA list one by one to improve the standardization and transparency of the SR.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-1073). All authors report funding from the Key Discipline Construction Project of Sichuan Administration of Traditional Chinese Medicine (202072). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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