Review Article

Shenfu injection as treatment for critical illness: a narrative review of clinical trials

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Background and Objective: Shenfu injection (SFI) is a traditional herbal medicine derived from components of ginseng and aconite and is commonly used in China to treat a variety of conditions. Shenfu has been suggested to have beneficial effects in various critical illnesses, including heart failure, cardiac arrest, and septic shock. In recent years, there have been a number of studies reporting that SFI improves patient outcomes when used concurrently with other treatments, but its use has not been adopted outside of China. This narrative review explored the results of clinical trials that have tested SFI's efficacy in various critical illnesses.

Methods: PubMed was searched for clinical trials, systematic reviews and meta-analyses published between 1990 and July 2022 relating to clinical trials using SFI in various critical illnesses. Systematic reviews and meta-analyses were included to enable inclusion of data from trials originally not published in English. The selected articles were then summarized in the following disease categories: heart failure, cardiac arrest, sepsis, and severe pulmonary disease.

Key Content and Findings: Clinical trials testing SFI in heart failure, cardiac arrest, sepsis, and pulmonary disease were reviewed. The design, methodology, and key findings of each trial or meta-analysis are summarized and discussed. Key limitations were also highlighted and discussed. Overall, several clinical trials suggest SFI may hold therapeutic potential for the treatment of critical illness, however, additional research is likely still needed.

Conclusions: Based on the current body of literature, further research—especially multi-center randomized, double-blind trials with detailed reporting of all methods and results according to international guidelines—is needed to evaluate whether SFI is a useful addition to existing treatments for these conditions.

Keywords: Chinese herbal medicine; cardiac arrest; heart failure; sepsis; pulmonary disease

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Introduction

Background

Herbal remedies have been utilized in China for the treatment of various illnesses for thousands of years (1). Shenfu injection (SFI) is an injectable formulation of a traditional Chinese herbal medicine derived from components of *Radix Ginseng* (ginseng) and *Radix Aconiti Lateralis Preparat*a (aconite root) and is commonly used in China to treat a variety of conditions, including shock and heart failure (2,3). The main active ingredients of SFI—ginsenosides and aconite alkaloids—are considered to have anti-apoptotic, anti-inflammatory, and immunomodulatory effects, as well as free radical scavenging properties (4,5). However, the full extent of the pharmacologic action of SFI is not fully understood (5).

Rationale and knowledge gap

In recent years, multiple clinical trials have examined SFI's potential therapeutic benefits in various critical conditions that cause significant morbidity and mortality worldwide (*Table 1*). Several meta-analyses have also shown SFI may improve outcomes for patients with multiple forms of critical illness (14-18). However, despite a growing body of literature, SFI remains widely unknown outside China, and many of the clinical trials are only published in the Chinese language.

Objective

The objective of this narrative review to provide a broad overview of the evidence behind SFI for critical illness in adults and identify knowledge gaps requiring further research. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-105/rc).

Methods

PubMed was searched for articles published between January 1990 and July 2022, using the following terms: "Shenfu injection" OR "Shen-fu injection" OR "Shen fu injection" AND "clinical trial". The search strategy is summarized in *Table 2*. A total of 220 potentially relevant articles were initially identified. After reading the titles and abstracts, 27 articles relating to clinical trials using SFI in various critical illnesses, including systematic reviews and meta-analyses, were selected for full analysis and divided into disease categories. Systematic reviews were included when they included trials results otherwise not available in the English language. Disease categories were discussed among authors, and four main categories pertaining to critical illness were selected: heart failure, cardiac arrest, sepsis, and severe pulmonary diseases. Articles pertaining to diseases unrelated to critical care (e.g., adjunct therapy to chemotherapy in various neoplastic conditions) were excluded upon agreement of all authors. Articles for which the full text was unavailable in English were subsequently excluded. Finally, the references of the included articles were screened for additional material not found in the initial literature search.

SFI for heart failure

SFI is commonly used to treat cardiac disease in China, and is frequently integrated into conventional therapy for heart failure (14). Multiple clinical trials have examined the use of SFI in patients suffering from heart failure. Jin *et al.* explored the utility of SFI as adjunct therapy to an intra-aortic balloon pump (IABP) for patients with cardiogenic shock following acute ST-segment elevation myocardial infarction (STEMI) (6). Sixty patients who underwent percutaneous coronary intervention (PCI) and subsequent IABP placement were enrolled, of whom 30 were randomly selected to receive 100 mL of SFI over 24 hours. Groups were comparable at baseline, but the authors do not state whether blinding took place or whether a placebo was used in the control group. The primary outcomes were major adverse cardiac and cerebrovascular events and mortality rate. Clinical recovery, left ventricular function, and inflammatory biomarkers [C-reactive protein (CRP), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α)] were measured every 24 hours for 72 hours. No significant differences in primary outcomes (adverse events or in-hospital/6-month mortality), length of hospitalization, or left ventricular function were noted between groups. Patients who received SFI required IABP support for a significantly shorter period of time (52.87±28.84 *vs.* 87.45±87.31 hours, P=0.047), and demonstrated lower levels of CRP, IL-1, and TNF-α at some, but not all, of the timepoints (6).

In a multi-center randomized, double-blind, placebo-controlled trial published in 2019, Wang *et al.* randomized 160 patients experiencing acute exacerbation of chronic congestive heart failure (CHF) to receive either SFI

Table 1 SFI as a treatment for critical illness: summary of key features and findings of RCTs evaluating SFI in critical illness

Author, year	N, condition	Intervention	Comparison	Blinding	Placebo	Key outcomes
Jin *et al.*, 2017 (6)	60, post-IABP placement after STEMI	Standard of care with 100 mL SFI over 24 hours following IABP placement post-PCI for STEMI	Standard of care	Not described by authors	Not described by authors	No difference in adverse events, mortality, length of hospitalization, or LV function. SFI was associated with shorter IABP support (52.87±28.84 *vs.* 87.45±87.31 h, P=0.047), as well as lower CRP, IL-1, and TNF-α at some time points
Wang *et al.*, 2019 (7)	144, acute CHF exacerbation	Standard of care with 50 mL SFI diluted in 100 mL saline once daily for 7±1 days following acute CHF exacerbation	Standard of care with saline placebos of equal-volume to the study drug	Double-blind	Equal volume saline placebo	Improved outcomes in the SFI group *vs.* the placebo group in the following clinical scales: NYHA (78.38% *vs.* 61.43%; RR =1.28, 95% CI: 1.02–1.59, P=0.03); TCM syndrome score (89.19% *vs.* 60%; RR =1.49, 95% CI: 1.21–1.83, P<0.001); Lee's heart failure score (70.27% *vs.* 52.17%; RR =1.35, 95% CI: 1.03–1.76, P=0.03); 6MWD (113 *vs.* 82.99 m, P=0.03). No significant differences in CCEs rate or death rate were noted between the two groups (P>0.05)
Zhang *et al.*, 2017 (5)	978, post in-hospital cardiac arrest	Standard of care with 100 mL IV SFI every 12 hours until discharge for up to 14 days post in-hospital cardiac arrest	Standard of care	Patients and assessors blinded, care team unblinded	Not described by authors	SFI was associated with higher-survival at 28 days (42.7% *vs.* 30.1%, P=0.02) and 90 days (39.6% *vs.* 25.9%, P=0.001), more favorable neurological outcome at discharge (70% *vs.* 59.3%, P=0.03), shorter mechanical ventilation (8.6±3.2 *vs.* 12.7±7.9 days), and shorter hospitalization (8.7±5.9 *vs.* 13.2±8.1 days)
Shao *et al.*, 2020 (8)	1,233, prehospital cardiac arrest	Standard of care with 20 mL SFI bolus after the first epinephrine dose and 30 mL IV hour-long infusion diluted 1:1 with saline during resuscitation of out-of-hospital cardiac arrest	Standard of care with saline placebos of equal-volume to the study drug	Patients and assessors blinded, care team unblinded	Equal volume saline placebo	No significant difference in survival to admission (6.7% *vs.* 5.6%, P=0.53) or discharge (2.9% *vs.* 1.2%, P=0.06). SFI was associated with improved neurologic outcomes at discharge (2.7 *vs.* 1%, P=0.05) and 1-year post-arrest (1.7% *vs.* 0.3%, P=0.04)
Li *et al.*, 2015 (9)	45, septic shock	EGDT with 100 mL SFI twice daily for septic shock	EGDT	None	None	Greater decrease in SOFA score over time (decreasing from 10±3.12 at baseline to 3.59±2.97 on day 7 *vs.* 9±2.97 at baseline to 4.61±3.36 on day 7, P<0.05). Shorter ventilator weaning times with SFI (7.5±3.5 *vs.* 9.1±3.2 days, P<0.05), as well as shorter ICU stays (16.1±9.2 *vs.* 18.7±8.3 days, respectively, P<0.05), but no difference in mortality
Li *et al.*, 2016 (10)	199, septic shock	Standard of care with 100 mL SFI once daily for 6 days	Standard of care with saline placebos of equal-volume to the study drug	None	Equal volume saline placebo	No difference overall. Patients initial lactate level ≥4.5 mmol/L had lower 7-day mortality with SFI (16.7% *vs.* 45.4%, P=0.03)
Zhang *et al.*, 2017 (11)	157, septic shock	Standard of care with 100 mL SFI once daily for 7 days	Standard of care with saline placebos of equal-volume to the study drug	Double-blind	Equal volume saline placebo	SFI associated with shorter vasopressor use (3.7±1.7 *vs.* 2.5±1.5 d, P=0.01), shorter ICU stays (10.5±3.2 *vs.* 12.2±2.8 d; P=0.01), as well as greater improvements in APACHE II (16.9±8.8 *vs.* 13.2±7.6, P=0.03) and Marshall Scores (8.5±3.3 *vs.* 6.8±2.6, P=0.01)
Fan *et al.*, 2019 (12)	65, septic shock	Standard of care (EGDT) with 100 mL SFI every 12 hours for 24 hours	Standard of care	Not described by authors	None	SFI associated with greater increase in MAP (61.22±3.31 to 81.65±4.3 mmHg in the SFI group *vs.* from 59.81±3.89 to 79.12±4.2 mmHg in the control group, (<0.05), and greater decrease in heart rate (119.55±12 to 76.52±5.84 BPM with SFI *vs.* 120.25±12.4 to 84.75±10.53 BPM, P<0.05)
Lv *et al.*, 2017 (13)	89, severe pulmonary disease	Standard of care with 100 mL SFI twice daily for 7 days	Standard of care with placebo	Not described by authors	Placebo use reported; specific placebo not described	SFI was associated with shorter durations of mechanical ventilation (6.8±3.3 *vs.* 9.7±4.2 days), shorter vasopressor use (3.6±2.7 *vs.* 4.9±3.0 days), shorter ICU stays (9.1±4.2 *vs.* 11.5±4.6 days), and decreased APACHE II scores (decreasing from 17.4±3.2 to 8.6±3.5 *vs.* from 16.9±4.1 to 12.6±3.7), when compared to placebo, respectively (P<0.05 for all)

SFI, Shenfu injection; RCTs, randomized controlled trials; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; LV, left ventricular; CRP, C-reactive protein; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α; CHF, congestive heart failure; NYHA, New York Heart Association; RR, relative risk; TCM, Traditional Chinese Medicine; CI, confidence interval; 6MWD, 6-minute walk distance; CCEs, composite cardiac events; EGDT, early goal-directed therapy; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation; MAP, mean arterial pressure; BPM, beats per minute.

Table 2 The search strategy summary

Items	Specification
Date of search	July 1st, 2022
Databases and other sources searched	PubMed
Search terms used	"Shenfu injection" OR "Shen-fu injection" OR "Shen fu injection" AND "clinical trial"
Timeframe	January 1st, 1990 – July 1st, 2022
Inclusion and exclusion criteria	Clinical trials or systematic reviews/meta-analyses of clinical trials were included. Articles for which the full text was not available in English were excluded
Selection process	The search was conducted independently by two authors (NB, ACS). Articles were then screened by the same two authors independently, according to the inclusion/exclusion criteria. Where consensus was not reached, KB had the deciding vote regarding inclusion/exclusion of an article. Finally, articles were divided into disease categories by all authors together, and relevant disease categories to include were agreed upon by all authors

(50 mL diluted in 100 mL saline) or placebo (150 mL saline) once daily for 7±1 days, in addition to standard therapy (7). Primary outcomes included the New York Heart Association (NYHA) classification and Traditional Chinese Medicine (TCM) syndrome scores (18); secondary outcomes included left-ventricular ejection fraction (LVEF), 6-minute walk distance (6MWD), Lee's CHF scores (not detailed by authors), and adverse cardiovascular events, including heart failure-related emergency department visits, composite cardiac events (CCEs), death, and rehospitalizations. Serum electrolytes and liver enzyme levels were monitored in all patients. All demographic parameters and clinical scores (NYHA classification and TCM syndrome score, Lee's CHF score, and 6MWD) were comparable at baseline between the two groups. Among the 144 patients who completed the protocol and underwent full analysis, those who received SFI in addition to standard therapy had significantly better clinical outcomes compared to patients in the control group: the NYHA classification improved in 78.38% of patients following SFI administration *vs.* only 61.43% in patients receiving placebo [relative risk (RR) =1.28, 95% confidence interval (95% CI): 1.02–1.59, P=0.03]; the TCM syndrome score improved by 89.19% following SFI administration compared to only 60% in the placebo group (RR =1.49, 95% CI: 1.21–1.83, P<0.001); Lee's heart failure score improved in 70.27% of patients in the SFI group compared to 52.17% in the placebo group (RR =1.35, 95% CI: 1.03–1.76, P=0.03); 6MWD had increased more in the SFI group than the placebo group following therapy (113 *vs.* 82.99 m increase, respectively, P=0.03). No significant differences in CCEs rate or death rate were noted between the two groups (7).

Multiple additional trials are only available in Chinese, but the results of some have been included in meta-analyses published in English. One meta-analysis including over 8,000 patients with either acute or chronic heart failure across 97 randomized controlled trials (RCTs) conducted between 1999 and 2011 found that adjunct therapy with SFI was associated with decreased mortality rate (RR =0.56, 95% CI: 0.41–0.75; P<0.01), improved cardiac function (WMD: 6.31; 95% CI: 5.18–7.44, P<0.01), and improvements in the NYHA Classification of Clinical Status and Killip's classification (RR =1.19, 95% CI: 1.17–1.21, P<0.01) (14). Additionally, patients treated with SFI had improved SV, CO, cardiac index, LVEF, and A peak E-wave (A/E) velocity ratio on echocardiography, lower serum NT-proBNP level, and improved 6MWD, although significant heterogeneity was noted. The authors concluded that further studies are warranted due to the methodological limitations of many of the reviewed RCTs, including a lack of a priori sample size calculation and blinding inconsistency (14). A network meta-analysis compared SFI with other Chinese herbal remedies and with Western medicine for pulmonary heart disease (cor pulmonale) and suggested that combining SFI with Western medicine may be superior to Western medicine alone, reporting a significant difference in their clinical effectiveness rates (OR =0.21, 95% CI: 0.12–0.25, P<0.05) (19,20). Additionally, in two recent reviews of systematic reviews and meta-analyses, Huang *et al.* and Li *et al.* both concluded that SFI can be a safe and effective treatment for heart failure (17,18). However, both authors report widespread methodological and quality limitations within this body of evidence. These include issues involving randomization and blinding, wide confidence intervals,

small sample size, funnel plot asymmetry, and limited adherence to guidelines for reporting methods and results (17,18).

SFI in cardiac arrest

SFI has been suggested to have potential benefit as adjunctive therapy to conventional post-resuscitation care bundles (21). To test this hypothesis, Zhang *et al.* conducted a multi-center randomized, parallel-group, assessor-blinded trial including 978 patients who had experienced an in-hospital cardiac arrest followed by successful return of spontaneous circulation (ROSC) (5). Patients were randomized to receive either 100 mL intravenous (IV) SFI or placebo (saline) every 12 hours for 14 days (or until hospital discharge) in addition to standard post-arrest care. Demographics and baseline cardiac arrest characteristics were comparable between the groups, with cardiac or respiratory conditions reported as the most predominant causes of cardiac arrests. Asystole was the most common initial arrest rhythm (>80% of patients). Patients who received SFI in addition to standard post-arrest care had significantly higher survival compared to patients in the control group at both 28- (42.7% *vs.* 30.1%, P=0.02) and 90-day (39.6% *vs.* 25.9%, P=0.001). Additionally, patients who received SFI had more-favorable neurological outcome at discharge (70% of patients in the SFI group had a cerebral performance category (CPC) score of 1 or 2 at discharge compared to 59.3% in the control group, P=0.03), shorter durations of mechanical ventilation (8.6± 3.2 days in the SFI group *vs.* 12.7±7.9 days in the control group, P<0.001), and shorter hospital stay (8.7±5.9 days in the SFI group *vs.* 13.2±8.1 days in the control group, P<0.001) (5). Although it is one of the larger clinical trials conducted on SFI, the protocol for prognostication and withdrawal of life support was unclear. There was also a lack of standardization of post-arrest care, with under 20% of patients in both groups receiving targeted temperature management (TTM), although the study protocol dictated the use of TTM as part of a standardized post-resuscitation care bundle. Additionally, the number of patients recruited was more than double the estimated number of patients required according to the power calculations (5,22).

In a multi-center, assessor-blinded RCT of out-of-hospital cardiac arrest (OHCA), Shao *et al.* randomized 1,233 patients to receive either SFI or saline during cardio-pulmonary resuscitation (CPR), in addition to standard CPR and defibrillation (8). In the SFI group, patients were given a single SFI bolus (20 mL) immediately after the first epinephrine dose (1 mg IV) and were then given an IV infusion of SFI (30 mL diluted 1:1 with saline) over an hour. The placebo group was given saline in identical volumes at similar time points. Demographics and baseline cardiac arrest characteristics (etiology and first monitored arrest rhythm) were comparable between the groups. Arrests of presumed cardiac etiology were predominant, and over 75% of patients were found in asystole. Outcomes measured included survival to hospital admission (primary outcome), ROSC, survival to hospital discharge, 1-year survival, favorable neurological outcome (defined as a CPC score of 1 or 2) at hospital discharge, and favorable neurological outcome after one year. There was no statistically significant difference in survival to admission [6.7% (40/599) in the SFI group *vs.* 5.6% (34/602) in the control group, P=0.53] and survival to discharge [2.9% (17/596) in the SFI group *vs.* 1.2% (7/597) in the control group, P=0.06]. Patients who received SFI in addition to standard care had significantly improved neurologic outcomes when compared to patients who received standard therapy alone at hospital discharge [2.7% (16/596) *vs.* 1% (6/597), respectively, P=0.05) and 1 year after the arrest [1.7% (10/595) *vs.* 0.3% (2/596), respectively, P=0.04]. No statistically significant results were noted in regard to ROSC achievement, survival to hospital admission, survival to hospital discharge, and 1-year survival (8).

SFI for sepsis and septic shock

Potential immunomodulating properties of SFI have been evaluated in a number of clinical trials looking at sepsis and septic shock. A meta-analysis looking at 904 patients in twelve clinical trials conducted between 2007–2014 where SFI was utilized in addition to conventional therapy for septic shock reported overall improved outcomes in patients who received SFI compared to patients who did not (15). The main benefits reported included improved hemodynamic parameters [heart rate, mean arterial pressure (MAP)], decreased lactate, and lower mortality, but the results were inconsistent across studies. The meta-analysis' authors state that many of the included studies had significant methodological limitations, such as failing to comply with standardized reporting guidelines (e.g., CONSORT) or failing to adhere to strict randomization, blinding, or inclusion criteria (15).

In a study by Li *et al.*, 45 patients with septic shock were randomized to receive 100 mL SFI IV twice daily in addition to conventional early goal directed therapy

(EGDT) *vs.* EGDT alone (9). The trial was not blinded as no placebo was used. Acute Physiology and Chronic Health Evaluation (APACHE-II) scores, Sequential Organ Failure Assessment (SOFA) scores, hemodynamic variables (heart rate, MAP, cardiac index, systemic vascular resistance index), plasma lactate levels, ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen ratio (PaO_2/FiO_2), and serum biochemistry parameters were assessed daily for up to 7 days. The duration of vasopressor use, mechanical ventilation, and intensive care unit (ICU) length of stay, organ failure-free time at 28 days, and 28-day hospital mortality were also compared between the groups. A specific primary outcome was not declared by the authors. Patients who received SFI had a more significant decrease in SOFA score from day 3 through day 7 compared to the control group, decreasing from 10±3.12 at baseline to 3.59±2.97 on day 7 in the SFI group *vs.* 9±2.97 at baseline to 4.61±3.36 on day 7 in the control group (P<0.05). Creatinine and blood urea nitrogen (BUN) levels had also decreased more significantly over 7 days in the SFI group *vs.* the control group (creatinine and BUN decreased from 138.66±45.29 to 59.63± 13.22 μmol/L and from 15.53±5.92 to 9.95±2.74 mmol/L, respectively, in the SFI group *vs.* from 129.11±41.42 to 71.4±12.76 μmol/L and 16.05±6.16 to 11.48±2.93 mmol/L, respectively, in the control group; P<0.05 for all). The SFI group saw improvements in other parameters (cardiac index, MAP, PaO_2/FiO_2, plasma lactate and bilirubin) when compared to the placebo group, but these improvements were seen inconsistently at only some interim time points. Additionally, patients who received SFI demonstrated shorter ventilator weaning times when compared to controls (7.5±3.5 *vs.* 9.1±3.2 days, respectively, P<0.05), as well as shorter ICU stays (16.1±9.2 *vs.* 18.7± 8.3 days, respectively, P<0.05), but no difference in mortality or organ failure-free time was noted. The large number of outcomes in this relatively small trial introduce significant risk for a Type I error (9).

In an open-label trial, Li *et al.* randomized a total of 199 patients admitted with septic shock at seven Chinese medical centers to receive either 100 mL of SFI or saline (placebo) once daily in addition to standard therapy for 6 days (10). There were no significant differences between the two groups at baseline. Hemodynamic parameters and routine blood variables were monitored for 6 days. The primary outcome was lactate clearance. Secondary outcomes were time to shock index normalization, vasopressor does, hospitalization and ICU length of stay, and 7- and 28-day mortality. There were no significant differences in any of the outcomes measured between patients who received SFI and patients who received a placebo. However, when only examining patients with an initial plasma lactate level of ≥4.5 mmol/L, the 7-day mortality rate was significantly lower in patients who received SFI compared to patients who received the placebo [4 (16.7%) *vs.* 10 (45.4%) respectively, P=0.03] (10). The association between plasma lactate levels and potential benefit of SFI was further evaluated in a systematic review and meta-analysis by Huang *et al.* (16). Nineteen RCTs with a total of 1,505 patients in septic shock were included for analysis, and the impact of SFI on 28-day mortality was evaluated in groups stratified by lactate level. While the addition of SFI to standard therapy did not decrease 28-day mortality across the entire study population, a statistically-significant decrease in 28-day mortality was found in a subgroup of patients with mean arterial lactate levels ranging from 4.5 to 7 mmol/L. Patients outside of this range did not seem to benefit from SFI (16).

Zhang *et al.* conducted a randomized, double-blind, placebo-controlled trial in patients with sepsis or septic shock (11). A total of 157 patients were randomly assigned to 100 mL of SFI or placebo (saline) once daily for 7 days in addition to standard therapy. Patients who received SFI had shorter duration of vasopressor therapy and shorter ICU stay than patients in the placebo group, as well as improved APACHE II and Marshall Scores after 7 days. There was no significant difference in 28-day mortality. Immunological function was also evaluated via $CD4^+$ and $CD8^+$ T-cell counts, human leukocyte antigen-DR expression on circulating monocytes (mHLA-DR), and *ex vivo* cytokine release from LPS-stimulated monocytes. The SFI group was found to develop significantly higher levels of $CD4^+$ and $CD8^+$ T-cell counts, IL-6, and TNF-α, as well as mHLA-DR expression rate. IL-10 release was significantly lower in monocytes from the SFI group (11).

Fan *et al.* assigned 65 patients admitted to an ICU with septic shock to receive either conventional therapy alone, or conventional therapy with the addition of SFI (100 mL IV every 12 hours) for 24 hours (12). Whether the study was randomized or blinded was not stated. Key parameters, including hemodynamic indices, of both groups were comparable at baseline. At baseline, the MAP did not differ significantly between groups. During the course of the trial, the MAP increased slightly more in the treatment group compared to the control group, respectively, from 61.22±3.31 *vs.* 59.81±3.89 mmHg at baseline to 73.45±5.09

vs. 70.22±4 mmHg after 12 hours, and to 81.65±4.3 *vs.* 79.12±4.2 mmHg after 24 hours. While this difference is statistically significant (P<0.05), it may not be considered clinically important. The heart rate had decreased in both groups, but the decrease was more significant in the treatment group, decreasing from 119.55±12 to 76.52±5.84 beats per minute (BPM) after 24 hours, compared to a milder decrease from 120.25±12.4 to 84.75±10.53 BPM after 24 hours in the control group (12).

SFI for severe pulmonary disease

There are a number of RCTs evaluating the utility of SFI in severe pulmonary disease. Lv *et al.* investigated the effects of SFI on severe pneumonia in elderly patients (13). Eighty-nine patients were randomized to receive 100 mL of SFI or placebo IV twice daily for 7 days in addition to standard therapy. Baseline parameters were comparable between the groups. After seven days, patients treated with SFI had significantly lower levels of some pro-inflammatory cytokines (TNF-α, IL-6, and IL-8), as well as higher levels of the anti-inflammatory cytokine IL-10 compared with controls (P<0.05 for all). Patients treated with SFI also had significantly shorter duration of mechanical ventilation (6.8±3.3 *vs.* 9.7±4.2 days), vasopressor use (3.6±2.7 *vs.* 4.9±3.0 days), and ICU stay (9.1±4.2 *vs.* 11.5±4.6 days) when compared to patients in the control group, as well as lower APACHE II scores at the end of the trial (decreasing from 17.4±3.2 to 8.6±3.5 in the SFI group, and from 16.9±4.1 to 12.6±3.7 in the control group) (P<0.05 for all) (13).

In a recent systematic review and meta-analysis, Lin *et al.* evaluated the efficacy of SFI in patients with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (23). Fifteen RCTs involving 1,198 patients were evaluated, and the effects of SFI were systematically evaluated in the following categories: clinical effective rate (primary outcome), pulmonary function [forced expiratory volume in one second (FEV1), FEV1/forced vital capacity (FVC) ratio (FEV1/FVC)], blood gas analysis PaO_2, partial pressure of carbon dioxide ($PaCO_2$), white blood cell count (WBC), and adverse reactions. The clinical effective rate was calculated using a fixed-effects model, involving data from 14 studies (with a total of 1,112 patients) which reported the clinical effectiveness of SFI vs control. A specific definition for clinical effectiveness was not provided by the authors. SFI was suggested to improve overall clinical effective rate [reported in 91.3% (514/463) of patients in the SFI group *vs.* 79.6% (437/549) of patients in the control group; RR =1.15, 95% CI: 1.09–1.21, P<0.00001]; improve FEV1 [standardized mean difference (SMD) =1.88, 95% CI: 0.89–2.88, P=0.0002] and FEV1/FVC [mean difference (MD) =3.96, 95% CI: 2.74–5.19, P<0.00001]; improve PaO_2 (MD =6.03, 95% CI: 4.58–7.48, P<0.00001); and reduce $PaCO_2$ (MD =–4.59, 95% CI: –6.91 to –2.26, P=0.00001). Additionally, a slight improvement in WBC counts were noted in patients treated with SFI vs controls in two trials (MD =–1.16, 95% CI: –1.63 to –0.68, P<0.00001). The authors note several significant limitations to the reviewed studies which may increase the risk of bias, including small sample sizes, limited details on the methodology (randomization, blinding, and sample size calculations were often not provided), and potential reporting bias, as all of the studies have reported only positive results. Furthermore, the main outcome measure was subjectively-determined (clinical efficacy) and thus subject to potential bias (23).

Discussion and future directions

SFI has been extensively used and researched in China, in both the clinical and preclinical settings. Overall, while the majority of RCTs and systematic reviews/meta-analyses indicate SFI has therapeutic efficacy in various medical conditions, there are several things to consider. First, some of the trials we reviewed have methodological limitations—such as lack of blinding or randomization, multiple outcome measures without a declared primary outcome, or incomplete reporting of methods, which may introduce bias and adds a layer of complexity to the interpretation of the results. Widespread methodological limitations and possible publication bias were also reported in previous reviews and meta-analyses on the topic (14,15,17,20). Additionally, several results are reported as statistically significant, but the very small numeric differences seem unlikely to be clinically significant. These limitations emphasize the need for additional, high-quality multicenter RCTs. Second, while hundreds of RCTs have been conducted over the last several decades in China, to our knowledge SFI has not been studied outside of China. Health care practices and patient characteristics vary by country, and whether SFI would be beneficial in-patient populations outside of China is untested. International, high-quality RCTs would allow for a more comprehensive evaluation of SFI's efficacy in a variety of different populations and medical systems. SFI is also not available in many countries, including the United States, representing a significant barrier to conducting clinical trials.

Despite a growing number of publications investigating the mechanism of action of SFI, additional research is warranted to better understand the effects of SFI in critically ill patients. For example, there is conflicting evidence regarding SFI's effect on cytokine levels in people with sepsis: Zhang *et al.* reported increased levels of IL-6 and TNF-α, and lower levels of IL-10 in patients treated with SFI compared to controls (11). These findings suggest that SFI may increase cellular immune response, which stands in contrast to the decreased serum IL-6 levels previously reported (24). Some of these discrepancies may be attributed to different methodologies, as some studies measured *ex vivo* cytokine levels, which may not accurately reflect *in vivo* status (25). However, future studies are needed to understand the pharmacodynamics of SFI in critically ill patients.

Another area of interest for future research is appropriate drug administration, safety and dosing. Many of the studies—even some that tested similar indications or scenarios—utilized different dosing and administration strategies. Moreover, most of the published data only includes the volume of drug administered, but not the specific dose (mg) or concentration (mg/mL), making the trials difficult to replicate. If further trials suggest efficacy, then future research to determine standardization around dose, interval and duration of therapy would be useful.

Several protocols describing clinical trials and systematic reviews or meta-analyses have been published in recent months. Anticipated topics for investigation include cardiac arrest, heart failure, coronary heart disease, sepsis, pediatric respiratory infections, and COVID-19 (26-33). SFI is currently listed as a recommended therapy for severe cases of COVID-19 by the China National Health Commission (NHC) (34). Given the current urgent need for therapeutic options to reduce the morbidity and mortality due to COVID-19, it will be especially interesting to see whether SFI may provide clinical benefit to those patients.

Limitations

As a narrative review, the present work is not the product of a systematic or exhaustive literature search, and it is possible that some key studies were not included. Many studies identified in the search were available in the Chinese language only, and we did not have the resources or translate these and thus these papers were excluded from this review. For this reason, we could not conduct a systematic review and similarly could not critically evaluate some items within the literature, namely the systematic reviews and studies available only in Chinese. We attempted to capture some of this work by including systematic reviews that were published in English, when available.

Conclusions

Multiple published clinical trials have reported that SFI may improve outcomes in a variety of medical conditions, including heart failure, cardiac arrest, sepsis and some forms of severe pulmonary disease. Based on the current body of literature, further research—especially multi-center randomized, double-blind trials with detailed reporting of all methods and results according to international guidelines—is needed to evaluate whether SFI is a useful addition to existing treatments for these conditions.

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Footnote

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