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Original Article

# Effectiveness and safety of Shenfu injection in septic patients with hypoperfusion: A multi-center, open-label, randomized, controlled trial

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ABSTRACT

*Background:* To evaluate the effectiveness and safety of the Shenfu injection (SFI) combined with standard bundle treatment in septic patients with hypoperfusion.

*Method:* This study was a multi-center, randomized, open-label, controlled trial conducted in four teaching hospitals in China. The septic patients with hypoperfusion and traditional Chinese medicine (TCM) syndrome with Yang-Qi deficiency were enrolled from January 2019, through September 2020. Eligible patients were randomly allocated in a 1:1 ratio to either receive 60 mL of SFI infusion per day plus standard treatment (SFI group) or standard bundle treatment alone (control group). The primary outcome was 28-day all-cause mortality. Secondary outcomes were 90-day all-cause mortality time to weaning from mechanical ventilation, time to weaning from vasopressors, time to discharge from the ICU and hospital, and laboratory results after randomization.

*Results:* A total of 188 patients completed the trail. This study revealed that the results of the SFI group and the control groups were not statistically significant in 28-day all-cause mortality (10.6% *vs.* 20.2%, respectively; $P$=0.106). The infusion of SFI was associated with a significant reduction in the duration of vasopressor use (median=4.0 days, interquartile range [IQR]: 2.0 days–6.0 days *vs*. median=5.0 days, IQR: 3.0 days–8.0 days, respectively; $P$=0.043). Patients in the SFI group had statistically greater reductions in plasma lactate levels compared with those in the control group at the first 12 h (median=1.1 mmol/L, IQR: 0.3–2.0 mmol/L *vs*. median=0.0 mmol/L, IQR: −0.2 to 0.8 mmol/L, respectively; $P$ <0.001) and 24 h (median=1.4 mmol/L, IQR: 0.3–2.2 mmol/L *vs*. median=0.4 mmol/L, IQR: −0.4 to 1.6 mmol/L, respectively; $P$=0.001).

*Conclusion:* SFI plus standard therapy did not significantly decrease 28-day all-cause mortality for septic patients with hypoperfusion and TCM syndrome with Yang-Qi deficiency.

**Trial registration** Chinese Clinical Trial Registry Identifier: ChiCTR1800020435

## Introduction

Sepsis is a complex disease characterized by dysregulation of the host's response to infection and is associated with a high risk of acute organ dysfunction.[1] The mortality rate among patients with sepsis remains high despite the establishment of guideline-based treatment options, which include removal of the infection source, early initiation of appropriate antimicrobial therapy, and restoration of tissue perfusion via fluid resuscitation.[2,3] Recent estimates suggest that sepsis contributes to between one-third and one-half of all in-hospital deaths in the United States.[4] Therefore, the development of adjuvant treatment for sepsis is urgently warranted.

In China, traditional Chinese medicine (TCM) plays an essential role in clinical practice. The Chinese herbal formula Shenfu injection (SFI) originates from Shenfu decoction and was ini-

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tially recorded as a therapeutic agent in *Jisheng Fang* written by Yan Yonghe in the 1250s; it consists of Radix "ginseng" (red ginseng) and Radix Aconiti Lateralis Preparata (prepared aconite root). The presumed therapeutic effect of Shenfu in TCM is a restoration of the "Qi" and "Yang" (Supplementary Material 1). In recent studies, this herbal compound exhibited immunomodulating effects, alleviated vasospasm in microcirculation, and improved hemodynamics.[5–7] SFI comprises multiple components, has multiple targets, exerts multiple effects, and shows complex pharmacologic actions.[8–10] Hence, it may be a promising treatment option for patients with sepsis.

A recent meta-analysis showed that SFI tended to decrease 28-day mortality in patients with septic shock (4.5 mmol/L < mean arterial lactate level < 7 mmol/L).[11] However, patients included in these trials were diagnosed according to the sepsis 1.0 or sepsis 2.0 definition,[12,13] which resulted in significant heterogeneity. Moreover, these trials involved different designs using SFI alone or in combination, which led to inconsistent results. Therefore, we conducted a study to evaluate the effectiveness and safety of SFI combined with standard bundle treatment in septic patients with hypoperfusion.

## Methods

### *Design and setting*

This was a multi-center, open-label, randomized, controlled trial conducted in four university medical centers, led by the Shanghai Jiaotong University School of Medicine Affiliated Ruijin Hospital (Shanghai, China). This trial was approved by the Ruijin Hospital Ethics Committee of Shanghai Jiaotong University School of Medicine and was registered in the Chinese Clinical Trial Registry (ChiCTR1800020435). Written informed consent was provided by the patients or their legal representative. The first patient was enrolled on January 2, 2019, and the last on September 31, 2020. The final date of follow-up was December 31, 2020.

### *Study population*

Patients in an intensive care unit (ICU) with a primary diagnosis of sepsis were screened for eligibility according to the following inclusion criteria: (1) meeting the diagnostic criteria for Sepsis-3 developed by the American Society of Critical Care Medicine/European Society of Intensive Care Medicine,[1] and meeting the diagnostic criteria for "deficiency syndrome" formulated by the National Committee of Deficiency Syndrome and Geriatric Diseases of Integrated Traditional Chinese and Western Medicine[14]; (2) age ≥18 years; (3) lactate levels ≥2 mmol/L or with hypoperfusion; clinical features mainly manifested as confusion, pale and clammy skin, decreased urine output, etc.; and (4) diagnosis within a maximum of 24 h prior to enrollment. Patients with septic shock requiring the administration of vasopressors were also included in the study. In case of misdiagnosis of sepsis, patients were removed from the study after enrollment.

The exclusion criteria were: (1) age <18 years; (2) diagnosis of sepsis with hypoperfusion >24 h earlier; (3) presence of known or suspected disease with a strong indication or contraindication for any of the study drugs; (4) non-infectious factors, such as acute cerebrovascular disease, acute coronary syndrome, drug poisoning, burns or trauma, active bleeding, and late-stage malignant tumors, which may lead to death; (5) pregnant or lactating women; (6) autoimmune disease history or other clear immunosuppressive states, such as the use of immunosuppressants and/or cytotoxic drugs, and diagnosis of acquired immune deficiency syndrome; (7) concurrent participation in another clinical trial; and (8) life expectancy of ≤48 h. Patients who left the ICU against their physician's advice could not complete the follow-up, or exhibited poor treatment compliance were considered dropouts.

### *Randomization and blinding*

TCM doctors are responsible for syndrome differentiation. Eligible patients with acute deficiency syndrome were randomized to the SFI group or the control group in a 1:1 ratio (without blocks) using a random number table. All participants and their families, outcome evaluators, laboratory technicians, and biostatisticians responsible for the statistical analysis were blinded to the assigned treatments. Therapeutic clinicians were not blinded to the interventions.

### *Intervention*

All eligible ICU patients were randomized to receive either 60 mL of SFI per day plus standard bundle treatment (SFI group) or standard treatment alone (control group). The preparation of SFI is described in Supplementary Material 1. Trial agents were administered via continuous intravenous infusion at a rate of 10 mL/h, 60 mL/day for 5–7 days (Supplementary Material 2).[15] Both groups received standard bundle therapy selected by the attending physician according to the 2016 International Management of Sepsis Guidelines, including early initial resuscitation, diagnosis of infection and early antimicrobial therapy, vasopressor strategy, mechanical ventilation, and renal replacement therapy.[13]

### *Data collection and follow-up processes*

The primary outcome was 28-day all-cause mortality. Secondary outcomes were 90-day all-cause mortality, time to weaning from mechanical ventilation, time to weaning from vasopressors, time to discharge from the ICU and hospital, decline in plasma lactate levels within 12 h and 24 h after the experimental intervention, decline in plasma C-reactive protein (CRP) levels within 72 h and 168 h after the experimental intervention, and decline in activated partial thromboplastin time (APTT) within 72 h and 168 h after the experimental intervention.

According to the instructions provided by the manufacturer, the main side effects of SFI include tachycardia, rash, dyspnea, dizziness, headache, nausea and vomiting, tremor, etc. Occurrence of these side effects during the present study was recorded. The association of safety outcomes with the study medication was determined by the investigator.

### *Power calculation and statistical analyses*

The sample size was calculated based on the expected reduction in 28-day all-cause mortality. We expected a 28-day all-cause mortality of 27% in patients with septic shock.[16] It was expected that the mortality rate in the SFI group would

decrease to 10%. Therefore, enrollment of 156 patients (78 per arm) would be necessary to achieve 80% power with a two-sided $\alpha$ level of 0.05. It was assumed that 20% of the patients would withdraw or be lost to follow-up during treatment. Thus, a total of 188 patients (94 per arm) would be required for the efficacy analysis.

Patient data were analyzed according to their randomization group, excluding those of patients who withdrew consent. Efficacy was determined using the full analysis set (all patients who did not drop out), while safety was determined using the safety set (all patients who received at least one dose of SFI). Continuous data in accordance with normal distribution are presented as the mean ± standard deviation and were analyzed using the Student's *t*-test. Continuous data of non-normal distribution are described by the median and interquartile range (IQR); comparisons between count data were performed using the Wilcoxon rank-sum test. Categorical variables are presented as frequencies and were analyzed using the chi-squared test. Comparisons of continuous variables between groups were carried out using the Mann–Whitney *U* test. Kaplan–Meier (log-rank test) was used to compare the survival rates between the two groups, and a Cox proportional hazards model was used to evaluate the difference in survival rate. Analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Two-sided *P*-values <0.05 indicate statistically significant differences.

## Results

### *Baseline patient characteristics*

A total of 345 patients with suspected sepsis were admitted during the study period. Of those, 192 patients were enrolled and 188 completed the trial (96 patients per group). The study population included 54 females and 138 males. Figure 1 presents the study flowchart. Four patients (two patients per group) were removed from the study due to withdrawal of informed consent after enrollment.

At the time of enrollment, the baseline characteristics of the patients (i.e., age, sex, underlying diseases, organ dysfunction at admission, Acute Physiology and Chronic Health Evaluation [APACHE] II score, Sequential Organ Failure Assessment [SOFA] score, combination therapy, such as mechanical ventilation, renal replacement treatment, and hydrocortisone use) were similar between the two groups (Table 1). The most common sites of infection in both groups were the abdomen and respiratory tract. However, the proportion of bile duct infection was lower in the SFI group compared with the control group (1.1% *vs.* 7.5%, respectively; *P*=0.030) (Table 1). The proportion of Gram-positive bacteria was also lower in the SFI group *vs.* the control group (8.5% *vs.* 20.2%, respectively; *P*=0.022) (Table 1).

### *Outcomes*

*28-day all-cause mortality*

A total of 29 patients (15.4%) expired within 28 days from enrollment. There was no significant difference in 28-day all-cause mortality after randomization between the SFI and control groups (10.6% *vs.* 20.2%, respectively; *P*=0.106) (Table 2). The Kaplan–Meier survival curve indicated that the 28-day survival was not significantly different between the SFI and control groups (hazard ratio=0.52; 95% confidence interval: 0.24 to 1.12; *P*=0.093) (Figure 2).

*Secondary outcomes*

There was no significant difference in all-cause mortality at 90 days after randomization between the SFI and control groups (18.1% *vs.* 29.0%, respectively; *P*=0.111). The duration of vasopressor use (median=4.0 days, IQR: 2.0 days–6.0 days *vs.* median=5.0 days, IQR: 3.0 days–8.0 days; *P*=0.043) was shorter in the SFI group compared with the control group. However, there was no statistically significant between-group difference in the length of ICU stay or the duration of mechanical ventilation (Table 2).

Patients in the SFI group had statistically greater reductions than those in the control group in 12-hour plasma lactate changes (median=1.1 mmol/L, IQR: 0.3–2.0 mmol/L *vs.* median=0 mmol/L, IQR: −0.2 to 0.8 mmol/L, respectively; *P* <0.001) and 24-h plasma lactate changes (median=1.4 mmol/L, IQR: 0.3–2.2 mmol/L *vs.* median=0.4 mmol/L, IQR: −0.4 to 1.6 mmol/L, respectively; *P*=0.001) (Table 2). Patients in the SFI group had statistically greater reductions compared with those in the control group in plasma CRP levels at the first 72 h (median=41.5 mmol/L, IQR: −5.5 to 92.5 mmol/L *vs.* median=7.0 mmol/L, IQR: −41.5 to 53.0 mmol/L, respectively; *P*=0.006) (Table 2). In contrast, there was no significant difference found between the two groups in terms of CRP change at 168 h (Table 2). In addition, there was no significant difference detected in APTT change at 72 h and 168 h (Table 2).

### *Subgroup analysis*

The subgroup analysis of primary outcome revealed that SFI plus standard therapy did not decrease 28-day all-cause mortality in any of the four groups (Figure 3).

### *Adverse events*

There was no occurrence of unexpected serious adverse events related to the study drug. Only one patient in the SFI group developed pruritus and wheal, which were not related to the treatment. The development of adverse effects did not lead to dose adjustments in any of the patients (Supplementary Material 1).

## Discussion

To the best of our knowledge, this might be the first registered multi-center randomized, controlled trial to evaluate the effectiveness and safety of SFI in septic patients with hypoperfusion and TCM syndrome with Yang-Qi deficiency. In this study, we found that there was no significant difference in 28-day all-cause mortality between the SFI and control groups. Additionally, the infusion of SFI was not associated with a significant reduction in 90-day all-cause mortality. This result was consistent with those reported by Li et al.[17] In our study, SFI was associated with a reduction in the duration of vasopressor usage. The plasma lactate levels decreased more significantly at 12 h and 24 h after enrollment in the SFI group compared with the control group.

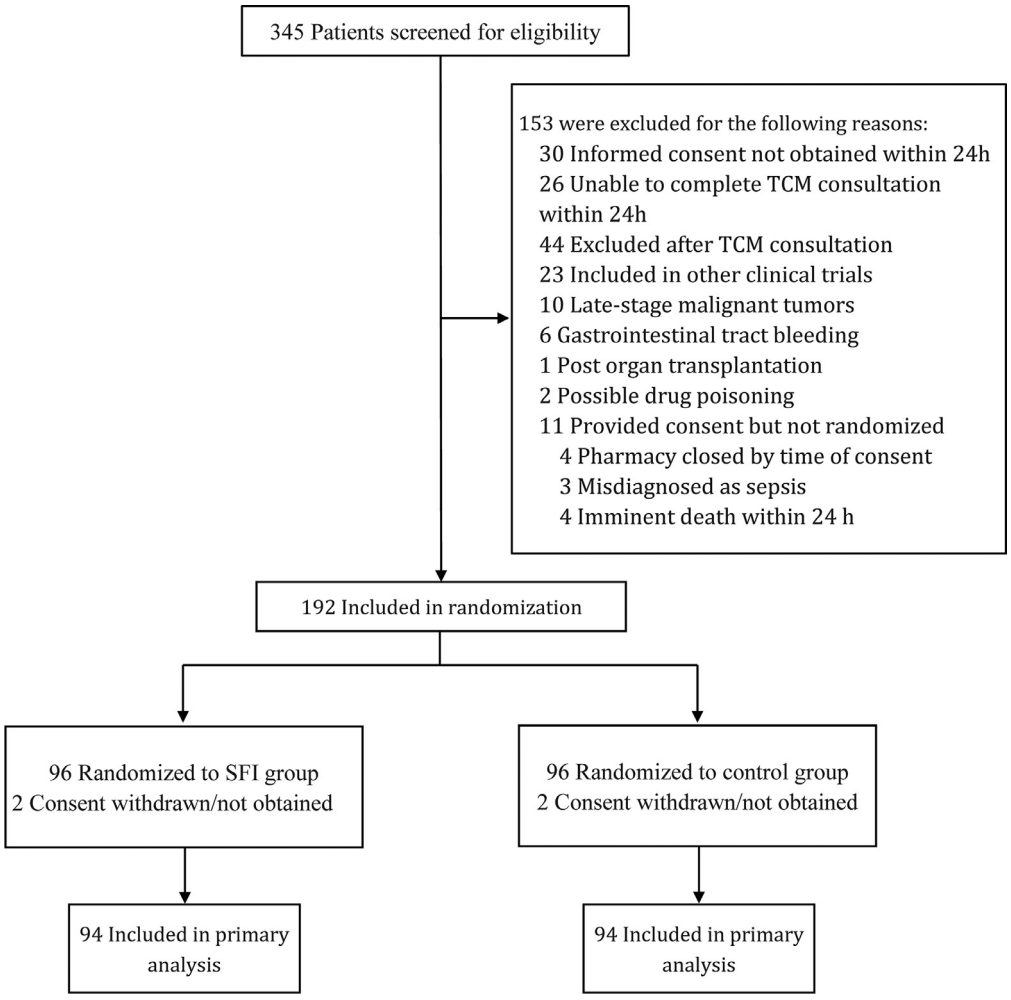


**Figure 1.** Flowchart of this study.
SFI: Shenfu injection; TCM: Traditional Chinese medicine.

TCM focuses on treating the "whole" person, addressing mental, physical, and psychological attributes. In TCM theory, syndrome (Zheng in Chinese) is a generalization for the state of the patient and has been used to diagnose and treat diseases.[18,19] SFI, produced using multi-stage countercurrent extraction and macroporous resin adsorption technology, is a well-established TCM formulation. It is composed of ginseng and aconite, which can reinforce Yang, dispel cold, and relieve pain. Typically, SFI is used to treat Yang depletion syndrome. The two medicines can interact with each other and, when used properly, they can instantly transform Qi into Yang.[7,20] Hence, in this study, the differentiation of the syndromes of patients was performed by TCM physicians based on the Diagnostic Criteria of TCM.[14] Previous randomized controlled trials examining the clinical effectiveness of SFI in patients with sepsis yielded inconsistent results. The present study was the first to combine TCM syndrome differentiation and a standard bundle therapy protocol to investigate the effectiveness of SFI in septic patients with hypoperfusion.

SFI mainly contains ginsenosides and aconitine; the latter functions as a β aconitine norepinephrine receptor agonist and can increase myocardial cyclic adenosine monophosphate (cAMP) levels or inhibit cAMP degradation, enhance myocardial contractility, and increase cardiac output to improve organ perfusion.[21] Furthermore, Xu et al.[22] reported that SFI protected against sepsis-induced myocardial injury by suppressing myocardial apoptosis and alleviating sepsis-induced mitochondrial damage. In addition, treatment with SFI significantly improved macrocirculation and microcirculation during cardiopulmonary resuscitation.[23] SFI can increase the number of capillary network openings, small artery diameter, blood flow velocity, and the density and proportion of perfusion blood vessels, as well as improve capillary microcirculation blood flow. Simultaneously, it can increase oxygen transport, consumption, and uptake rate, improve tissue oxygen metabolism, and reduce blood lactic acid.[23] In the study performed by Li et al.[17], lactate levels were significantly decreased at 6 h after treatment with SFI. In our study, patients in the SFI group had significant reductions in plasma lactate levels at the first 12 h and 24 h. In addition, SFI plus standard therapy significantly shortened the duration of vasopressor use in our study. This finding is consistent with the results reported by Zhang et al.[5] This evidence indicates that treatment with SFI may achieve earlier improvement of circulation, particularly in terms of microcirculation.

According to the hour-1 bundle revised in 2018, early administration of vasopressors is recommended for the restoration of sufficient perfusion pressure to vital organs.[24,25] Use of SFI was also recommended for the treatment of sepsis, particularly dur-

**Table 1**
Demographic and baseline clinical characteristics of patients in the SFI and control groups.

| Characteristics | SFI group (*n*=94) | Control group (*n*=94) | *P*-value |
|---|---|---|---|
| Sex | | | 0.627 |
| Female | 25 (26.6) | 28 (29.8) | |
| Male | 69 (76.4) | 66 (70.2) | |
| Age (years) | 67 (56.8–75.3) | 68 (55.8–75.0) | 0.994 |
| Comorbidity | | | |
| Tumor | 43 (45.7) | 48 (51.1) | 0.466 |
| Hypertension | 43 (45.7) | 50 (53.2) | 0.307 |
| Diabetes | 16 (17.0) | 27 (28.7) | 0.056 |
| COPD | 8 (8.5) | 3 (3.2) | 0.120 |
| Coronary heart disease | 16 (17.0) | 10 (10.6) | 0.205 |
| Chronic kidney disease | 7 (7.5) | 2 (2.2) | 0.091 |
| Hypothyroidism | 2 (2.1) | 3 (3.2) | 0.650 |
| Autoimmunity disease | 5 (3.3) | 7 (7.5) | 0.551 |
| Organ dysfunction at admission | | | |
| Heart dysfunction | 28 (29.8) | 26 (27.7) | 0.747 |
| Acute respiratory dysfunction | 73 (71.6) | 62 (67.4) | 0.528 |
| Acute kidney injury | 40 (42.6) | 43 (45.7) | 0.659 |
| Coagulation dysfunction | 35 (37.2) | 42 (44.7) | 0.299 |
| Infection site | | | |
| Abdomen | 50 (53.2) | 59 (62.8) | 0.184 |
| Respiratory tract | 31 (33.0) | 26 (27.7) | 0.428 |
| Blood stream | 15 (16.0) | 15 (16.0) | 1.000 |
| Bile duct | 1 (1.1) | 7 (7.5) | 0.030 |
| Skin | 1 (1.1) | 2 (2.1) | 0.561 |
| Mediastinum | 4 (4.3) | 4 (4.4) | 1.000 |
| Central nervous system | 2 (2.1) | 1 (1.1) | 1.000 |
| Urinary tract | 5 (5.3) | 3 (3.2) | 0.470 |
| Microbiological etiology | | | |
| Gram-negative | 57 (60.6) | 62 (66.0) | 0.449 |
| Gram-positive | 8 (8.5) | 19 (20.2) | 0.022 |
| Fungi positive | 9 (9.6) | 10 (10.6) | 0.809 |
| Virus positive | 1 (1.1) | 1 (1.1) | 1.000 |
| Pathogen negative | 25 (26.6) | 21 (21.3) | 0.497 |
| APACHE II score at admission | 20 (16.0–25.0) | 19 (13.8–25.0) | 0.301 |
| SOFA at admission | 7 (3.8–10.0) | 7.5 (5.0–10.0) | 0.216 |
| Organ function support | | | |
| Mechanical ventilation | 53 (56.4) | 57 (60.6) | 0.554 |
| RRT | 15 (16.0) | 14 (14.9) | 0.840 |
| Hydrocortisone use | 31 (33.0) | 29 (30.9) | 0.754 |
| Vasopressor | | | |
| Noradrenaline | 57 (60.6) | 63 (67.0) | 0.362 |
| Epinephrine | 9 (9.6) | 10 (10.6) | 0.809 |
| Dopamine | 2 (2.1) | 2 (2.1) | 1.000 |
| Vasopressin | 4 (4.3) | 1 (1.1) | 0.174 |
| Others | 1 (1.1) | 0 (0) | 0.316 |
| Physiological variable | | | |
| WBC ($\times 10^9$/L) | 13.1 (8.7–19.9) | 12 (8.4–16.8) | 0.226 |
| CRP (mg/L) | 158.8 (105.0–219.5) | 149.0 (81.0–244.0) | 0.518 |
| PCT (ng/mL) | 6.9 (1.2–32.3) | 3.9 (1.3–23.5) | 0.847 |
| PLT ($\times 10^9$/L) | 134.0 (69.3–198.8) | 143.0 (71.0–201.0) | 0.931 |
| Lactate (mmol/L) | 1.9 (1.4–3.0) | 1.8 (1.2–3.6) | 0.908 |
| Scr (μmol/L) | 90.0 (56.5–147.0) | 97.5 (69.0–153.5) | 0.284 |
| ALT (U/L) | 27.0 (14.8–69.8) | 28.0 (14.0–56.3) | 0.395 |
| AST (U/L) | 37.0 (24.0–65.0) | 34.0 (24.0–81.5) | 0.756 |

Data were presented as *n* (%) and median (interquartile range).
ALT: Alanine aminotransferase; APACHE: Acute Physiology and Chronic Health Evaluation; AST: Aspartate aminotransferase; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; IQR: Interquartile range; PCT: Procalcitonin; PLT: Platelet; RRT: Renal replacement treatment; Scr: Serum creatine; SFI: Shenfu injection; SOFA: Sequential Organ Failure Assessment; WBC: White blood cells.

**Table 2**
Primary and secondary outcomes of patients in the SFI and control groups.

| Outcome | SFI group (*n*=94) | Control group (*n*=94) | *P*-value |
|---|---|---|---|
| Primary outcome | | | |
| 28-day all-cause mortality | 10 (10.6) | 19 (20.2) | 0.106 |
| Secondary outcomes | | | |
| 90-day all-cause mortality | 17 (18.1) | 27 (29.0) | 0.111 |
| ICU LOS (days) | 12.0 (7.0–28.0) | 17.5 (9.0–31.0) | 0.075 |
| Hospital LOS (days) | 26.0 (15.0–37.0) | 28.5 (21.0–45.8) | 0.201 |
| Duration of mechanical ventilation (days)* | 7.0 (5.0–15.0) | 7.0 (3.0–15.0) | 0.241 |
| Duration of vasopressors (days)† | 4.0 (2.0–6.0) | 5.0 (3.0–8.0) | 0.043 |
| Δ lactate, 12 h (mmol/L) | 1.1 (0.3–2.0) | 0.0 (−0.2 to 0.8) | <0.001 |
| Δ lactate, 24 h (mmol/L) | 1.4 (0.3–2.2) | 0.4 (−0.4 to 1.6) | 0.001 |
| Δ CRP, 72 h (mg/L) | 41.5 (−5.5 to 92.5) | 7.0 (−41.5 to 53.0) | 0.006 |
| Δ CRP, 168 h (mg/L) | 82.0 (27.0–148.8) | 56.0 (0.0–152.0) | 0.161 |
| Δ APTT, 72 h (s) | 3.3 (−2.7–8.3) | 0.6 (−2.8 to 5.3) | 0.298 |
| Δ APTT, 168 h (s) | 5.3 (−0.4 to 15.6) | 3.0 (−1.5 to 8.8) | 0.220 |

Data were presented as *n* (%) and median (interquartile range).
APTT: Activated partial thromboplastin time; CRP: C-reactive protein; ICU: Intensive care unit; LOS: Length of stay; SFI: Shenfu injection.
* Including patients who received mechanical ventilation (53 *vs*. 57 patients in the SFI and control groups, respectively).
† Including patients who received vasopressor support (60 *vs*. 63 patients in the SFI and control groups, respectively).

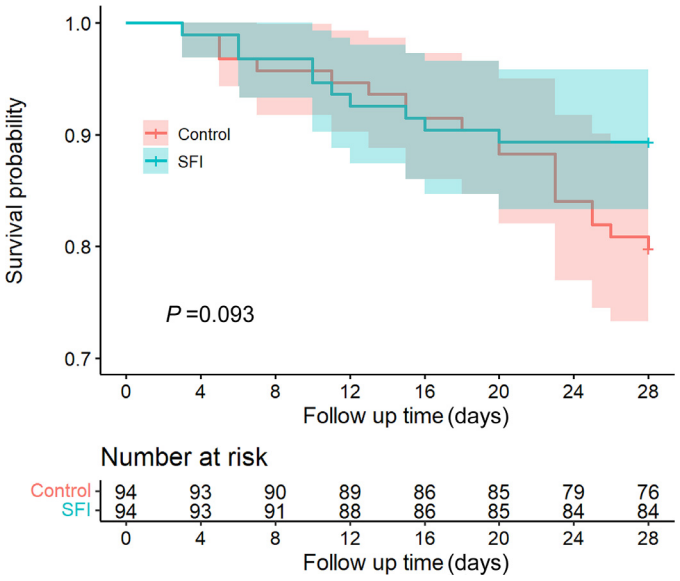


**Figure 2.** Kaplan–Meier estimates of survival rate distribution among patients in the SFI and control groups. Hazard ratio for mortality: 0.52; 95% CI: 0.24 to 1.12; *P*=0.093. *P*-value was calculated using a Cox proportional hazards model that included the randomized trial group.
CI: Confidence interval; SFI: Shenfu injection.

ing the early stage.[17,26] Therefore, we included patients with sepsis or septic shock within a maximum of 24 h after diagnosis. A meta-analysis revealed that SFI could not decrease 28-day mortality for patients with septic shock.[11] However, a trend for decrease in 28-day mortality was observed for patients with arterial lactate levels between 4.5 mmol/L and 7 mmol/L. In our subgroup analysis, we investigated the subgroups of patients who might benefit from the use of SFI according to the age, disease severity, lactate levels at admission, and the presence or absence of shock. The subgroup analysis did not show benefits of treatment with SFI. In agreement with our study, the study reported by Zhang et al.[5] did not show significant survival benefit after treatment with SFI in terms of 28-day all-cause

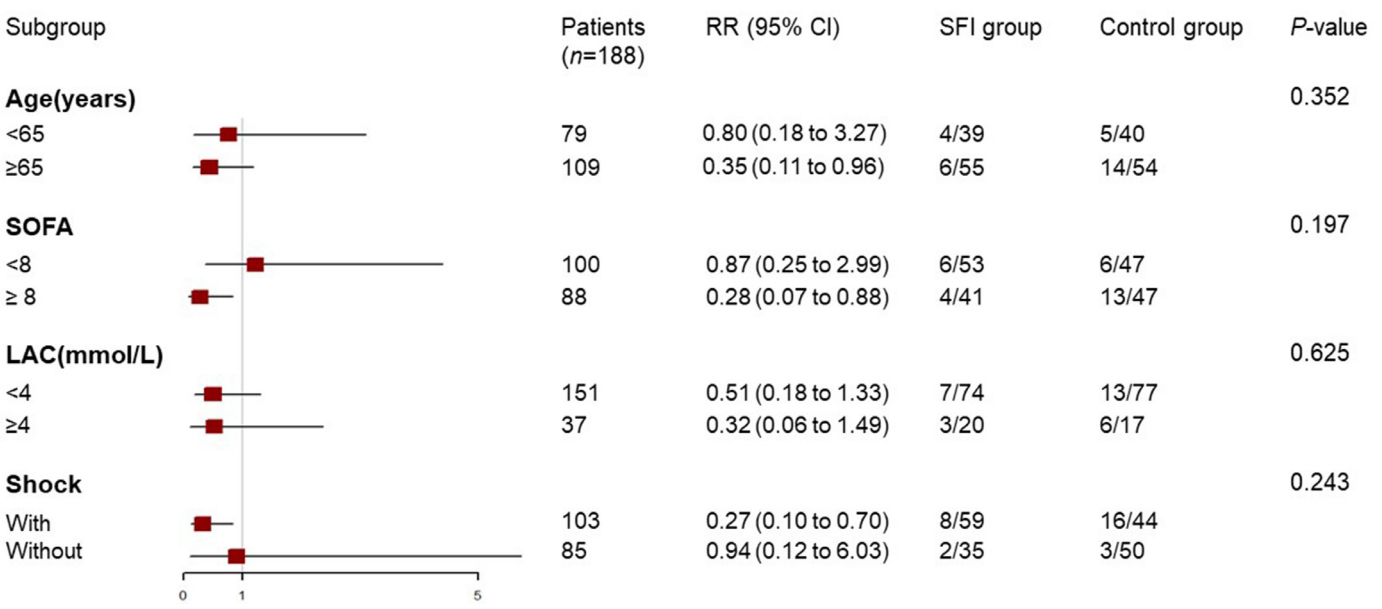


**Figure 3.** Subgroup analysis of mortality at 28 days. The forest map shows the grouped variables of the subgroup analysis, RR, 95% CI for each subgroup, as well as the number of patients (denominator) and number of deaths (numerator) in each subgroup.
CI: Confidence interval; LAC: Lactate; RR: Relative risk of mortality; SFI: Shenfu injection; SOFA: Sequential Organ Failure Assessment.

mortality. However, there remain two main differences between these investigations. Firstly, almost all patients enrolled in the present study had undergone operation, which ensured effective removal of the infection source. In the previous study, the most common infection site was the respiratory tract, which indicated that most participants were internal medical patients. Secondly, the enrollment time of participants may differ between the two studies due to the different inclusion criteria. We enrolled septic patients with hypoperfusion instead of septic shock patients; hence, there was no requirement for re-evaluation after fluid resuscitation. Therefore, our research study further investigated the effects of SFI in septic patients under different conditions.

Fundamental studies have shown that ginsenoside (a major active ingredient of SFI) plays an important role in scavenging free radicals, inhibiting inflammatory mediators, and regulating host immune response.[8,27–29] In this trial, we recorded a significant change in CRP levels within 3 days between the SFI and control groups. In a rat model of sepsis, SFI ameliorated the mucosal barrier function in a dose-dependent manner.[30] Basic research also demonstrated that SFI could improve the coagulation function. In the study conducted by Zhang et al.,[31] SFI decreased intercellular adhesion molecule 1 (ICAM-1) expression. This observation suggested that SFI downregulates the expression of vascular adhesion molecules and reduces endothelial activation and vascular permeability. Similarly, further clinical and basic research suggested that SFI improved sublingual microcirculatory perfusion in patients with septic shock, potentially through the inhibition of endothelial dysfunction.[32] However, in our study, SFI did not exert a significant effect on the coagulation function.

This study has several limitations. Firstly, regarding sample size calculation, we expected a reduction in mortality by >50% in the intervention group compared with the control group, which was difficult to achieve. Consequently, this criterion may negatively influence the interpretation of results. Secondly, this study included patients with sepsis within a maximum of 24 h after diagnosis. The study enrollment required apparent clinical evidence of organ hypoperfusion, which could have delayed the administration of SFI in the treatment group. Thirdly, our study was an assessor-blinded randomized controlled trial. In our study, the participants were critically ill and most of them were sedated; therefore, it was not necessary to blind these patients. SFI is yellow in appearance, and clinicians are aware of this intervention. However, the endpoint indicators assessed in the investigation were objective. Fourthly, all participants were enrolled from the ICUs of four teaching hospitals in China, thereby limiting generalizability to other countries or regions. Finally, we did not record the total amount of vasoactive drugs used in each group at the time of data collection, which may have affected the results.

## Conclusions

SFI plus standard therapy did not significantly decrease 28-day all-cause mortality for septic patients with hypoperfusion and TCM syndrome with Yang-Qi deficiency. Treatment with SFI can promote the recovery of lactic acid levels in septic patients with hypoperfusion.

## Author Contributions

**Di Liu:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Tingting Pan:** Writing – review & editing, Data curation, Conceptualization. **Xiang Li:** Validation, Supervision, Resources. **Duming Zhu:** Validation, Resources. **Yingchuan Li:** Validation, Resources. **Hongyu He:** Resources. **Fang Wu:** Resources. **Lijing Jiang:** Resources. **Yang Chen:** Project administration, Data curation. **Xiaoli Wang:** Data curation. **Jialin Liu:** Supervision, Investigation, Formal analysis, Conceptualization. **Ruoming Tan:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hongping Qu:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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## Ethics Statement

This study was approved by the Ruijin Hospital Ethics Committee of Shanghai Jiaotong University School of Medicine and was registered in the Chinese Clinical Trial Registry (ChiCTR1800020435). Written informed consent was obtained from the patient or their legal representative. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our researc

## Conflict of 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.

## Data Availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2024.01.007.

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