



## Efficacy and safety of Shenfu injection for septic shock: A systematic review and meta-analysis of randomized controlled trials

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### ABSTRACT

**Objective:** To evaluate the efficacy and safety of Shenfu injection (SFI) combined with standard therapy versus standard therapy for septic shock, three groups of patients with septic shock were analyzed based on the level of mean arterial lactate. They were mean arterial lactate level < 4.5 mmol/L, 4.5 mmol/L ≤ mean arterial lactate level < 7 mmol/L and mean arterial lactate level ≥ 7 mmol/L.

**Methods:** Randomized controlled trials (RCT) from PubMed, Cochrane library, Embase, CENTRAL, SinoMed, Wanfang, CNKI, and Weipu (VIP) databases from the inception to September 2018 were searched. Relative risks (RR), weighted mean difference (WMD), along with 95% confidence interval (95%CI) were used to analyze the main outcomes. Statistical analysis was performed using Rev.Man 5.3. The qualities of the involved studies were assessed by the ROB according to the Cochrane handbook.

**Results:** 19 randomized controlled trials with 1505 participants were included. Compared with standard therapy, SFI plus standard therapy cannot decrease the 28-day mortality for all of the three groups. Compared with the other two subgroups (mean arterial lactate level < 4.5 mmol/L and mean arterial lactate level ≥ 7 mmol/L), the 4.5 mmol/L ≤ mean arterial lactate level < 7 mmol/L group has a trend to decrease 28-day mortality (RR: 0.67; 95% CI: 0.38–1.19; *P* = 0.17). In addition, adding SFI could have further increased mean arterial pressure (MAP) at 6-hours (RR: 7.05; 95% CI: 4.14–9.97) and further normalized heart rate (HR) when compared with standard therapy (RR: -17.48; 95% CI: [-19.39–(-15.57)]).

**Conclusion:** For septic shock patients with 4.5 mmol/L ≤ mean arterial lactate level < 7 mmol/L, when the Traditional Chinese Medicine syndrome meet Yang-Qi deficiency, clinicians could choose SFI as a supplementary drug. But further high-quality and large-scale RCT should be performed to verify it.

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### 1. Introduction

Despite the updated sepsis definition and surviving sepsis campaign (SSC) guidelines, septic shock remains associated with high mortality [1–5]. According to the 2016 SSC guideline [5], vasopressor therapy is one of the cornerstones in the management of septic shock when fluid resuscitation is insufficient to maintain a mean arterial pressure (MAP) above 65 mmHg. In terms of vasopressor agents, norepinephrine (NE) is the recommended first-line vaso-

pressor [6]. However, in order to maintain the MPA target, high doses of NE may be required, which may increase the risk of life-threatening arrhythmias, immunosuppression and mortality [7–9].

Recently, numerous studies were performed to hunt the adjunctive treatment [10–12]. According to the latest randomized controlled trial published on intensive care medicine, there was no significant difference in 28-day mortality rate between the terlipressin group (40%) and the NE group (38%) (odds ratio 0.93 [95% CI 0.55–1.56]; *P* = 0.80). Besides, serious adverse events were more common in the terlipressin group than in the NE group (30% vs 12%; *P* < 0.001) [13]. Therefore, though NE is not more effective than terlipressin in decreasing 28-day mortality, NE could decrease serious adverse events in septic shock patients compared with terlipressin. Herein, to correct hypotension in septic shock, NE still is the first-line recommended vasopressor. Johan Martensson et al.

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[14] performed a review, and the meta-analysis showed that terlipressin cannot decrease the mortality of septic shock compared with NE.

The Shenfu injection (参附注射液, SFI) originated from a classic formula in traditional Chinese medicine and was widely used as a common vasopressor in national hospital emergency department [15–16]. Despite numerous new studies that investigated the efficacy of SFI for septic shock, there remains uncertainly whether SFI is beneficial for patients with septic shock or not, especially for mortality. This review aims to perform an updated systematic review to evaluate the efficacy and safety of SFI for septic shock.

## 2. Methods

This meta-analysis was conducted according to the recommendations and checklist from the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [17].

### 2.1. Search strategy

PubMed, Cochrane Library, EMBASE, Chinese BioMedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), Wan-fang Database were searched from inception to August 2018. Moreover, the International Clinical Trials Registry Platform, the Chinese Clinical Trial Registry and the reference section of each study will also be searched. The detailed search strategy could be seen by [https://www.crd.york.ac.uk/PROSPEROFILES/107895\\_STRATEGY\\_20180823.pdf](https://www.crd.york.ac.uk/PROSPEROFILES/107895_STRATEGY_20180823.pdf).

### 2.2. Eligibility criteria of original studies

Inclusion criteria: (1) Participants: diagnosed as septic shock, without limitation in gender and ethnicity, the diagnostic criteria should be explicit and normative; (2) The intervention was SFI plus standard therapy; (3) The comparison intervention was standard therapy, including fluid resuscitation, vasopressin, positive inotropic agents, mechanical ventilation and other symptomatic therapy; (4) The following outcomes were evaluated: ① primary outcome: mortality in 28-day. ② Secondary outcomes: Mean arterial pressure (MAP), serum lactic acid and heart rate (HR) at 6-hours; vasoactive drugs doses; adverse effect. (5) The study design was a randomized controlled trial.

A study was excluded if it was: (1) A study that administered SFI as a control was excluded; (2) A study with review, comments, duplicate publication and abstract only was excluded.

### 2.3. Study selection

Two reviewers independently identified trials for inclusion criteria by screening the title and abstract of each record and retrieved their full-text if necessary. Any disagreement between two reviewers was solved by discussion with the third reviewer. Otherwise, the agreement was harmonized by consensus.

### 2.4. Data extraction and quality assessment

We designed a pre-defined data extraction form and two reviewers independently extracted the following information from the selected trials: the first author, published year, sample size, mean age, mean arterial lactate level, intervention, control, outcomes. Any disagreement between two reviewers was discussed with the third reviewer until a consensus was reached.

Two reviewers assessed the risk of bias for each study using the Cochrane risk of bias tool. The Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and conflict of interest were taken into account for assessment. Disagreement about the risk of assessment was tackled by discussion between another two reviewers.

### 2.5. Data synthesis

RevMan software (Version 5.3) provided by the Cochrane Collaboration was used for data analysis. Dichotomous variable was presented as relative risk (RR). Continuous outcome was presented as mean difference and its 95% confidential interval (CI). Statistical heterogeneity was predefined as a  $P$  value of  $<0.05$  with the Chi-square test or an  $I^2$  test value of  $>50\%$ . When significant heterogeneity was identified, we intended to perform several sensitivity analyses to investigate the possible sources for heterogeneity. Publication bias was assessed by using a funnel plot where there were more than ten trials in a meta-analysis. The level of statistical significance was set at a  $P$  value of  $<0.05$ .

### 2.6. Subgroup analysis

Subgroup analysis was performed based on the threshold of mean arterial lactate level before enrollment in this meta-analysis.

## 3. Results

### 3.1. Description of included studies

We identified 636 records based on search strategy, and 342 potentially eligible records were obtained after removing duplicate publications. After screening the titles and abstracts, a total of 308 studies were excluded. 19 studies [18–36] with 1505 participants were included, 14 studies [18–31] were included in the meta-analysis and 15 studies were excluded with various reasons (Fig. 1). The characteristics of the included studies were presented as Table 1 shows. The summary of meta-analysis was described as Table 2 shows.

### 3.2. Risk of bias of included studies

The risk of bias assessment is shown in Supplemental Fig. 1a, b. Almost all of the included trials had low risk of bias in selective outcome reporting and incomplete outcome data. The main source of bias in the included trials was the lack of detail in describing the allocation concealments.

### 3.3. 28-day mortality

Seven studies [18–24] with 568 participants employed 28-day mortality as outcome measure. Of these, four studies [18–21] meet the threshold of mean arterial lactate level  $<4.5$  mmol/L, two studies [19,22] meet the threshold  $4.5$  mmol/L  $\leq$  mean arterial lactate level  $<7$  mmol/L, and two studies [23,24] meet the threshold of mean arterial lactate level  $\geq 7$  mmol/L. Since there was no obvious heterogeneity among included studies ( $I^2 = 0\%$ ), thus we selected the fixed-effects model to analysis 28-day mortality. For subgroup analysis, SFI plus standard therapy cannot decrease the 28-day mortality for all of the three groups. Compared with the other two subgroups,  $4.5$  mmol/L  $\leq$  mean arterial lactate level  $<7$  mmol/L group has a trend to decrease 28-day mortality (RR: 0.67; 95% CI: 0.38–1.19;  $P = 0.17$ ) (Fig. 2).

### 3.4. Arterial lactate at 6-hours

Eight studies [23,25–31] employed arterial lactate at 6-hours as outcome measure. Four of eight included studies [25–28] meet the threshold  $4.5$  mmol/L  $\leq$  mean arterial lactate level  $<7$  mmol/L, and the other four studies [23,29–31] meet the threshold of mean arterial lactate level  $\geq 7$  mmol/L. Random effect model was selected due to the heterogeneity ( $I^2 > 50\%$ ). Compared with standard therapy, adding SFI could further decreased arterial lactate level at 6-hours in patients with  $4.5$  mmol/L  $\leq$  mean arterial lactate level  $<7$  mmol/L (RR:  $-1.21$ ; 95% CI:  $[-1.49, -0.93]$ ). Whereas, for patients with mean arterial lactate level  $\geq 7$  mmol/L, adding

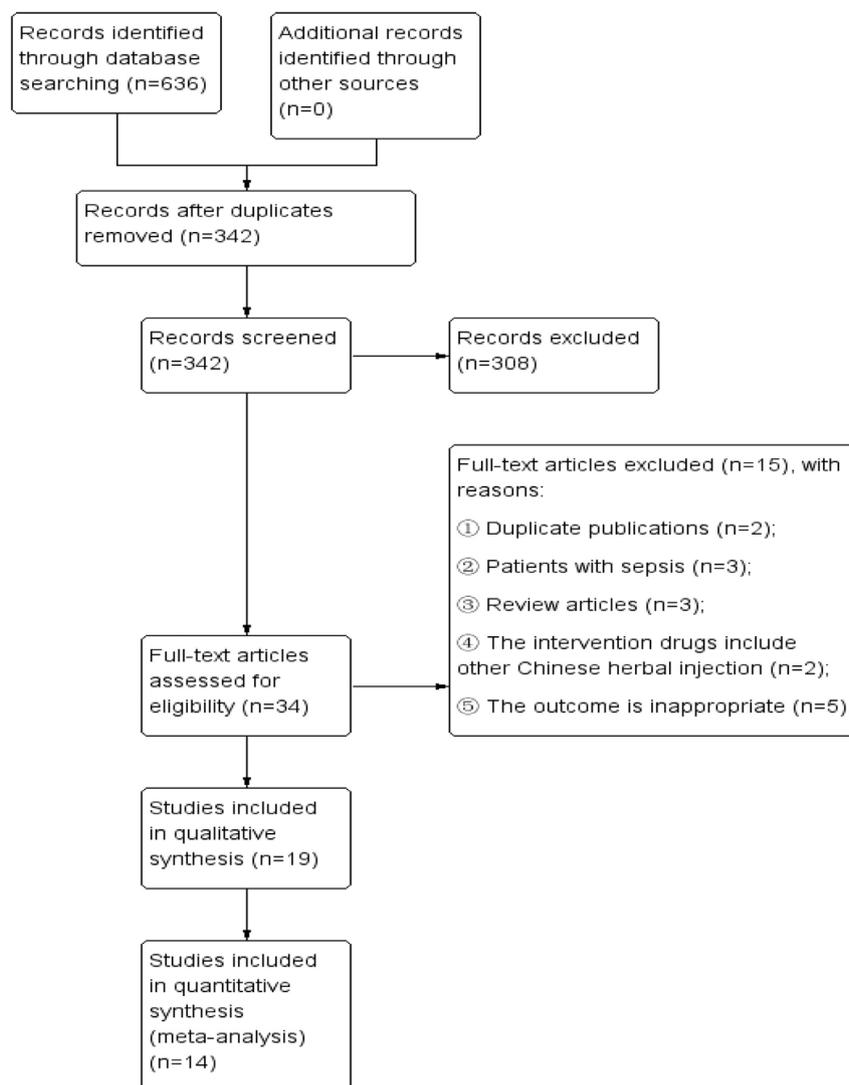


Fig. 1. Study flow diagram.

SFI couldn't further decreased arterial lactate level at 6-hours (RR:  $-0.45$ ; 95% CI:  $-1.94$ – $1.03$ ) (Fig. 3).

### 3.5. MAP at 6-hours

There were six studies [23,26–29,31] reported MAP at 6-hours, we selected random effect model since there was obvious heterogeneity in both of the two subgroups ( $I^2 > 50\%$ ). Among these studies, three studies [26–29] included patients with  $4.5 \text{ mmol/L} \leq \text{mean arterial lactate level} < 7 \text{ mmol/L}$ , in this subgroup, the meta-analysis showed that compared with standard therapy, adding SFI could increase MAP at 6-hours (RR:  $7.05$ ; 95% CI:  $4.14$ – $9.97$ ). However, for patients with mean arterial lactate level  $\geq 7 \text{ mmol/L}$ , SFI plus standard therapy cannot further increased MAP at 6-hours when compared with standard therapy alone (RR:  $2.67$ ; 95% CI:  $-0.56$ – $5.90$ ) (Fig. 4).

### 3.6. HR at 6-hours

Five studies [23,26–28,30] employed HR at 6-hours as outcome measure. There was obvious heterogeneity among these included studies, thus, random effect model was utilized for statistical analysis. Three of five studies [26–28] included patients with  $4.5 \text{ mmol/L} \leq \text{mean arterial lactate level} < 7 \text{ mmol/L}$ , the results indicated that SFI plus standard therapy could further normalized HR when compared with standard therapy (RR:  $-17.48$ ; 95% CI:  $[-19.39$ –

$-15.57]$ ). The other two studies [23,30] included patients with mean arterial lactate level  $\geq 7 \text{ mmol/L}$ , we found that SFI plus standard therapy cannot further decreased HR at 6-hours when compared with standard therapy alone (RR:  $-11.03$ ; 95% CI:  $-30.38$ – $8.33$ ) (Fig. 5).

### 3.7. Vasoactive agents using

There were six studies [18–20,27,32,34] provided the data of vasoactive agents using. As the endpoint outcome measure was not unified, we listed the endpoint in Supplemental Table 1. From the known mean arterial lactate level, we found SFI cannot decrease the using of vasoactive agents ( $P > 0.05$ ).

### 3.8. Safety assessment of SFI

There were six studies [19,32–36] provided the details of safety information. We found that SFI didn't increase side effect. Moreover, SFI may have protective effect on renal and liver function. Thus, it is safe to use SFI treat septic shock (Supplemental Table 2).

### 3.9. Publication bias analysis

The publication bias was explored via funnel plot (Fig. 6). Except Li MQ et al. and Li Y et al.'s studies were published in Eng-

**Table 1**  
The characteristics of the included studies

Study ID	Sample size (N)	Mean age (x ± s, years)	Intervention	Control	Outcome measure	Baseline of arterial lactate (mmol/L)
Li MQ et al., 2015 [41]	N = 45 (T:21;C:24)	56.4 ± 15.2	EGDT,NE,Dobutamine +100 ml SFI ivgtt q12 h	EGDT,NE,Dobutamine	a,b,c,d,e	T:3.35 ± 1.87 C:3.19 ± 1.48
Li Y et al., 2016 [28]	N = 199 (T:102;C:97)	T:54.0 ± 16.9 C:54.0 ± 16.9	Routine treatment + SFI 30 ml/h pump	Routine treatment	a,e,f	NA
Xiao YC et al., 2017 [29]	N = 71 (T:36;C:35)	T:65.72 ± 12.24 C:66.42 ± 13.75	Routine treatment + SFI 100 ml + 5% GS 250 ml ivgtt qd	Routine treatment+0.9% NS 100 ml + 5% GS 250 ml ivgtt qd	a,e	T:4.52 ± 1.30 C:4.06 ± 1.41
Zhou L et al., 2013 [30]	N = 75 (T:36;C:39)	T:69.72 ± 13.4 C:67.35 ± 15.8	6 h EGDT + 24 h bundle+100 ml SFI + 5% GS 250 ml ivgtt qd	6 h EGDT + 24 h bundle+5% GS 250 ml ivgtt qd	a	T:3.61 ± 1.24 C:4.11 ± 1.97
Lai ZZ et al., 2018 [27]	N = 50 (T:25;C:25)	T:55.4 ± 17.5 C:50.2 ± 13.6	MV,EGDT,NE,Dobutamine 5µg/(kg.min) + 100 ml SFI ivgtt q12 h	MV,EGDT,NE,Dobutamine 5µg/(kg.min)	a	T:4.5 ± 1.1 C:4.6 ± 1.2
Dong GY et al., 2014 [31]	N = 91 (T:46;C:45)	68.34	6 h EGDT + 100 ml SFI + 0.9% NS 250 ml ivgtt qd	6 h EGDT + 0.9% NS 250 ml ivgtt qd	a,c,d	T:11.95 ± 3.70 C:7.25 ± 3.89
Zhang SY et al., 2017 [32]	N = 71 (T:36;C:35)	60.23 ± 5.1	6 h EGDT +24 h bundle + 100 ml SFI + 5% GS 250 ml ivgtt qd	6 h EGDT + 24 h bundle	a	T:7.32 ± 4.98 C:7.57 ± 4.02
Li P et al., 2012 [33]	N = 60 (T:30;C:30)	T:54.12 ± 12.45 C:52.53 ± 13.7	Routine treatment + SFI 100 ml + 5% GS 250 ml ivgtt qd + Ulinastatin 30wU + 30 ml NS iv tid	Routine treatment	b	T:6.49 ± 2.13 C:6.93 ± 1.85
Liu WM et al., 2014 [50]	N = 108 (T:54;C:54)	NA	6 h EGDT + 24 h bundle + NE + 100 ml SFI pump	6 h EGDT + 24 h bundle + NE	b,c,d	T:5.94 ± 1.53 C:6.07 ± 1.26
Wu DJ et al., 2014 [11]	N = 81 (T:42;C:39)	T:49.2 ± 16.5 C:48.6 ± 16.2	6 h EGDT + 60 ml SFI pump	6 h EGDT	b,c,d,e	T:6.8 ± 1.2 C:7.0 ± 1.3
Xu LW et al., 2012 [38]	N = 49 (T:22;C:27)	T:54.0 ± 0.3 C:55.0 ± 0.2	6 h EGDT + 24 h bundle + dopamine + 100 ml SFI pump	6 h EGDT + 24 h bundle + dopamine	b,c,d	T:5.41 ± 1.70 C:5.52 ± 1.40
Liu Y et al., 2017 [34]	N = 60 (T:30;C:30)	T:66.73 ± 5.78 C:66.57 ± 5.49	6 h EGDT + 100 ml SFI + 0.9% NS 100 ml ivgtt q12 h	6 h EGDT + 0.9% NS 100 ml ivgtt q12 h	b,c	T:7.13 ± 1.56 C:7.12 ± 1.67
Xu Y et al., 2012 [12]	N = 98 (T:48;C:50)	T:57 ± 7 C:60 ± 8	Routine treatment + 100 ml SFI pump	Routine treatment	b,d	T:11.2 ± 2.5 C:11.9 ± 3.2
Yin MX et al., 2017 [48]	N = 60 (T:30;C:30)	T:58.45 ± 6.32 C:59.12 ± 5.45	6 h EGDT + 100 ml SFI + 0.9% NS 150 ml ivgtt q12 h	6 h EGDT + 0.9% NS 150 ml ivgtt q12 h	b,c	T:7.31 ± 0.47 C:7.15 ± 0.87
Sun SR et al., 2008 [35]	N = 60 (T:34;C:26)	NA	6 h EGDT + 60 ml SFI pump	6 h EGDT	e,f	NA
Zhang W et al., 2011 [13]	N = 93 (T:48;C:43)	NA	6 h EGDT + 60 ml SFI pump	6 h EGDT	e,f	NA
Tian XM et al., 2017	N = 80 (T:40;C:40)	T:51.46 ± 19.32 C:50.74 ± 18.95	Routine treatment + SFI 100 ml + 5% GS 250 ml ivgtt qd	Routine treatment	f	T:4.27 ± 1.35 C:4.3 ± 1.4
Li CL et al., 2014	N = 68 (T:34;C:34)	T:34.8 ± 19.2 C:36.5 ± 21.6	Routine treatment + SFI 50 ml ivgtt qd	Routine treatment	f	NA
Lin MJ et al., 2012	N = 120 (T:60;C:60)	NA	Routine treatment + dopamine + 100 ml SFI + 5%GS 500 ml ivgtt qd	Routine treatment + dopamine	f	NA

Note: T = treatment group; C = control group; NA = not applicable; EGDT = early goal-directed therapy; SFI = Shenfu injection; NE = norepinephrine; a = 28-day mortality; b = Arterial lactate at 6-hours; c = mean arterial pressure at 6-hours; d = heart rate at 6-hours; e = vasoactive agent using; f = side effect.

lish, the others were published in Chinese academic journals, the potential of publication bias couldn't be excluded.

#### 4. Discussion

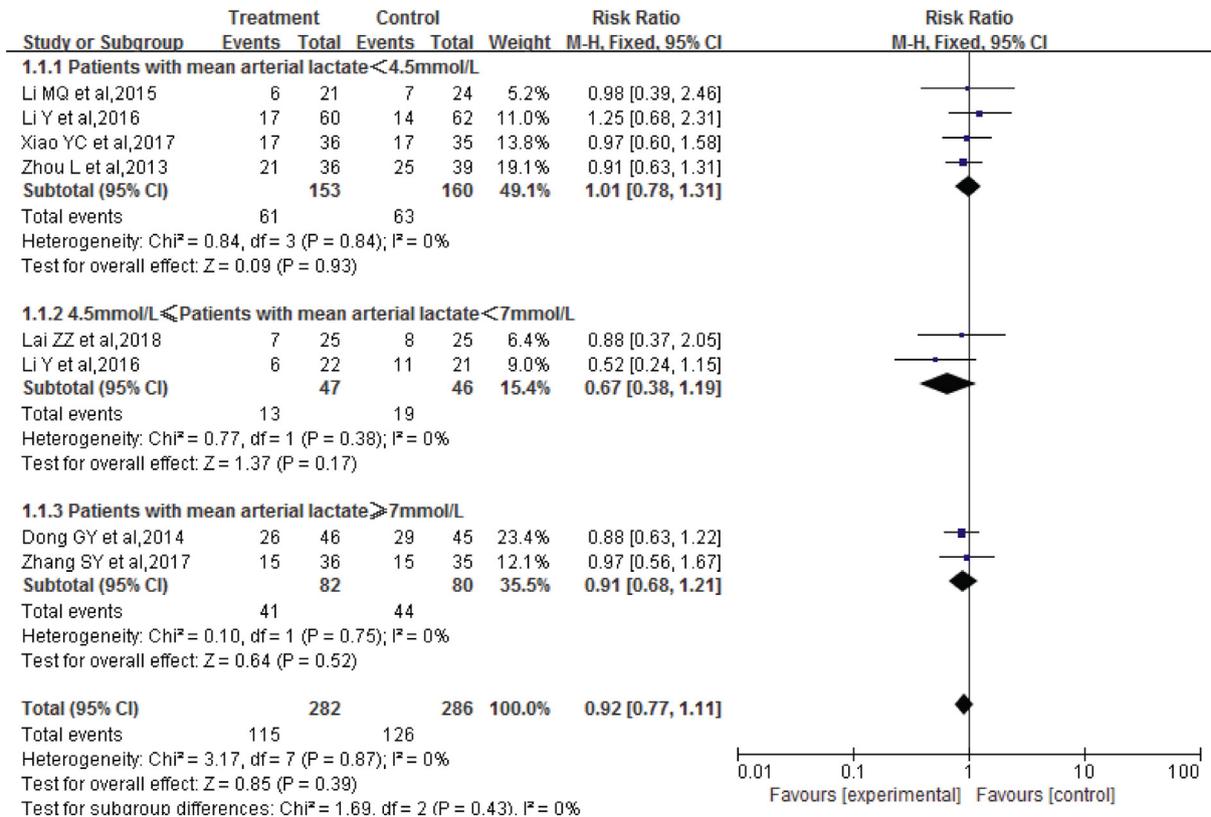
To our best knowledge, this is the first meta-analysis to evaluate the efficacy and safety of SFI for different participants with septic shock according to the level of arterial lactate. The main

findings of the review are as follows: first, compared with standard therapy, SFI plus standard therapy couldn't decrease 28-day mortality for all kinds of patients with septic shock whatever the level of arterial lactate. Whereas, when analyzed the subgroup results, we found that SFI has a trend to decrease the 28-day mortality for patients with  $4.5 \text{ mmol/L} \leq \text{arterial lactate} < 7 \text{ mmol/L}$ . Second, it is interesting that there were significantly statistic difference between patients with  $4.5 \text{ mmol/L} \leq \text{arterial lactate} < 7 \text{ mmol/L}$  and patients with arterial lactate  $\geq 7 \text{ mmol/L}$  in arterial lactate,

**Table 2**  
Summary of meta-analysis

Outcome	Subgroup	No. of studies	No. of participants	Effect size (95% CI)	I <sup>2</sup>	P
28-day mortality	a	4	313	RR, 1.01 [0.78, 1.31]	0	0.93
	b	2	93	RR, 0.67 [0.38, 1.19]	0	0.17
	c	2	162	RR, 0.91 [0.68, 1.21]	0	0.52
Arterial lactate at 6-hours	b	4	298	WMD, -1.21 [-1.49, -0.93]	0	<0.00001
	c	4	309	WMD, -0.45 [-1.94, 1.03]	96%	0.55
MAP at 6-hours	b	3	238	WMD, 7.05 [4.14, 9.97]	70%	<0.00001
	c	3	211	WMD, 2.67 [-0.56, 5.90]	86%	0.11
HR at 6-hours	b	3	238	WMD, -17.48 [-19.39, -15.57]	45%	<0.00001
	c	2	189	WMD, -11.03 [-30.38, 8.33]	97%	0.26

Note: MAP, mean arterial pressure; HR, heart rate; a, mean arterial lactate level < 4.5 mmol/L; b,  $4.5 \text{ mmol/L} \leq \text{mean arterial lactate level} < 7 \text{ mmol/L}$ ; c, mean arterial lactate level  $\geq 7 \text{ mmol/L}$ ; CI, confidence interval; RR, relative risks; WMD, weighted mean difference.

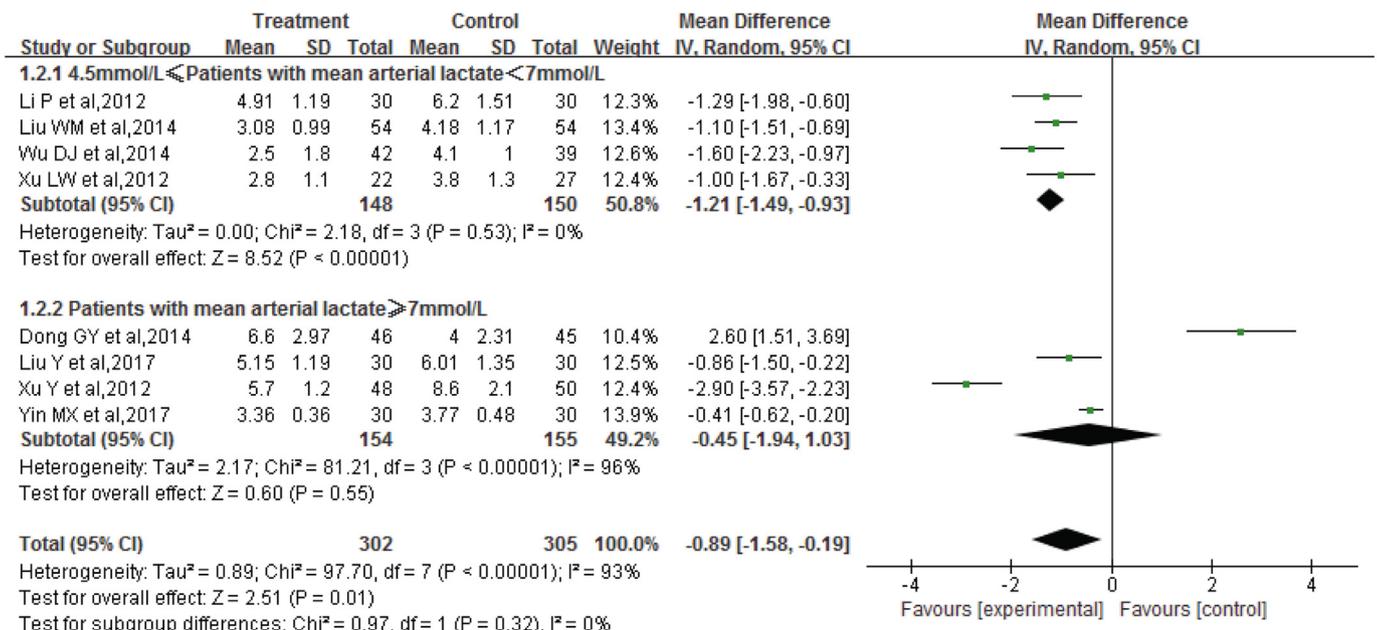


**Fig. 2.** 28-day mortality. Note: for subgroup analysis, SFI plus usual therapy cannot decrease the 28-day mortality for all of the three groups. Compared with the other two subgroups, 4.5 mmol/L ≤ mean arterial lactate level < 7 mmol/L group has a trend to decrease 28-day mortality.

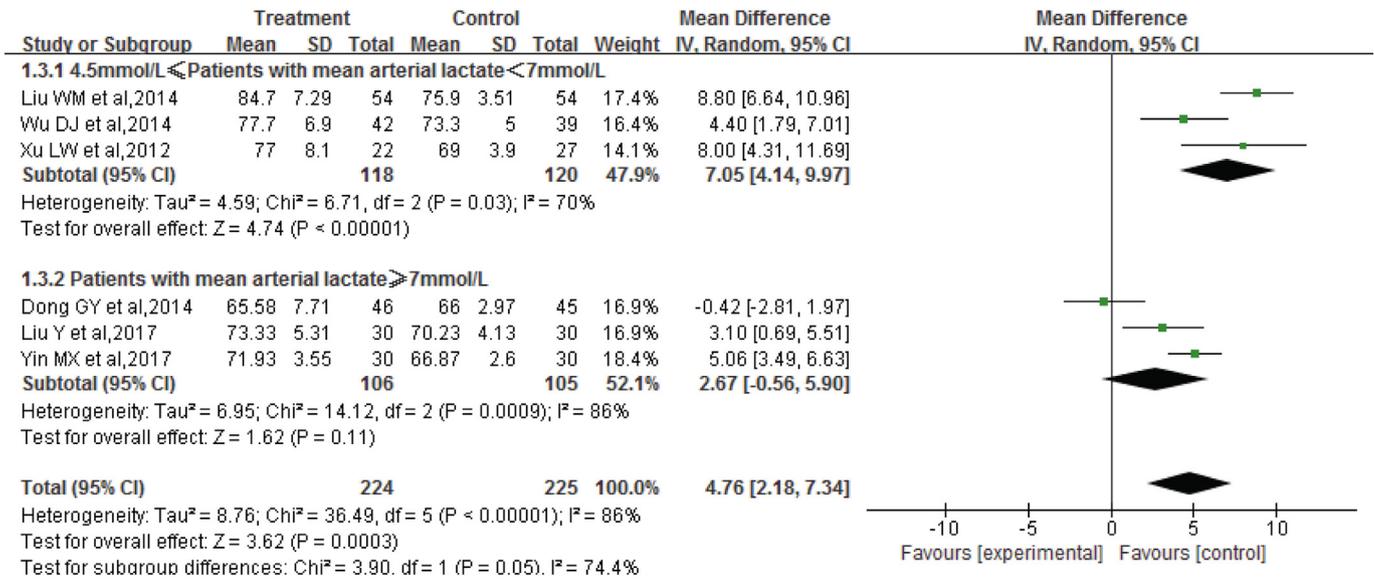
MAP, HR at 6 h respectively. Third, in terms of vasoactive agents' uses, though the endpoint of outcome measure was not unified, we found that there was no statistic difference between SFI plus standard therapy and standard therapy for patients with arterial lactate ≤ 4.5 mmol/L in all of the single studies. Due to the lack of arterial lactate level, we cannot analyze whether SFI plus standard therapy could decrease the doses of vasoactive drugs compared with standard therapy in another two groups (4.5 mmol/L

L ≤ patients with arterial lactate < 7 mmol/L and patients with arterial lactate ≥ 7 mmol/L).

As we all know, the effect of SFI is restoring Yang and rescuing patients from collapse, all of participants in the included studies meet the TCM syndrome Yang-Qi deficiency. We acknowledge that the level of arterial lactate is affected by many factors, such as the infectious diseases and vasoactive agents. Hence, it is difficult for clinicians choosing an appropriate timing or criterion to use SFI



**Fig. 3.** Arterial lactate at 6-hours. Note: compared with usual therapy, adding SFI could further decreased arterial lactate level at 6-hours in patients with 4.5 mmol/L ≤ mean arterial lactate level < 7 mmol/L. Whereas, for patients with mean arterial lactate level ≥ 7 mmol/L, adding SFI couldnot further decreased arterial lactate level at 6-hours.



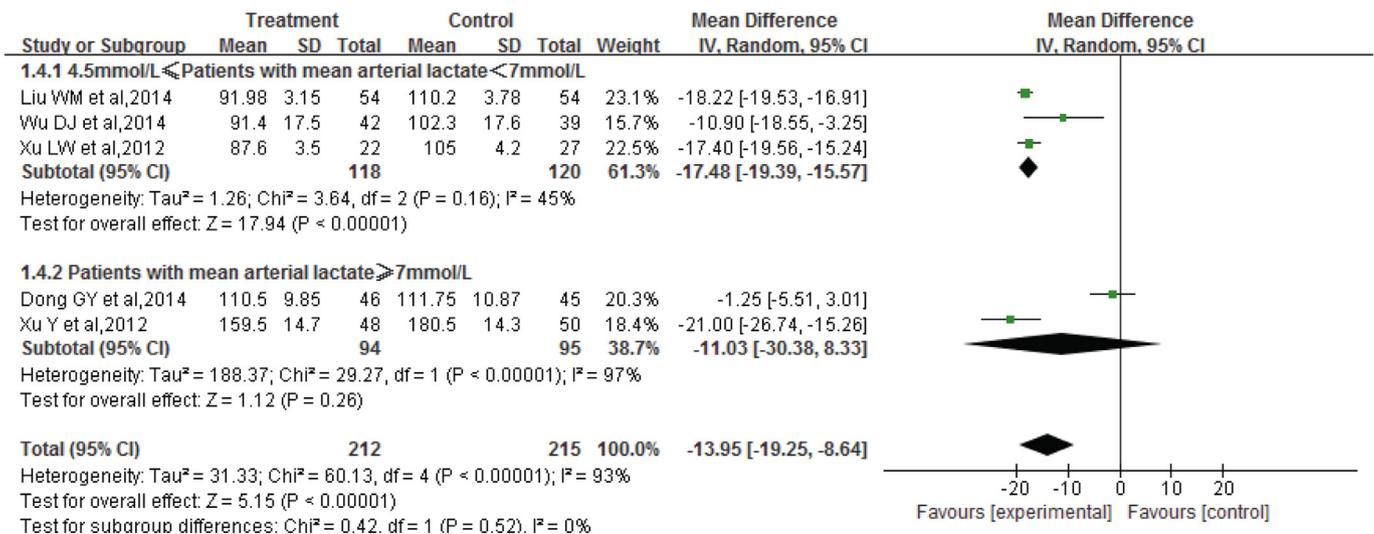
**Fig. 4.** MAP at 6-hours. Note: compared with usual therapy, adding SFI could increase MAP at 6-hours. However, for patients with mean arterial lactate level  $\geq 7$  mmol/L, SFI plus usual therapy cannot further increase MAP at 6-hours when compared with usual therapy alone.

on septic shock. Through our work, we did find that SFI maybe a suitable assist drug for septic shock patients with  $4.5 \text{ mmol/L} \leq$  mean arterial lactate level  $< 7 \text{ mmol/L}$ . Meanwhile, they should meet the Traditional Chinese Medicine syndrome Yang-Qi deficiency.

Though there exist three similar reviews [37–39], there are some differences between our review and the three reviews. First, we found that some of the included studies in the previous three reviews didn't meet the criterion of septic shock, since some studies included sepsis without shock. Second, in terms of the endpoint of mortality, there remains uncertain for clinicians to choose. Through our review, we found that it cannot decrease 28-day mortality in all of the three subgroup patients, but there exists a trend to decrease 28-day mortality in  $4.5 \text{ mmol/L} \leq$  patients with arterial lactate  $< 7 \text{ mmol/L}$  compared with the other two groups. In addition, we chose arterial lactate at 6 h because the surviving sepsis campaign guidelines recommended re-measuring arterial lactate within 6 h, and previous study showed that 6 h from septic shock recognition was the optimal timing of lactate re-measurement for predicting mortality [40–41]. We didn't choose lactate clearance

rate as the endpoint because Seung Mok Ryoo et al. [42] demonstrated that serum lactate level at 6 h can be a more effective tool for prognosis of septic shock patients compared with lactate clearance. Third, we selected vasoactive drugs doses as an important endpoint, partly because of the side effect of NE and dopamine [7,9]. Importantly, the intervention must be based on the specific patients, other than the all kinds of patients. Thus in our review, we divided the patients with septic shock into three subgroups according to the level of lactate. Interestingly, the results showed that SFI plus standard therapy is more effective than standard therapy in increasing MAP, normalizing HR, and reducing the level of arterial lactate in  $4.5 \text{ mmol/L} \leq$  patients with arterial lactate  $< 7 \text{ mmol/L}$  group.

Shenfu injection, originated from ancient formula in traditional Chinese medicine, is composed of red Radix Ginseng (Hongshen) and Radix Aconitum Carmichaeli (Fupian) [43]. HPLC-MS/MS analysis of SFI is explicit by Yang H et al.'s study [44]. The main active components of SFI include ginsenoside and aconite total alkaloids (Supplemental Fig. 2) [45]. Numerous animal studies investigated the pharmacological mechanism of SFI [46–48]. Guo ZJ et al. [49]



**Fig. 5.** HR at 6-hours. Note: for patients with  $4.5 \text{ mmol/L} \leq$  mean arterial lactate level  $< 7 \text{ mmol/L}$ , the results indicated that SFI plus usual therapy could further normalize HR when compared with usual therapy; For patients with mean arterial lactate level  $\geq 7 \text{ mmol/L}$ , SFI plus usual therapy cannot further decrease HR at 6-hours when compared with usual therapy alone.

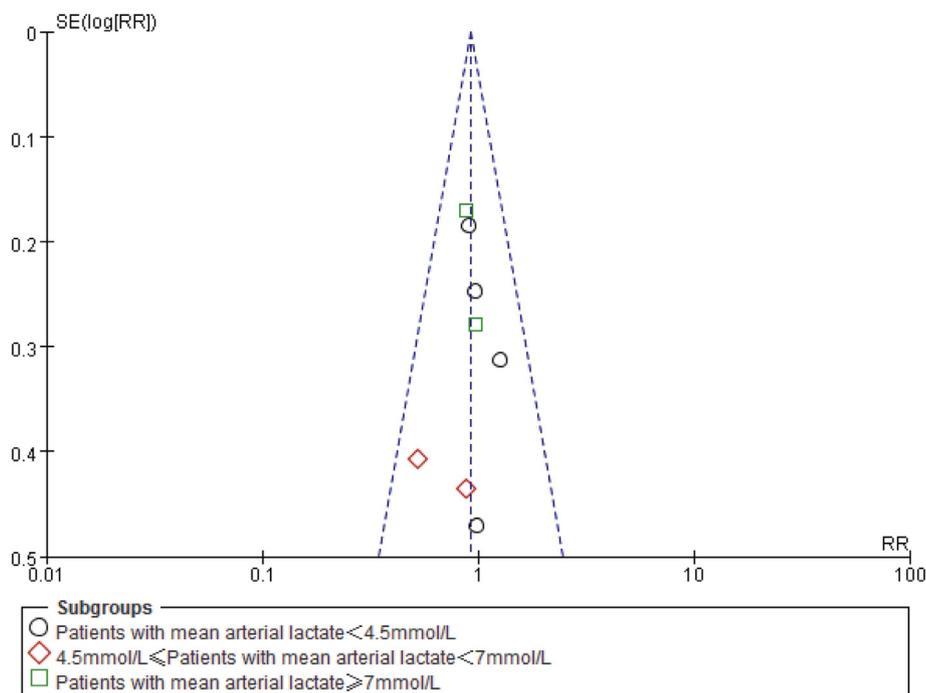


Fig. 6. Publication bias analysis.

indicated that, compared with epinephrine, SFI alleviates myocardial dysfunction by upregulating expression of sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase. SFI can also reverse the change of caspase-3/7 activity, inhibit proliferation, reduce apoptotic cardiac myocyte, and inhibit the expression Bcl-2, Bax, and caspase-3 [46]. In addition, SFI could decrease the expression of TNF- $\alpha$ , improve the microcirculation and extend the length of tissue and cellular viability without oxygen [45,48]. Moreover, both of the clinical and animal studies indicated that SFI could improve recovery of immunologic function by balancing cytokine secretion [47]. When investigate the pharmacological mechanism of ginsenoside and aconite total alkaloids alone, ginsenoside could regulate intracellular 2,3 DPG levels to promote the release and uptake of oxygen [50].

Importantly, in order to explore the main active ingredient and the potential mechanism of SFI's vasorelaxation, one study [51] investigated effects of Hongshen injection (HSI) containing ginsenoside and Fupian injection (FPI) containing aconite total alkaloids on isolated rat thoracic aortic ring contraction induced by KCl or NE, the results showed that ginsenoside contributes to SFI's vasodilator effect and aconite total alkaloids had no apparent vasodilator effect. Since KCl and NE act on the voltage-dependent calcium channels (VDC) and receptor-operated calcium channels (ROC) respectively. Interestingly, to further explore the mechanism, they found that for KCl-induced vasoconstriction, the relaxation effect of HSI is worse than that of SFI, and the effect of SFI is synergy between HSI and FPI; for NE-induced vasoconstriction, the relaxation effect of HSI is better than that of SFI, and the effect of SFI is antagonism between HSI and FPI. From these results, we found that the effect levels of different components in SFI on these two kinds of calcium channels are different, and SFI could enhance weak effect and inhibiting strong effect, which meet the compatibility rules of TCM. These results could be one of the reasons why SFI has protective effect for myocardial dysfunction, since the heart need blood supply when coronary artery relaxed. Some data evidence indicated that the vasorelaxation of SFI is associated with NO generated in epithelial cells [46], but the exact mechanism need to be further studied.

Several limitations exist in this review. First, all of the included studies were performed in China, which cannot represent patients with septic shock in other regions. Second, most of the included studies were published in Chinese, only two studies were pub-

lished in English. Third, since the treatment of septic shock is comprehensive, the effects of other united medication can't exclude. Hence, for septic shock patients, when the Traditional Chinese Medicine syndrome meets Yang-Qi deficiency, clinicians could choose SFI as a supplementary drug. Though there are more and more studies use different threshold of lactate [18,41–42,52], we acknowledge that we use unconventional threshold of 4.5 mmol/L and 7 mmol/L, instead of 4 mmol/L commonly used in septic studies [1,5].

## 5. Conclusion

For septic shock patients with  $4.5 \text{ mmol/L} \leq$  mean arterial lactate level  $< 7 \text{ mmol/L}$ , when the Traditional Chinese Medicine syndrome meet Yang-Qi deficiency, clinicians could choose SFI as a supplementary drug. But further high-quality and large-scale RCT should be performed to verify it.

## Conflict of interests

The authors declared that there is no conflict of interests regarding the publication of this paper.

## Authors' contribution

Po Huang and Qingquan Liu created the research idea and designed the study. Po Huang, Guozhen Zhao, Shuo Feng acquired the data. Po Huang, Yuhong Guo, Bo Li and Qingquan Liu analyzed and interpreted the data. Bo Li, Shuo Feng performed the statistical analysis. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work.

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## References

- [1] Shankar-Hari M et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315(8):775–87.
- [2] Dellinger R, Carlet J, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32(3):858–73.
- [3] Dellinger R, Levy M, Carlet J, Bion J, Parker M, Jaeschke R, Reinhart K, Angus D, Brun-Buisson C, Beale R et al.: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008, 36(1):296–327.
- [4] Dellinger R, Levy M, Rhodes A, Annane D, Gerlach H, Opal S, Sevransky J, Sprung C, Douglas I, Jaeschke R et al.: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013, 39(2):165–228.
- [5] Rhodes A, Evans L, Alhazzani W, Levy M, Antonelli M, Ferrer R, Kumar A, Sevransky J, Sprung C, Nunnally M et al.: Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017, 43(3):304–377.
- [6] Coopersmith C, De Backer D, Deutschman C, Ferrer R, Lat I, Machado F, Martin G, Martin-Loeches I, Nunnally M, Antonelli M et al.: Surviving sepsis campaign: research priorities for sepsis and septic shock. *Intensive Care Med* 2018, 44(9):1400–1426.
- [7] Martin C, Medam S, Antonini F, Alingrin J, Haddam M, Hammad E, et al. Norepinephrine: not too much, too long. *Shock* 2015;44(4):305–9.
- [8] Bracht H, Asfar P, Radermacher P, Calzia E. Vasopressin in vasodilatory shock: hemodynamic stabilization at the cost of the liver and the kidney? *Crit Care* 2007;11(6):178.
- [9] Russell J. Vasopressin in vasodilatory and septic shock. *Curr Opin Crit Care* 2007;13(4):383–91.
- [10] Musallam N, Altshuler D, Merchan C, Zakhary B, Aberle C, Papadopoulos J. Evaluating vasopressor discontinuation strategies in patients with septic shock on concomitant norepinephrine and vasopressin infusions. *Ann Pharmacother* 2018;52(8):733–9.
- [11] Hammond D, Ficek O, Painter J, McCain K, Cullen J, Brotherton A, et al. Prospective open-label trial of early concomitant vasopressin and norepinephrine therapy versus initial norepinephrine monotherapy in septic shock. *Pharmacotherapy* 2018;38(5):531–8.
- [12] Kampmeier T, Arnemann P, Hessler M, Seidel L, Becker K, Morelli A, et al. Comparison of first-line and second-line terlipressin versus sole norepinephrine in fulminant ovine septic shock. *Sci Rep* 2018;8(1):7105.
- [13] Liu Z, Chen J, Kou Q, Lin Q, Huang X, Tang Z, Kang Y, Li K, Zhou L, Song Q et al: Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. *Intensive Care Med* 2018.
- [14] Johan Mårtensson. Terlipressin or norepinephrine, or both in septic shock? *Intensive Care Med* 2018;44:1964–6.
- [15] Fan K, Wang J, Kong L, Zhang F, Hao H, Zhao H, Tian Z, Yin M, Fang H, Yang H et al.: Effect of Shen-Fu injection ( ) on hemodynamics in early volume resuscitation treated septic shock patients. *Chin J Integr Med* 2017.
- [16] Zhang Q, Li C, Shao F, Zhao L, Wang M, Fang Y. Efficacy and safety of combination therapy of Shenfu injection and postresuscitation bundle in patients with return of spontaneous circulation after in-hospital cardiac arrest: a randomized, assessor-blinded, controlled trial. *Crit Care Med* 2017;45(10):1587–95.
- [17] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.
- [18] Li M, Pan C, Wang X, Mo X, Shi Z, Xu J, et al. Effect of the Shenfu injection combined with early goal-directed therapy on organ functions and outcomes of septic shock patients. *Cell Biochem Biophys* 2015;72(3):807–12.
- [19] Li Y, Zhang X, Lin P, Qiu H, Wei J, Cao Y, Pan S, Walline J, Qian C, Shan Z et al.: Effects of Shenfu injection in the treatment of septic shock patients: a multicenter, controlled, randomized, open-label trial. *Evid Based Complement Alternat Med* 2016, 2016:2565169.
- [20] Xiao YC, Li Y, Wang GQ, et al. “Clinical observation on the treatment of septic shock patients with Shenfu injection”, *Journal of Emergency in Traditional Chinese medical*, 2007, 26(09):1665–1667.
- [21] Zhou L, Zhang W, Chen XW, et al. “Effects of Shenfu injection on tissue perfusion and systemic oxygen metabolism in patients with septic shock”, *Journal of Emergency in Traditional Chinese medical*, 2013, 22(09):1505–1507.
- [22] Lai ZZ, Meng JB, Hu MH, et al. “Effects of Shenfu injection on hemodynamics and myocardial injury markers in patients with low cardiac output in septic shock”, *Journal Zhejiang integrated traditional Chinese and western medicine*, 2008, 28(08):641–644.
- [23] Dong GY, Shen B. Effect of Shenfu injection in the early cluster treatment of septic shock. *Journal of Emergency in Traditional Chinese medical* 2014;23(05):944–5.
- [24] Zhang SY. Observation of therapeutic effect of Shenfu injection on improving septic shock. *Journal of Modern medicine and clinic* 2017;32(06):1034–8.
- [25] Li P, Liu BY, Fu JY. Effect of shenfu injection combined with ulinastatin on lactate in patients with septic shock. *Journal of Shanxi Chinese medicine* 2012;33(10):1337.
- [26] Liu WM, Liang QA, Jin TX, et al. Clinical application of Shenfu injection combined with norepinephrine in the treatment of septic shock. *Journal of Emergency in Traditional Chinese medical* 2014;24(08):1550–2.
- [27] Wu DJ. “Analysis of the clinical effects of Shenfu injection in the treatment of septic shock”, *Chinese J Tradit Chin Med*, 2014, 32(04):937–939.
- [28] Xu LW, Xu L. Clinical study on early target treatment of septic shock by Shenfu injection combined with dopamine. *Journal of Emergency in Traditional Chinese medical* 2012;21(11):1740–1.
- [29] Liu Y, Kong L, Fan KL, et al. Effects of Shenfu injection on early hemodynamics of sepsis shock under the monitoring of PICCO. *Journal of Emergency in Traditional Chinese medical* 2007;26(11):1993–5.
- [30] Xu Y, Chen BQ, Zhong L, et al. Intervention study on early recovery of septic shock treated by integrated Chinese and western medicine. *Journal of Health soft science* 2012;26(06):578–80.
- [31] Yin MX, Kong L, Fan KL, et al. Effects of Shenfu injection on tissue perfusion of early volume resuscitation in patients with septic shock. *Journal of Emergency in Traditional Chinese medical* 2007;26(04):666–8.
- [32] Sun SR, Mo XJ, Ma CL. Effects of early and whole-course intervention of Shenfu injection on organ function in patients with severe sepsis. *Journal of Emergency in Traditional Chinese medical* 2008;10:1392–3.
- [33] Li CL, Chen J. Application of Shenfu injection in treating patients with ICU sepsis. *Journal of Emergency in Traditional Chinese medical* 2014;23(04):608–9.
- [34] Zhang W, Wu B, Guan J, et al. Application of Shenfu injection in treating septic shock. *Med Inform* 2011;24(09):4903–4.
- [35] Tian XM, Wang M, Ren CY, et al. “Clinical efficacy of Shenfu injection in the treatment of septic shock (Yang desyndrome)” *Journal of Beijing Chinese medicine*, 2017, 36(01):88–91.
- [36] Lin MJ, Wang SL, Dong YR. Clinical observation on the treatment of shock with Shenfu injection. *Journal of Emergency in Traditional Chinese medical* 2012;21(07):1132–3.
- [37] Mou Z, Lv Z, Li Y, Wang M, Xu Q, Yu X. Clinical effect of Shenfu injection in patients with septic shock: a meta-analysis and systematic review. *Evid Based Complement Alternat Med* 2015;2015(863):149.
- [38] Hu J, Fu ZY, Xie YM, et al. Systematic evaluation of Shenfu injection in the treatment of septic shock. *China Journal of Chinese Materia Medica* 2013;38(18):3209–14.
- [39] Tao WJ, Li G, Yang Z. Meta analysis of early resuscitation in adult septic shock patients with Shenfu injection. *J Pharm* 2008;27(03):152–6.
- [40] Lara B, Enberg L, Ortega M, Leon P, Kripper C, Aguilera P, et al. Capillary refill time during fluid resuscitation in patients with sepsis-related hyperlactatemia at the emergency department is related to mortality. *PLoS ONE* 2017;12(11):e0188548.
- [41] Gong S, Song J, Zhou J, Yu Y, Dai H, Wang M, et al. Venous-to-arterial carbon dioxide difference to arteriovenous oxygen content difference ratio combined with lactate to predict prognosis of patients with septic shock. *Zhonghua Nei Ke Za Zhi* 2016;55(9):673–8.
- [42] Ryoo S, Lee J, Lee Y, Lee J, Lim K, Huh J, et al. Lactate level versus lactate clearance for predicting mortality in patients with septic shock defined by sepsis-3. *Crit Care Med* 2018;46(6):e489–95.
- [43] Yan X, Wu H, Ren J, Liu Y, Wang S, Yang J, et al. Shenfu formula reduces cardiomyocyte apoptosis in heart failure rats by regulating microRNAs. *J Ethnopharmacol* 2018;227:105–12.
- [44] Li P, Lv B, Jiang X, Wang T, Ma X, Chang N, et al. Identification of NF-κB inhibitors following Shenfu injection and bioactivity-integrated UPLC/Q-TOF-MS and screening for related anti-inflammatory targets in vitro and in silico. *J Ethnopharmacol* 2016;194:658–67.
- [45] Zhang Q, Li C, Wang S, Gu W. Effects of Chinese medicine Shen-Fu injection on the expression of inflammatory cytokines and complements during post-resuscitation immune dysfunction in a porcine model. *Chin J Integr Med* 2016;22(2):101–9.
- [46] Wang Y, Li Y, Li L, Yang D, Zhou K, Li Y. Protective effects of Shenfu injection against myocardial ischemia-reperfusion injury via activation of eNOS in rats. *Biol Pharm Bull* 2018;41(9):1406–13.
- [47] Gu W, Zhang Q, Li C. Effects of Shen-Fu injection ( ) on apoptosis of regulatory T lymphocytes in spleen during post-resuscitation immune dysfunction in a porcine model of cardiac arrest. *Chin J Integr Med* 2016;22(9):666–73.
- [48] Jin Y, Gao H, Zhang X, Ai H, Zhu X, Wang J. Shenfu injection ( ) inhibits inflammation in patients with acute myocardial infarction complicated by cardiac shock. *Chin J Integr Med* 2017;23(3):170–5.
- [49] Guo Z, Wu C, Li C. Shen-Fu injection ( ) alleviates post-resuscitation myocardial dysfunction by up-regulating expression of sarcoplasmic reticulum Ca(2+)-ATPase. *Chin J Integr Med* 2016;22(7):503–9.
- [50] Dongxu Zhao, Minglei Zhang, Hongping Yuan, et al. Ginsenoside Rb1 protects against spinal cord ischemia-reperfusion injury in rats by downregulating the Bax/Bcl-2 ratio and caspase-3 and p-Ask-1 levels. *Exp. Mol. Pathol.* 2018;105:229–35.
- [51] Zhu J, Kang L, Ye Q, Fan G, Liang Y, Yan C, et al. Effects of Shenfu injection and its main components on the contraction of isolated rat thoracic aortic rings. *PLoS ONE* 2013;8(10):e78026.
- [52] Moran J, Santamaria J. Reconsidering lactate as a sepsis risk biomarker. *PLoS ONE* 2017;12(10):e0185320.