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Traditional Chinese medicine for septic patients undergoing ulinastatin therapy
A meta-analysis

Ren-Fei Shan, MD*, Yan-An Zhu, MD, Jie Qin, BS, Jian-Ping Chen, BS

Abstract

Purpose: This study aimed to assess the efficacy of traditional Chinese medicine (TCM) in septic patients treated with ulinastatin.

Methods: PubMed, EmBase, and the Cochrane library were searched up to January 2021 to identify randomized controlled trials. The weight mean difference (WMD) and relative risk (RR) with 95% confidence intervals were used with the random-effects model.

Results: Twenty-three randomized controlled trials with 1903 septic patients were included. TCM significantly reduced the APACHE II score (WMD: −5.18; $P < .001$), interleukin-6 (WMD: −63.00; $P < .001$), tumor necrosis factor-α (WMD: −8.86; $P < .001$), c-reactive protein (WMD: −9.47; $P < .001$), mechanical ventilation duration (WMD: −3.98; $P < .001$), intensive care unit stay (WMD: −4.18; $P < .001$), procalcitonin (WMD: −0.53; $P < .001$), lipopolysaccharide (WMD: −9.69; $P < .001$), B-type natriuretic peptide (WMD: −159.87; $P < .001$), creatine kinase isoenzyme MB (WMD: −45.67; $P < .001$), cardiac troponin I (WMD: −0.66; $P < .001$), and all-cause mortality risk (RR: 0.55; $P < .001$).

Conclusions: TCM lowers inflammation levels and reduces the risk of all-cause mortality for septic patients.

Abbreviations: CI = confidence interval, ICU = intensive care unit, RCT = randomized controlled trial, RR = relative risk, TCM = traditional Chinese medicine, WMD = weight mean difference.

Keywords: Chinese traditional, medicine, meta-analysis, septic, ulinastatin

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction syndrome that develops as the host response to infection.[1,2] Studies have reported that the prognosis of sepsis is poor, and mortality in severe sepsis is around 25%, with septic shock occurring in nearly 50%.[3,4] The prevalence of sepsis increases by 1.5% annually, and the number of sepsis cases reached 49 million in 2017.[5–7] The diagnosis of sepsis is based on infection-related dysfunction of the lung, kidney, liver, cardiovascular system, blood, or central nervous system. The progression of sepsis is rapid and it is considered as a high-risk condition in the intensive care unit (ICU).

There is currently no standard approach for sepsis management. Ulinastatin is a urinary trypsin inhibitor considered an important protease inhibitor that exists in urine, blood, and other tissues; it is widely used for sepsis.[8,9] The use of ulinastatin in sepsis can modulate pro-inflammatory mediators and cytokines, and can provide a protective effect on several organs.[10–12] The suggested mechanism of ulinastatin is a decrease of inflammatory mediators and the frequency of immune cell apoptosis in sepsis models.[13] However, the treatment effects of ulinastatin for sepsis in clinical studies remained conflicting.[14,15] In traditional Chinese medicine (TCM), Xuebijing is widely used for treatment of sepsis. Its main components are safflower yellow pigment A and protocatechualdehyde, which can inhibit the inflammation level, improve microcirculation, and regulate immune function. Xuebijing consists of *Carthamus tinctorius* L, *Paeonia lactiflora* Pall, *Ligusticum chuanxiong* Hort, *Salvia miltiorrhiza* Bge, and *Angelica sinensis* (Oliv.) Diels. The herb of *C tinctorius* L can activate blood circulation and remove blood stasis. *P lactiflora* Pall and *L chuanxiong* Hort act as accessory drugs playing an important role in cooling the blood, dispersing blood stasis, and detoxifying. *S miltiorrhiza* Bge and *A sinensis* (Oliv.) Diels can enrich the blood and disperse stasis.[16]

The combined use of TCM and ulinastatin for septic patients has already been illustrated. Whether TCM can yield superior effects for septic patients undergoing ulinastatin treatment remains controversial. We therefore performed this randomized controlled trial (RCTs) to assess the treatment efficacy of TCM for septic patients treated with ulinastatin.

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2. Methods

2.1. Data sources, search strategy, and selection criteria

This study was performed and guided by the reporting items for systematic reviews and meta-analysis.[17] RCTs that investigated the efficacy of TCM plus ulinastatin versus ulinastatin alone for septic patients were eligible for our study. No restrictions were placed on publication language and status. We searched PubMed, EmBase, the Cochrane library, and China National Knowledge Infrastructure for eligible trials up to January 2021. The following search terms were applied: "sepsis" OR "severe sepsis" OR "pyemias" OR "pyohemia" OR "pyohemias" OR "pyaemia" OR "pyaemias" OR "septicemia" OR "septicemias" OR "poisoning, blood" OR "blood poisoning" AND "xuebijing" AND "ulinastatin." The reference lists were reviewed to identify any new eligible trial.

Two reviewers independently performed the study selection, and conflicts between reviewers were settled mutually by discussion. The study was included if: patients: sepsis, irrespective of the severity of disease; intervention: TCM and ulinastatin; control: ulinastatin; outcomes: APACHE II, interleukin (IL)-6, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), mechanical ventilation (MV) duration, ICU stay, all-cause mortality, procalcitonin (PCT), lipopolysaccharide (LPS), B-type natriuretic peptide (BNP), creatine kinase isoenzyme MB (CK-MB), cardiac troponin I (cTnI), or lactic dehydrogenase (LDH); and study design: the study had to have a RCT design. This study did not contain any participates and ethics approval and informed consent are not applicable.

2.2. Data collection and quality assessment

Two reviewers independently abstracted the following items from each trial, first author, publication year, country, sample size (number of patients in intervention and control groups), mean age, male proportion, baseline APACHE II, disease status, intervention and control, and treatment course. These 2 reviewers then assessed the quality of the included trials using the Jadad scale, which is based on 5 items. The scoring system for each trial ranged from 0 to 5.[18] Any disagreement between reviewers was resolved by the primary reviewer reviewing the full text of included trials.

2.3. Statistical analysis

The effects of TCM on septic patients were assigned as continuous and categorical outcomes, then weighted mean difference (WMD) and relative risk (RR) with a 95% confidence interval (CI) were analyzed in individual trials. The random-effects model was used to calculate the pooled effect estimate, which could consider underlying variants across included trials.[19,20] The I^2 and Cochran Q statistic were used to assess the heterogeneity of each outcome; the significant heterogeneity was defined as an $I^2 > 50.0\%$ or $P < .10$.[21,22] The robustness of the pooled conclusion for each outcome was evaluated using sensitivity analysis.[23] Subgroup analysis for APACHE II, IL-6, TNF-α, CRP, MV duration, ICU stay, and all-cause mortality were performed based on mean age, male proportion, and treatment duration. Then an interaction t test was used to compare differences between subgroups.[24] The funnel plot, Egger, and Begg test results were used to assess publication bias.[25,26] All P-values are 2-sided, and the inspection level was .05. All of the analyses in this study were performed with STATA software (Version 10.0; StataCorp, TX).

3. Results

3.1. Literature search

The literature search in electronic databases yielded 891 articles after duplicate articles were removed. A total of 812 studies were removed because these articles reported irrelevant topics. A total of 79 studies were downloaded for full-text evaluation, and 56 studies were removed because patients were not treated with ulinastatin (n=29), they were not RCT (n=21), and review papers (n=6). Reviewing the reference lists, we identified 11 potentially relevant articles, while no new eligible study was found. Finally, 23 RCTs were included in the final meta-analysis (Fig. 1).[27–49]

3.2. Study characteristics

The characteristics of the identified studies are summarized in Table 1. Of the 23 included trials, there were 1903 septic patients. All the studies were performed in China, and the sample size ranged from 40 to 240. The mean age of patients across trials ranged from 33.2 to 66.2 years, and the male proportion for each trial ranged from 48.3% to 84.8%. The treatment duration ranged from 3 to 14 days. Study quality was evaluated by the Jadad scale, 9 trials had 3 scores, 10 trials, 2 scores, and the remaining 4 trials, 1 score. The details of the abstracted data for the investigated outcomes are shown in Supplementary material 1, http://links.lww.com/MD/G388.

3.3. APACHE II

Nine trials reported the effect of TCM on the APACHE II score. The pooled result indicated that the use of TCM was associated with a lower APACHE II score for septic patients treated with ulinastatin (WMD: −5.18; 95% CI: −7.05 to −3.31; P < .001; Fig. 2). Moreover, a significant heterogeneity was observed ($I^2 = 90.6\%$; $P < .001$). The pooled conclusion was robust and not changed (Supplementary material 2, http://links.lww.com/MD/G389). The significant difference with TCM on the APACHE II score were observed in all subgroups. Mean age ($P < .001$) or male proportion ($P = .002$) could affect the treatment efficacy of TCM on APACHE II (Table 2). No significant publication bias for APACHE II was detected (P_{Egger}: .071; P_{Begg}: .118; Supplementary material 3, http://links.lww.com/MD/G390).

3.4. IL-6

Fourteen trials reported the effect of TCM on IL-6 levels. The pooled result suggested TCM significantly reduced IL-6 (WMD: −63.00; 95% CI: −75.27 to −50.72; P < .001; Fig. 3). Moreover, we noted significant heterogeneity for IL-6 ($I^2 = 95.5\%$; $P < .001$). Sensitivity analysis indicated the pooled conclusion was not altered (Supplementary material 2, http://links.lww.com/MD/G389). The subgroup analysis found that TCM was associated with lower IL-6 in all subgroups, and that the male proportion ($P < .001$) or treatment duration ($P < .001$) could affect the efficacy of TCM on IL-6 (Table 2). The Begg test showed no publication bias for IL-6 ($P = .324$), while potential significant publication bias was observed with the Egger test ($P = .001$) (Supplementary material 3, http://links.lww.com/MD/G390).
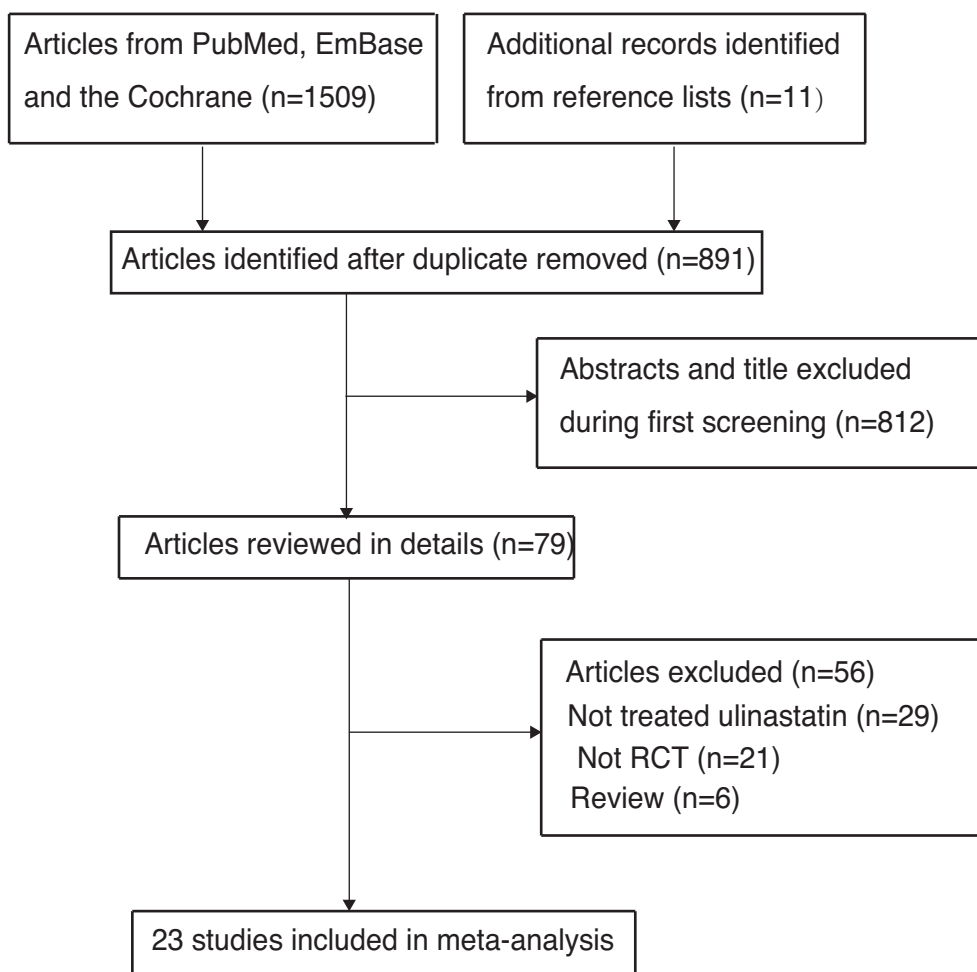
Figure 1. Flowchart of the literature search and study selection.

3.5. TNF-α

Thirteen trials reported the effect of TCM on TNF-α level. TCM significantly reduced TNF-α levels (WMD: −8.86; 95% CI: −12.31 to −5.41; $P < .001$; Fig. 4), and a significant heterogeneity was obtained ($I^2 = 96.4\%$; $P < .001$). The pooled conclusion was robust and stable (Supplementary material 2, http://links.lww.com/MD/G389). We noted that TCM significantly reduced TNF-α in mostly subgroups, while TCM was not associated with a TNF-α level if treatment duration >7 days. Moreover, mean age ($P < .001$), male proportion ($P < .001$), and treatment duration ($P < 0.001$) could affect the efficacy of TCM on TNF-α (Table 2). The Begg test showed no evidence of publication bias, while potential significant publication bias existed for TNF-α using the Egger test ($P < .001$) (Supplementary material 3, http://links.lww.com/MD/G390).

3.6. CRP

Eight trials reported the effect of TCM on CRP levels. The pooled result suggested TCM significantly reduced the CRP level (WMD: −9.47; 95% CI: −12.17 to −6.78; $P < .001$; Fig. 5). We noted significant heterogeneity for CRP ($I^2 = 85.6\%$; $P < .001$), and the pooled conclusion was stability after sequentially removing a single study (Supplementary material 2, http://links.lww.com/MD/G389). The significant differences between groups for CRP levels were observed in all subgroups, and male proportion ($P = .010$) or treatment duration ($P < .001$) could affect the efficacy of TCM on CRP (Table 2). There was no evidence of publication bias for CRP (P_{Egger}: .640; P_{Begg}: .902; Supplementary material 3, http://links.lww.com/MD/G390).

3.7. MV duration

Eleven trials reported the effect of TCM on MV duration. The pooled result found that TCM was associated with a shorter MV duration (WMD: −3.98; 95% CI: −4.74 to −3.21; $P < .001$; Fig. 6). We noted significant heterogeneity for MV duration ($I^2 = 64.9\%$; $P = .002$) and the pooled conclusion was stability (Supplementary material 2, http://links.lww.com/MD/G389). Subgroup analysis indicated TCM significantly reduced MV duration in all subgroups (Table 2). No evidence of publication bias for MV duration was observed (P_{Egger}: .517; P_{Begg}: .876; Supplementary material 3, http://links.lww.com/MD/G390).

3.8. ICU stay

Twelve trials reported the effect of TCM on ICU stay. The pooled result suggested TCM was associated with a shorter ICU stay

Table 1

The baseline characteristics of included studies and involved patients.

Study	Country	Sample size	Age, yr	Male (%)	APACHE II	Disease status	Intervention	Control	Treatment duration, d	Study quality
Mao, et al 2008 [27]	China	114 (57/57)	50.8	84.8	16.8	Severe sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	3
Sun, et al 2010 [28]	China	40 (20/20)	NA	NA	NA	Severe sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	10	1
Ye, et al 2010 [29]	China	50 (27/23)	40.0	66.0	16.9	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	2
Abu, et al 2013 [30]	China	30 (15/15)	47.1	61.8	NA	Severe sepsis	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (300,000 U/12 h) plus basic treatment	Ulinastatin (300,000 U/12 h) plus basic treatment	7	1
Zeng, et al 2013 [31]	China	54 (27/27)	47.2	55.6	44.8	Septic shock	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	2
Jiang, et al 2013 [32]	China	86 (43/43)	49.4	53.5	NA	Severe sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	3
Zhao, et al 2013 [33]	China	88 (44/44)	62.6	55.3	24.4	Severe sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7–10	2
Zhou, et al 2013 [34]	China	122 (61/61)	43.5	54.2	NA	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (900,000 U/12 h) plus basic treatment	Ulinastatin (900,000 U/12 h) plus basic treatment	14	2
Cao, et al 2015 [35]	China	240 (135/105)	64.7	57.8	17.4	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (100,000 U/12 h) plus basic treatment	Ulinastatin (100,000 U/12 h) plus basic treatment	7	2
Li, et al 2015 [36]	China	80 (40/40)	48.2	55.8	NA	Severe sepsis	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (300,000 U/12 h) plus basic treatment	Ulinastatin (300,000 U/12 h) plus basic treatment	7	2
Shan, et al 2016 [37]	China	70 (35/35)	42.5	60.0	30.8	Septic shock	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	3
Ji, et al 2016 [38]	China	60 (30/30)	66.2	48.3	23.5	Sepsis	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	1
Li, et al 2016 [39]	China	80 (40/40)	36.9	57.5	NA	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (100,000 U/12 h) plus basic treatment	Ulinastatin (100,000 U/12 h) plus basic treatment	7	2
Bian, et al 2017 [40]	China	52 (26/26)	39.0	63.5	NA	Sepsis	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (100,000 U/12 h) plus basic treatment	Ulinastatin (100,000 U/12 h) plus basic treatment	10	3
Chen, et al 2017 [41]	China	69 (35/34)	33.2	59.4	NA	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	10	2
Lu, et al 2018 [42]	China	45 (25/20)	59.8	62.2	23.3	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (400,000 U/12 h) plus basic treatment	Ulinastatin (400,000 U/12 h) plus basic treatment	5	3
Zhang, et al 2018 [43]	China	60 (30/30)	58.0	63.3	NA	Sepsis	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	6	2
Yu, et al 2018 [44]	China	84 (42/42)	49.2	55.6	16.7	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	3
Li, et al 2018 [45]	China	80 (40/40)	38.6	60.0	NA	Sepsis	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (300,000 U/12 h) plus basic treatment	Ulinastatin (300,000 U/12 h) plus basic treatment	7	1
Wei, et al 2018 [46]	China	150 (75/75)	57.5	59.3	25.6	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	3
	China	86 (43/43)	45.8	52.3	NA	Sepsis			7	3

(continued)

Table 1

(continued).

Study	Country	Sample size	Age, yr	Male (%)	APACHE II	Disease status	Intervention	Control	Treatment duration, d	Study quality
Xu, et al 2019 [47]							TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (300,000 U/ 12 h) plus basic treatment	Ulinastatin (300,000 U/12 h) plus basic treatment		
Zhang, et al 2020 [48]	China	67 (35/32)	44.9	59.4	NA	Septic shock	TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (100,000 U/ 12 h) plus basic treatment	Ulinastatin (100,000 U/12 h) plus basic treatment	3	3
Wei, et al 2020 [49]	China	96 (48/48)	55.9	60.4	NA	Sepsis	TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/ 12 h) plus basic treatment	Ulinastatin (200,000 U/12 h) plus basic treatment	7	2

(WMD: −4.18; 95% CI: −5.39 to −2.97; $P < .001$; Fig. 7). We noted significant heterogeneity for ICU stay ($I^2 = 76.8\%$; $P < .001$). Sensitivity analysis indicated the pooled conclusion was stability (Supplementary material 2, http://links.lww.com/MD/G389). Significant differences between groups for ICU stay were observed in all subgroups, and mean age ($P = .012$) or male proportion ($P = .006$) could affect the efficacy of TCM on ICU stay (Table 2). No significant publication bias for ICU stay was detected (P_{Egger}: .166; P_{Begg}: .451; Supplementary material 3, http://links.lww.com/MD/G390).

3.9. All-cause mortality

Twelve trials reported the effect of TCM on all-cause mortality risk. We noted that the TCM significantly reduced all-cause mortality risk (RR: 0.55; 95% CI: 0.43–0.70; $P < .001$; Fig. 8). There was no significant heterogeneity for all-cause mortality ($I^2 = 0.0\%$; $P = .989$). The pooled conclusion was not changed when excluding any specific trial (Supplementary material 2, http://links.lww.com/MD/G389). Subgroup analysis found that TCM was associated with a lower risk of all-cause mortality in all subgroups (Table 2). No evidence of publication bias for all-cause

mortality was seen (P_{Egger}: .116; P_{Begg}: .244; Supplementary material 3, http://links.lww.com/MD/G390).

3.10. PCT, LPS, BNP, CK-MB, cTnI, and LDH

The effects of TCM on PCT and LPS were available in 11 and 5 trials, respectively. TCM significantly reduced the levels of PCT (WMD: −0.53; 95% CI: −0.67 to −0.39; $P < .001$; Fig. 9), and LPS (WMD: −9.69; 95% CI: −11.19 to −8.19; $P < .001$; Fig. 10). Moreover, we noted significant heterogeneity for PCT ($I^2 = 97.3\%$; $P < .001$), but no evidence of heterogeneity for LPS ($I^2 = 0.0\%$; $P = .983$).

The number of trials that reported the effects of TCM on BNP, CK-MB, cTnI, and LDH were 6, 4, 4, and 3, respectively (Fig. 11). We noted TCM significantly reduced the levels of BNP (WMD: −159.87; 95% CI: −230.26 to −89.48; $P < .001$), CK-MB (WMD: −45.67; 95% CI: −64.67 to −26.68; $P < .001$), and cTnI (WMD: −0.66; 95% CI: −0.94 to −0.39; $P < .001$), while it did not affect LDH levels (WMD: 22.31; 95% CI: −150.88 to 195.51; $P = .801$). There was significant heterogeneity for BNP ($I^2 = 85.6\%$; $P < .001$), CK-MB ($I^2 = 68.4\%$; $P = .024$), cTnI ($I^2 = 99.7\%$; $P < .001$), and LDH ($I^2 = 99.1\%$; $P < .001$).
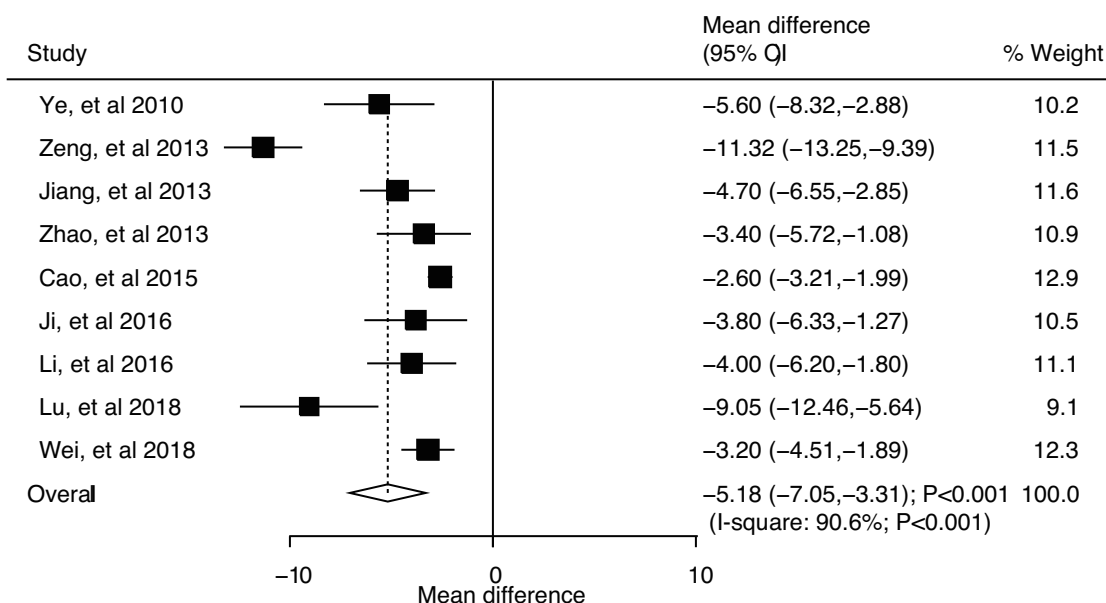
Figure 2. The effect of TCM on APACHE II in septic patients treated with ulinastatin. TCM = traditional Chinese medicine.

Table 2

Subgroup analyses for investigated outcomes.

Outcomes	Factors	Subgroup	Effect estimate and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity	P value between subgroups
APACHE II	Age, yr	≥50.0	−2.71 (−3.29 to −2.14)	<.001	0.0	.555	<.001
		<50.0	−6.23 (−8.98 to −3.49)	<.001	90.6	<.001	
	Male (%)	≥60.0	−7.17 (−10.53 to −3.80)	<.001	58.3	.121	.002
		<60.0	−4.69 (−6.74 to −2.63)	<.001	91.8	<.001	
	Treatment duration	≤7 days	−5.41 (−7.48 to −3.34)	<.001	91.8	<.001	.820
		>7 days	−3.40 (−5.72 to −1.08)	.004	−	−	
IL-6	Age, yr	≥50.0	−65.79 (−102.12 to −29.47)	<.001	94.3	<.001	.705
		<50.0	−63.27 (−78.99 to −47.56)	<.001	96.3	<.001	
	Male (%)	≥60.0	−58.49 (−78.11 to −38.86)	<.001	88.2	<.001	<.001
		<60.0	−68.05 (−87.30 to −48.79)	<.001	95.9	<.001	
	Treatment duration	≤7 days	−70.31 (−85.64 to −54.99)	<.001	94.0	<.001	<.001
		>7 days	−43.47 (−78.28 to −8.66)	.014	95.7	<.001	
TNF-α	Age, yr	≥50.0	−8.07 (−9.88 to −6.26)	<.001	34.5	.191	<.001
		<50.0	−9.49 (−14.21 to −4.76)	<.001	97.0	<.001	
	Male (%)	≥60.0	−11.43 (−16.08 to −6.77)	<.001	86.1	<.001	<.001
		<60.0	−7.42 (−11.20 to −3.65)	<.001	95.7	<.001	
	Treatment duration	≤7 days	−9.57 (−11.69 to −7.46)	<.001	74.2	<.001	<.001
		>7 days	−4.41 (−9.40 to 0.59)	.084	94.5	<.001	
CRP	Age (years)	≥ 50.0	−10.54 (−15.04 to −6.04)	<.001	90.8	<.001	.274
		< 50.0	−8.65 (−12.31 to −4.99)	<.001	79.9	.002	
	Male (%)	≥60.0	−10.68 (−16.34 to −5.01)	<.001	89.0	<.001	.010
		<60.0	−8.86 (−11.74 to −5.99)	<.001	79.6	.002	
	Treatment duration	≤7 days	−10.29 (−12.99 to −7.59)	<.001	83.1	<.001	<.001
		> 7 days	−4.20 (−6.99 to −1.41)	.003	-	-	
MV duration	Age, yr	≥50.0	−4.08 (−5.23 to −2.93)	<.001	73.2	.005	.129
		<50.0	−4.20 (−5.35 to −3.05)	<.001	57.8	.050	
	Male (%)	≥60.0	−4.07 (−5.62 to −2.51)	<.001	79.4	.002	.111
		<60.0	−4.20 (−5.07 to −3.33)	<.001	47.6	.089	
	Treatment duration	≤7 days	−4.14 (−5.05 to −3.24)	<.001	67.8	.002	.470
		>7 days	−3.25 (−5.15 to −1.36)	.001	67.5	.080	
ICU duration	Age, yr	≥50.0	−4.72 (−6.74 to −2.70)	<.001	85.0	<.001	.012
		<50.0	−3.92 (−5.01 to −2.84)	<.001	25.0	.255	
	Male (%)	≥60.0	−4.75 (−7.20 to −2.29)	<.001	87.4	<.001	.006
		<60.0	−3.99 (−4.85 to −3.13)	<.001	7.9	.366	
	Treatment duration	≤7 days	−4.42 (−5.81 to −3.03)	<.001	78.2	<.001	.051
		>7 days	−3.06 (−5.19 to −0.93)	.005	57.4	.126	
All-cause mortality	Age, yr	≥50.0	0.59 (0.42–0.83)	.002	0.0	.966	.503
		<50.0	0.50 (0.34–0.72)	<.001	0.0	.868	
	Male (%)	≥60.0	0.57 (0.36–0.90)	.017	0.0	.794	.830
		<60.0	0.54 (0.40–0.72)	<.001	0.0	.958	
	Treatment duration	≤7 days	0.56 (0.42–0.75)	<.001	0.0	.972	.703
		>7 days	0.50 (0.31–0.82)	.006	0.0	.668	

4. Discussion

This study assessed the treatment efficacy of TCM for septic patients undergoing ulinastatin treatment. A total of 1903 septic patients across a broad range of characteristics from 23 RCTs were selected in the final meta-analysis. This study found that the TCM use of Xuebijing significantly improved APACHE II, IL-6, TNF-α, CRP, MV duration, ICU duration, all-cause mortality, PCT, LPS, BNP, CK-MB, and cTnI, while it had no significant effect on LDH for septic patients. Subgroup analyses found the treatment efficacy of TCM for septic patients could be affected by mean age, male proportion, and treatment duration.

A prior meta-analysis identified 16 RCTs and found that supplementation of TCM Xuebijing could improve the risk of 28-day mortality, lower APACHE II scores, the WBC count, and body temperature in septic patients without serious adverse events, while it had no significant effect on mortality during treatment.[50] However, patients enrolled in this meta-analysis underwent various treatment strategies. Xiao et al[51] found the combined use of TCM Xuebijing and ulinastatin could improve MV duration, ICU stay, PCT, APACHE II, IL-6, TNF-α, reduce the risk of 28-day mortality, and multiple organ dysfunction syndrome in septic patients. However, one of the included studies did not mention septic patients treated with ulinastatin.[52] Moreover, several additional RCTs were published recently[42–49] and the treatment efficacy of TCM for septic patients undergoing ulinastatin needs to be re-evaluated. Furthermore, whether the treatment efficacy of TCM in septic patients differs according to mean age, male proportion, and treatment duration needs further evaluation.

Therefore, the current study was performed to compare the effects of TCM plus ulinastatin with ulinastatin alone for septic patients. The summarized results indicate that TCM Xuebijing can significantly improve the severity of disease, inflammation, MV duration, ICU stay, and all-cause mortality in septic patients
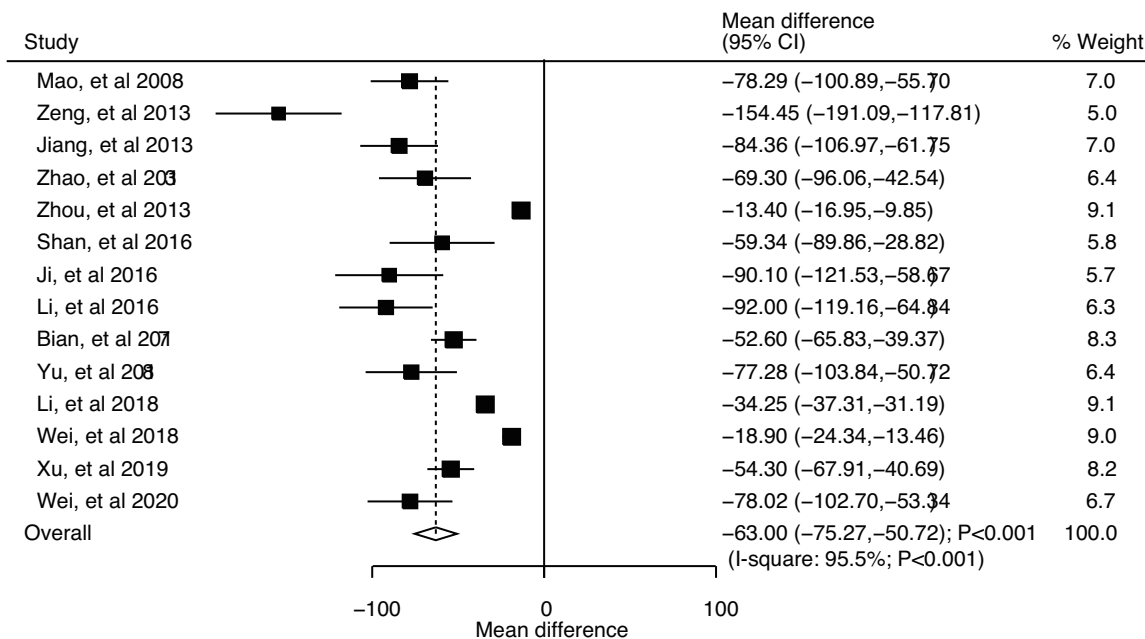
Figure 3. The effect of TCM on IL-6 in septic patients treated with ulinastatin. IL-6 = interleukin 6, TCM = traditional Chinese medicine.

undergoing ulinastatin therapy. Most of the included studies reported similar results, while 2 studies did not find a significant effect of TCM on ICU stay.[28,42] Most studies did not find a significant effect of TCM on the risk of all-cause mortality. The reason for this could be that events occurred less than expected, and the 95% CI for all-cause mortality in an individual study was broad. The significant effects of TCM Xuebijing in septic patients treated with ulinastatin could be because Xuebijing removes toxins, it detoxifies, dredging the veins, promoting blood

circulation, and removing blood stasis.[53] The main components of Xuebijing activate blood circulation, remove blood stasis, clear toxins, and strengthen body resistance.[16] Several mechanisms of Xuebijing for treating sepsis include: anti-inflammatory; Xuebijing can inhibit pro-inflammatory cytokine release, or the production of high mobility group box-1 protein, promote anti-inflammatory cytokine release in early-stage sepsis, and downregulate the expression of the TLR4/NF-κB signaling pathway; an anticoagulant effect; Xuebijing plays an important
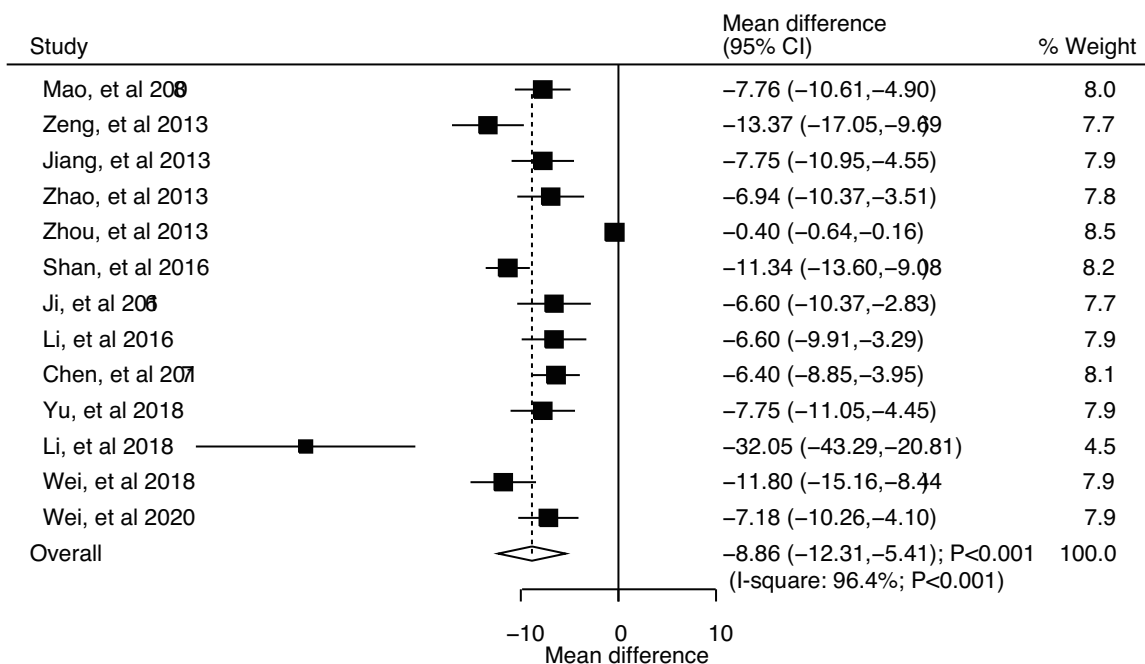

Figure 4. The effect of TCM on TNF-α in septic patients treated with ulinastatin. TCM = traditional Chinese medicine, TNF-α = tumor necrosis factor α.
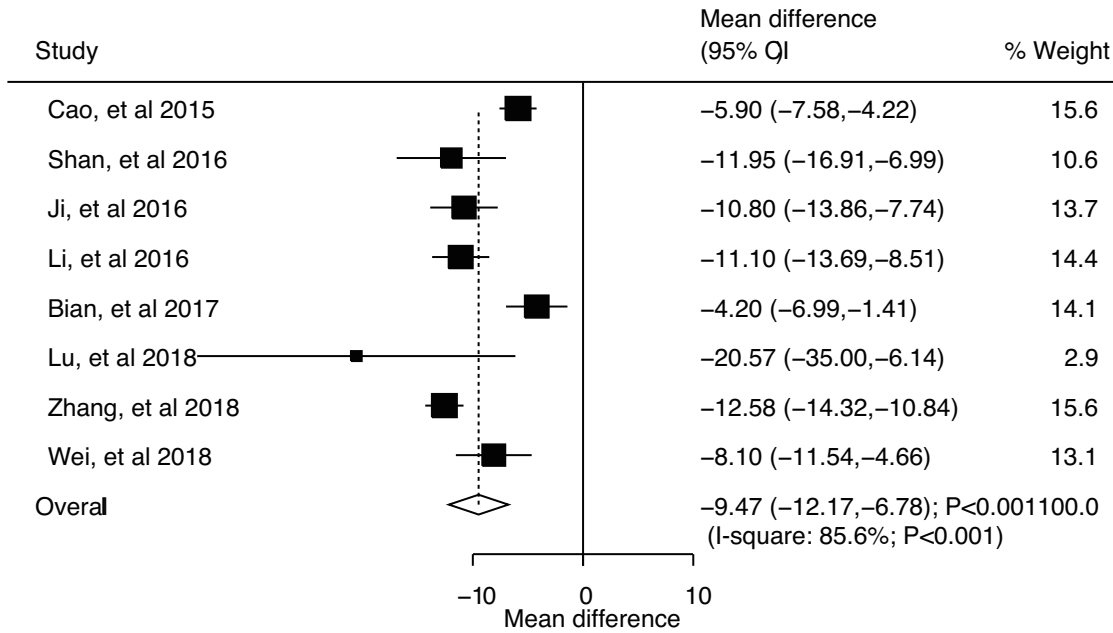
Figure 5. The effect of TCM on CRP in septic patients treated with ulinastatin. CRP=C-reactive protein, TCM=traditional Chinese medicine.

role in tissue factor release, procoagulant, anticoagulant, and fibrinolytic pathways; immunomodulation; Xuebijing can polarize the immune response of Th2 to Th1, enhance Treg apoptosis, and reduce the apoptosis of immune cells; protection of the vascular endothelium; antioxidative stress function, and other mechanisms, including inhibiting intercellular adhesion molecule-1 expression and vascular cell adhesion molecule-1 in liver tissue and intercellular adhesion molecule-1 in lung tissue.[54]

Therefore, combined use of Xuebijing and ulinastatin can alleviate the symptoms of sepsis, reduce the progression of multiple organ failure and collapse caused by the body's endogenous inflammatory mediators, and reduce the probability of sepsis continuing to deteriorate.[55,56]

Subgroup analyses found that the treatment effects of TCM in septic patients treated with ulinastatin can be affected by age, male proportion, and treatment duration. We noted the effects
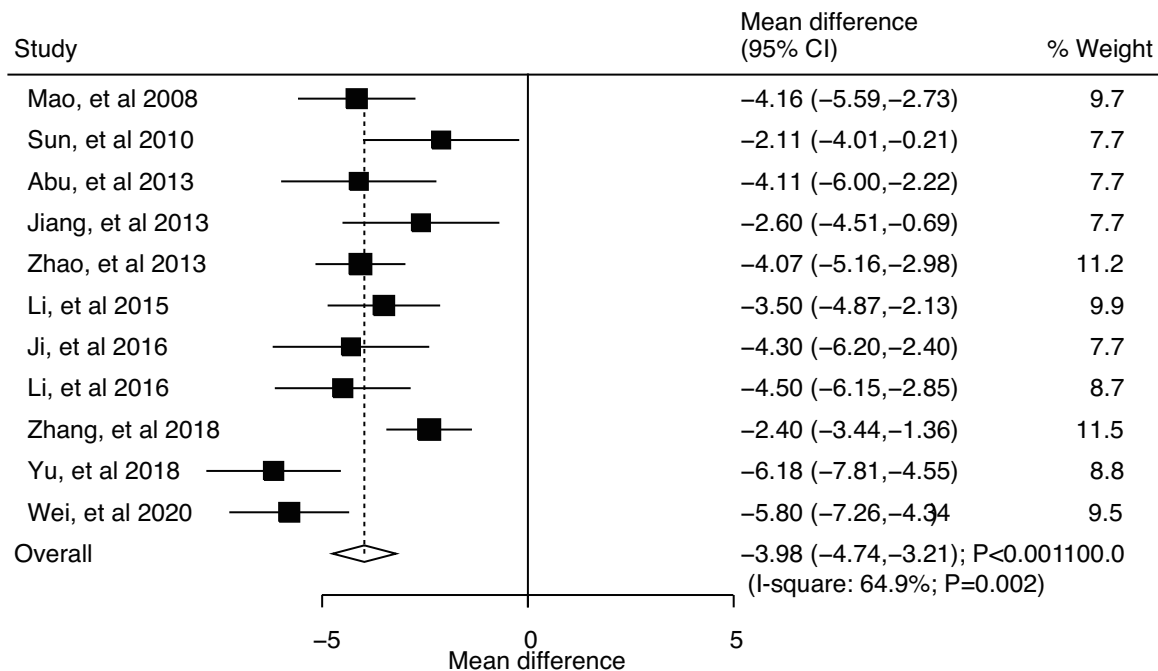

Figure 6. The effect of TCM on MV duration in septic patients treated with ulinastatin. MV=mechanical ventilation, TCM=traditional Chinese medicine.
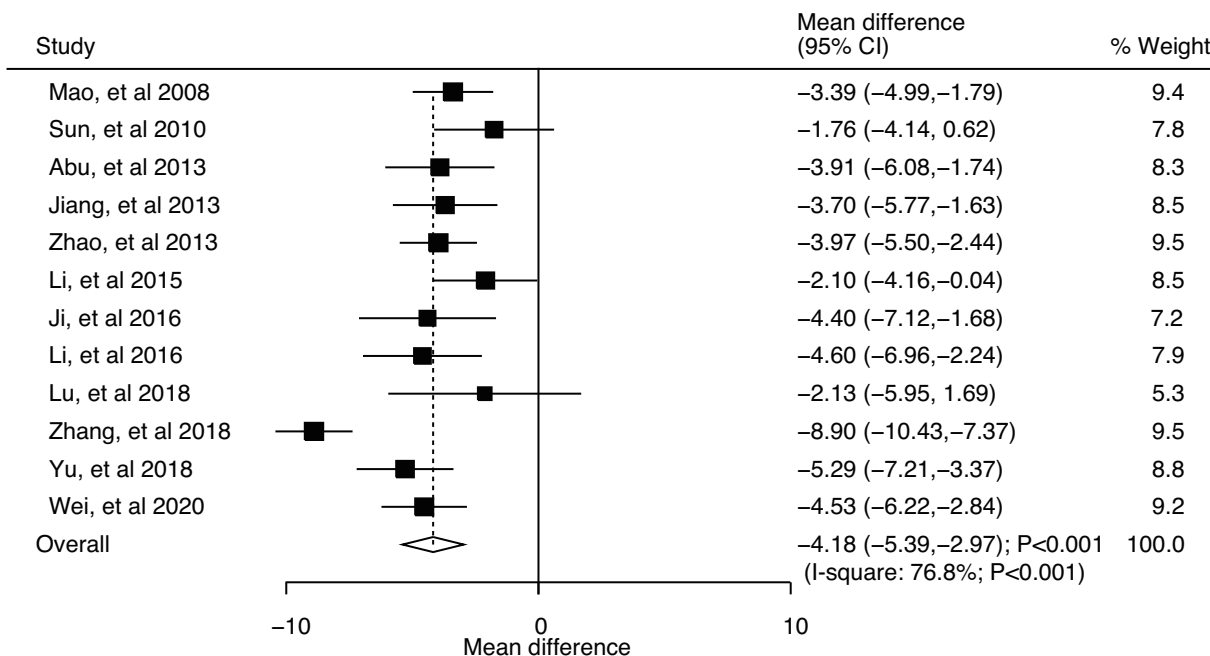
Figure 7. The effect of TCM on ICU duration in septic patients treated with ulinastatin. ICU = intensive care unit, TCM = traditional Chinese medicine.

of TCM on symptom of sepsis. The improvement in inflammation in younger septic patients was greater than in elderly septic patients, while ICU stay in elderly septic patients was shorter than in younger septic patients. The potential reason for this could be that the mortality risk in elderly patients is higher. Moreover, the improvement in disease severity and inflammation in male patients might be superior to women, which could be caused by disease severity. Finally, we noted that a shorter treatment duration was associated with better prognosis, which could be explained by disease severity and the smaller number that reported a treatment duration >7 days.
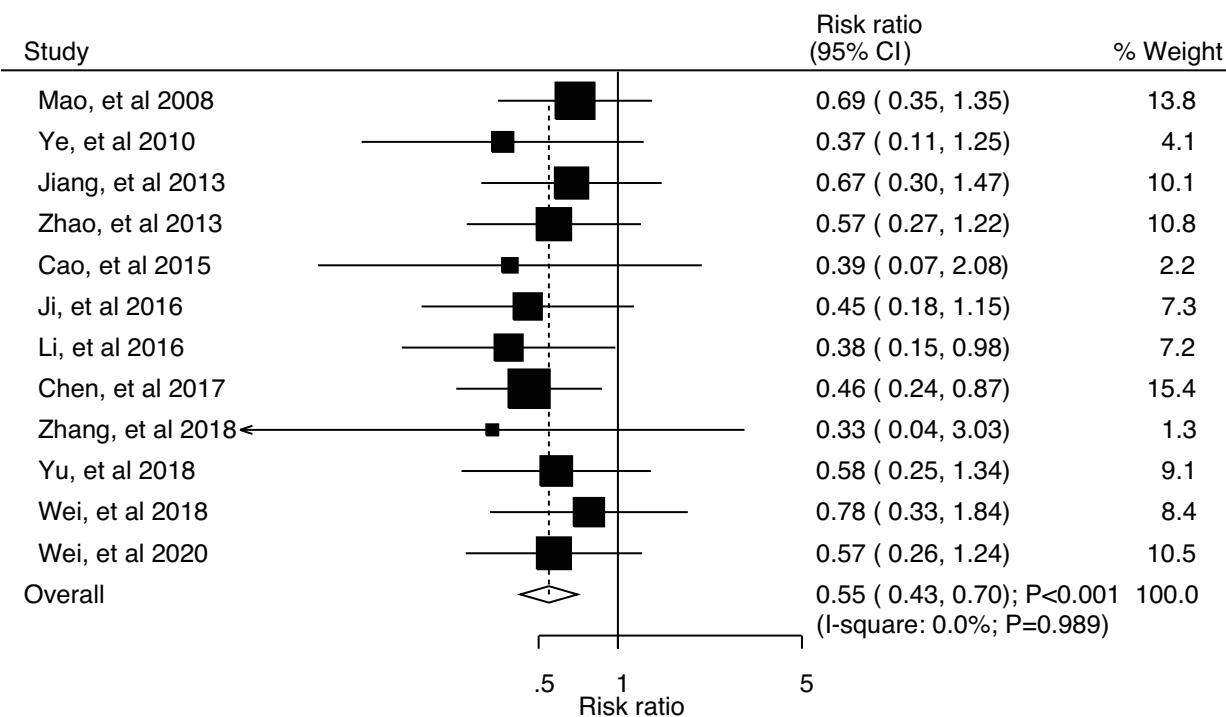

Figure 8. The effect of TCM on all-cause mortality in septic patients treated with ulinastatin. TCM = traditional Chinese medicine.
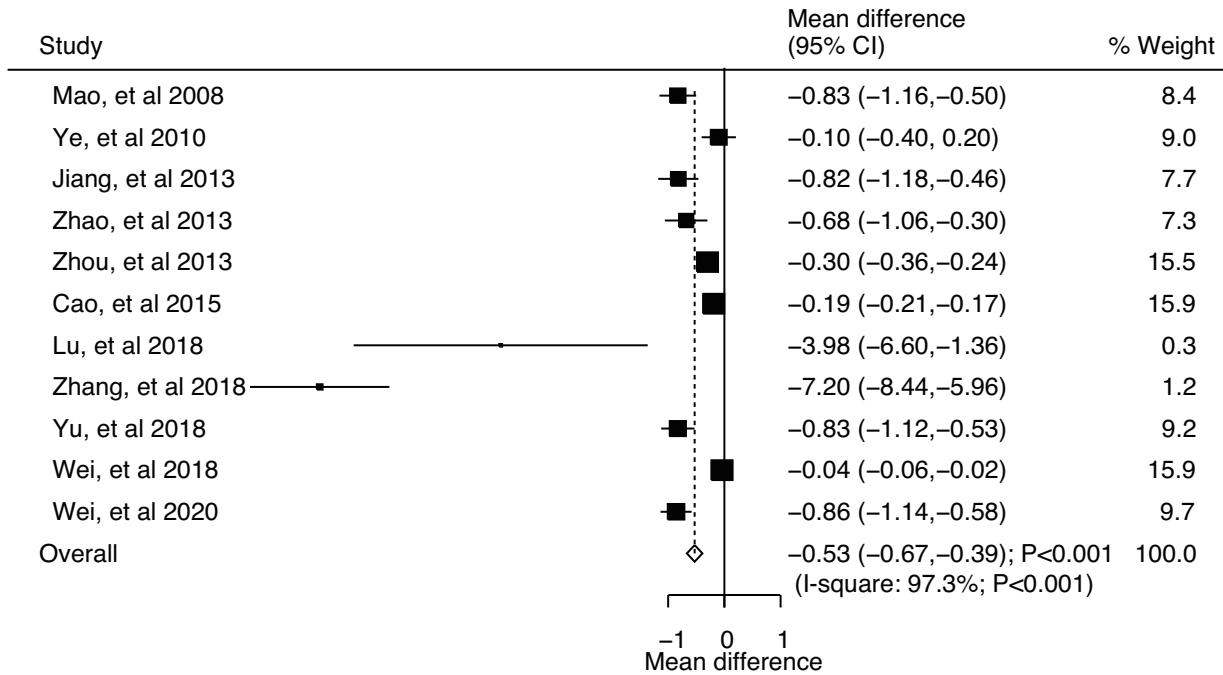
Figure 9. The effect of TCM on PCT in septic patients treated with ulinastatin. PCT=procalcitonin, TCM=traditional Chinese medicine.

The shortcomings of this study should be acknowledged: the quality of included trials was low to moderate, and the evidence level for pooled conclusion was restricted; the conclusions should be considered with caution since all trials were performed in China; the conclusions could be biased due to disease severity and underlying treatment strategies; the detailed analyses were restricted because they were based on pooled data; and

publication bias was inevitable because the analysis is based on published articles.

This study found that TCM plus ulinastatin could yield additional benefits in APACHE II score, IL-6, TNF-α, CRP, MV duration, ICU stay, all-cause mortality, PCT, LPS, BNP, CK-MB, and cTnI in septic patients, while it has no significant effect on LDH levels. Furthermore, RCTs should be performed to
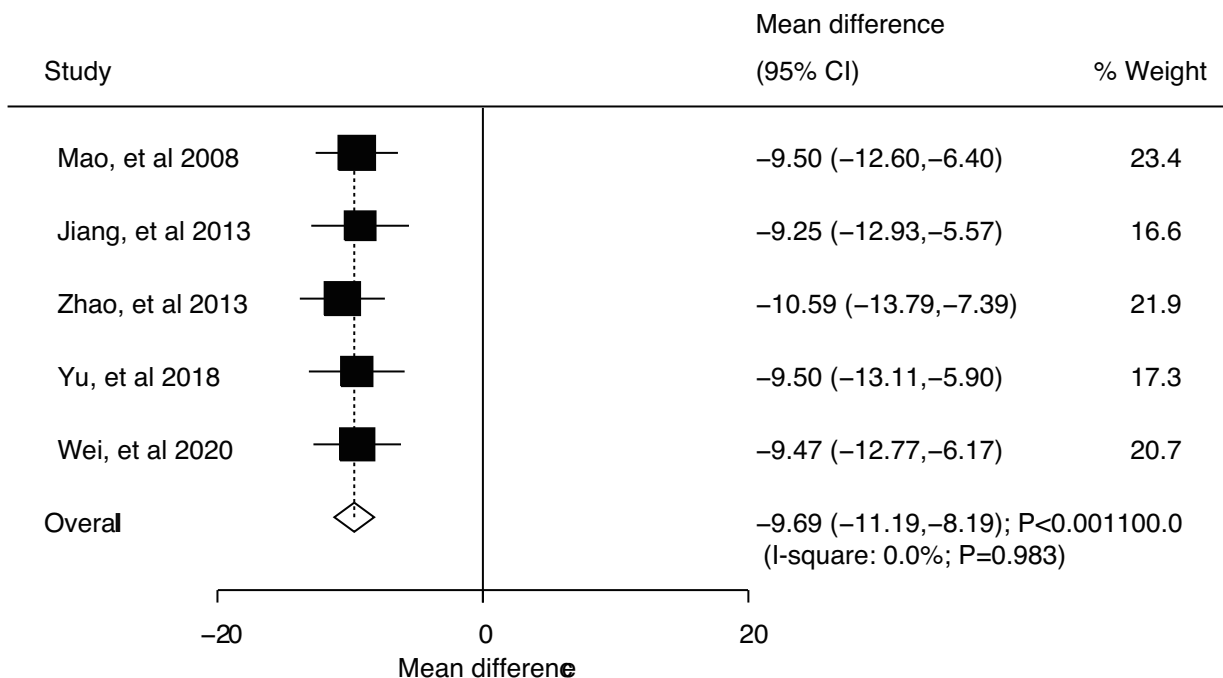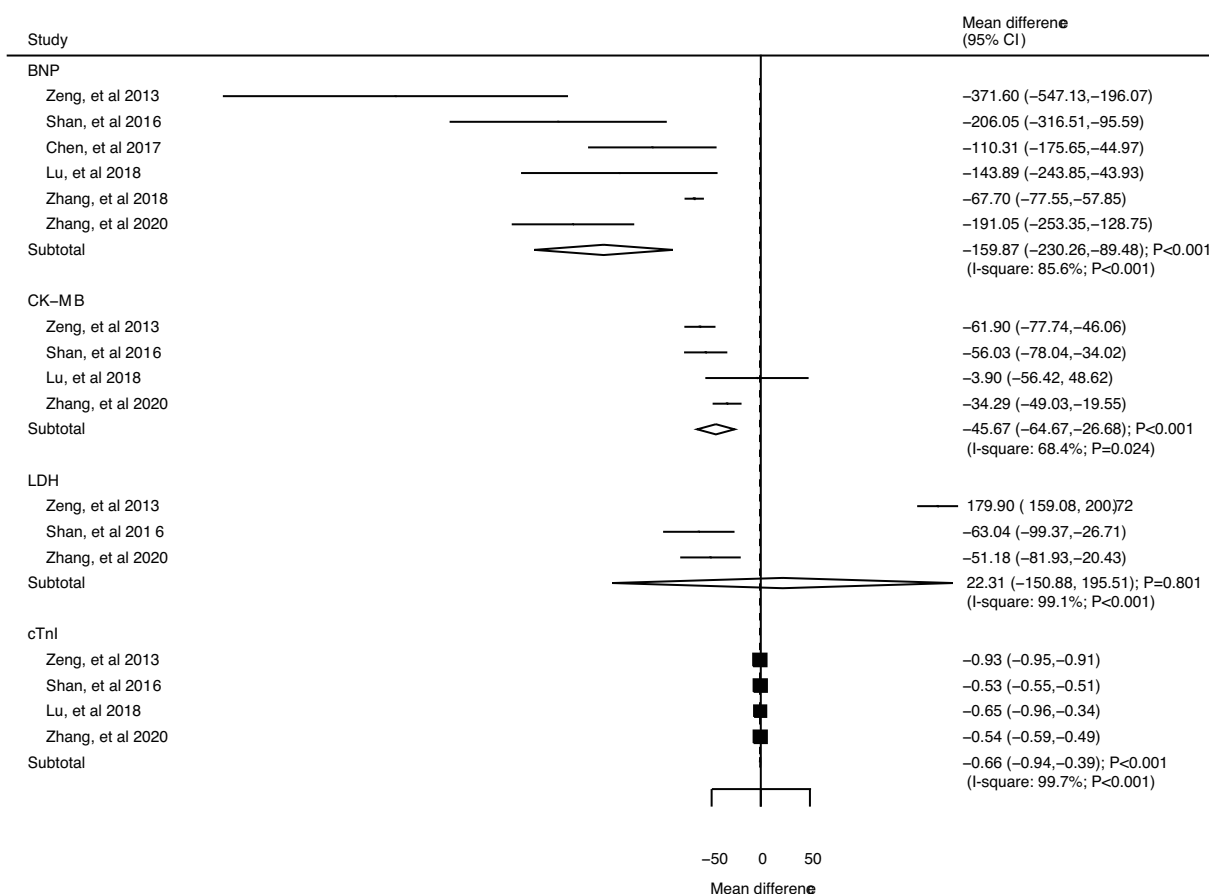

Figure 10. The effect of TCM on LPS in septic patients treated with ulinastatin. LPS=lipopolysaccharide, TCM=traditional Chinese medicine.

Figure 11. The effects of TCM on BNP, CK-MB, cTnI, and LDH in septic patients treated with ulinastatin. BNP = B-type natriuretic peptide, CK-MB = creatine kinase isoenzyme MB, cTnI = cardiac troponin, LDH = lactic dehydrogenase, TCM = traditional Chinese medicine.

determine the effects of TCM Xuebijing plus ulinastatin for septic patients with specific characteristics.

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