Review Article

Effectiveness of Xuebijing injection for sepsis: an overview of systematic reviews and meta-analyses

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Background: The effectiveness of Xuebijing injection (XBJ) on sepsis outcomes remain unclear, although a number of systematic reviews (SRs) and meta-analyses (MAs) on XBJ treatment for sepsis have been published. The aim of this overview is to evaluate the methodological quality and evidence quality of extant SRs/MAs and to provide comprehensive evidence of XBJ for sepsis.

Methods: Eight databases were comprehensively searched to collect MAs and SRs of XBJ for sepsis from their inception to September 30, 2020. The Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system were used to evaluate the methodological quality of SRs/MAs and the evidence quality of outcomes extracted from the included reviews.

Results: Twelve SRs/MAs were included for the overview, with number of randomized controlled trials (RCTs) from 8 to 49 and of participants from 399 to 3,884. According to the AMSTAR 2 results, all included SRs/MAs were rated as critically low-quality studies. According to the evaluation results of the GRADE system, out of 45 outcomes, only 1 (2.2%) was of high quality, only 10 (22.2%) were of moderate quality, 28 (62.2%) were of low quality, and 6 (13.3%) were of very low quality.

Discussion: XBJ is promising in the treatment of sepsis, but high-quality evidence is still lacking. In the future, rigorous MAs are needed following methodological requirements to provide robust evidence for definitive conclusions.

Keywords: Overview; Xuebijing; sepsis; systematic review; meta-analysis

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Sepsis is a devastating condition caused by dysregulated host response to infection which leads to organ failure and death (1). In 2017, an estimated 49 million incident cases of sepsis were recorded worldwide among which more than 40% were children younger than 5 years, and 11 million sepsis-related deaths were reported, representing about 1/5 of all global deaths (2). Sepsis not only imposes a high burden on hospitalized patients (3), but also affects their quality of life, because half of the discharged patients are still not completely recovered (4,5). It has become a global public health concern due to its high mortality and morbidity and substantial economic burden (6). Moreover, with aging of the population, the presence of more people suffering from chronic diseases or on immunosuppressive medications, and the increase in invasive procedures, the incidence of sepsis will continue to increase (7,8).

Sepsis is a medical emergency and should be treated as quickly and efficiently as possible once it has been identified. Each hour of delay in treatment over the ensuing 6 hours was associated with an average decrease in survival of 7.6% (9). Current managements for the treatment of sepsis are fluid resuscitation, source control, antibiotic therapy and organ support therapy (7). Despite modern advances in critical care, most of the managements for sepsis are largely supportive but not specific. In other words, sepsis is a common illness associated with substantial lethality but has no specific treatment. Sepsis thus still remains a scientific and clinical challenge. There is an urgent need to find new drugs and therapies for sepsis. Recently, Xuebijing injection (XBJ) originating from complementary and alternative medicines has been developed to treat sepsis.

XBJ consists of the following five Chinese herbs: *Hong Hua* (*Carthamus tinctorius* L.), *Chi Shao* (*Paeonia lactiflora* Pall.), *Chuan Xiong* (*Ligusticum chuanxiong* Hort.), *Dan Shen* (*Salvia miltiorrhiza* Bge.) and *Dang Gui* [*Angelica sinensis* (Oliv.) Diels] (10). Its main components are hydroxysafflor yellow A, paeoniflorin oxide, *Ligusticum chuanxiong* lactone I and paeoniflorin, etc. (11). And it has been approved for the treatment of sepsis in China since 2004 and has been widely used as an add-on treatment for sepsis or septic shock with few side effects (10). XBJ has many pharmacological mechanisms including anti-inflammatory, anti-coagulation, immune regulation, vascular endothelial protection, anti-oxidative stress and others (12).

Currently, a number of randomized controlled trials (RCTs) have been conducted (13-15), and subsequently increasing numbers of systematic reviews (SRs) and meta-analyses (MAs) (10,16-18), have arisen to evaluate the effectiveness of XBJ for sepsis. However, most of the SRs/MAs reported that the evidence supporting the effectiveness of XBJ is insufficient, and those SRs/MAs reported varied and heterogeneous results and low methodological quality, making it difficult to draw a comprehensive conclusion on the effectiveness of XBJ on sepsis. Furthermore, no critically designed overview has been performed to assess the reporting and methodological quality of the published SRs/MAs so far.

Therefore, this overview aims to evaluate the methodological quality and evidence quality of extant SRs/MAs and to provide comprehensive evidence to identify whether XBJ is an effective treatment for sepsis. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/lcm-21-13).

Methods

This overview of SRs/MAs has been conducted according to the methodological recommendations by the Cochrane Collaboration (19), and has been registered with INPLASY (20) (registration no. INPLASY2020120126).

Search strategy

The four international electronic databases of PubMed, Embase, Cochrane Library, and Web of Science and four Chinese electronic databases of the China National Knowledge Infrastructure Database (CNKI), WANFANG DATA, Chongqing VIP (CQVIP) and Chinese Biomedical Literature Database (CBM) were searched from their inception to September 30, 2020 without language restriction. The basic search strategies were as follows: ("sepsis" OR "severe sepsis" OR "septic shock") AND ("xuebijing" OR "xue bi jing" OR "XBJ") AND ("systematic review" OR "meta-analysis"). Meanwhile, we also searched conference abstracts and the reference lists of all retrieved articles to avoid missing relevant SRs/MAs. Details of the literature search strategy are shown in Appendix 1.

Literature screening

The database in Endnote software (version X9) were created. Duplicates were eliminated first, then titles and abstracts were read for the preliminary screening. Whenever we could not definitively exclude articles based on the titles and abstracts, full texts were downloaded and filtered again until all SRs/MAs were confirmed. Literatures were screened by two investigators (YL Shi and CT Chen), and any inconsistencies were discussed with the other two investigators (YD Xu and YJ Chen).

The inclusion criteria were: (I) patients were diagnosed with sepsis; (II) the intervention groups were XBJ plus routine treatment (RT); (III) the control groups were RT alone, and RT comprises fluid resuscitation, source control, antibiotic therapy and organ support therapy (7); (IV) at least one outcome followed was measured: 28-day mortality, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (the higher the score, the more frequent the need for monitoring and treatment), infection [measured by white blood cells (WBC) or procalcitonin (PCT) or C-reactive protein (CRP)], or coagulation function [measured by platelet (PLT) or activated partial thromboplastin time (APTT) or prothrombin time (PT)]; 5)

SRs/MAs of RCTs.

The exclusion criteria were: (I) interventions which combined XBJ with other drugs that affect the efficacy judgment (e.g., ulinastatin); (II) protocols of SRs/MAs, commentaries; (III) studies that published in abstracts forms for which full texts were unavailable; (IV) duplicate reports of the same study.

Data extraction

One researcher (YL Shi) extracted the following basic information: first author, publication date, number of included trials and participants, interventions, outcomes reported, quality assessment tools, and overall conclusions. Another researcher (CT Chen) checked it against the original, and if there was any discrepancy, the original text was referred and the data will be revised accordingly.

Methodological quality

The methodological quality of the included reviews was assessed by researchers (YL Shi and CT Chen) according to the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool (21), which contains 16 items with 7 items (2,4,7,9,11,13,15) were considered crucial domains that critically affect the validity of a review and its conclusions. Any inconsistencies were resolved via discussion with the other two authors (YD Xu and YJ Chen).

Each item was evaluated as "methodological requirements met", "methodological requirements partly met" or "methodological requirements not met". Overall confidence in the results of the reviews was rated "high" (none or one non-critical weakness), "moderate" (>1 non-critical weakness but no critical flaws), "low" (1 critical ± non-critical weakness), and "critically low" (>1 critical flaw ± non-critically weakness).

Evidence quality

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (22) was applied to evaluate the evidence quality of the concerned outcomes (28-day mortality, APACHE II scores, WBC, PCT, CRP, PLT, APTT, PT). For each outcome, we awarded a high grade to begin with as these were RCTs and downgraded if there were problems relating to risk of bias, inconsistency, indirectness, imprecision, or publication bias. We classified evidence quality as high, moderate, low, or very low. The two researchers (YL Shi and CT Chen) independently assessed the quality of evidences and resolved disputes through discussions with the other two researchers (YD Xu and YJ Chen).

Results

Literature selection

A total of 125 articles were identified from the database. Through strict screening, 12 reviews (10,16-18,23-30) were finally included in this overview. The flow diagram of literature screening is shown in *Figure 1*. The characteristics of excluded studies are shown in Appendix 2.

Study characteristics

Twelve SRs/MAs were included for the overview, with number of RCTs from 8 to 49 and of participants from 399 to 3,884. All of the 12 reviews conducted MAs. Two tools of quality assessment were employed in MAs, including Cochrane Handbook for Systematic Reviews of Interventions (10,18,26-28,30) and Jadad scale (10,16,17,23-25,29). The characteristics of the included 12 reviews are demonstrated in *Table 1*.

Methodological quality evaluation of included MAs

According to the AMSTAR 2 results, all included MAs were rated as critically low quality. The main causes influencing the methodological quality of reviews are item 2 (none of the included reviews contain an explicit statement that the review methods were established prior to the conduct of the review), item 3 (none of the included reviews explain their selection of the study designs for inclusion in the review), item 7 (none of the included reviews provide a list of excluded studies) and item 10 (none of the included reviews report on the sources of funding for the studies included in the review). The methodological quality evaluations of included reviews are presented in *Figure 2*.

Evidence quality evaluation of outcomes

We evaluated the evidence quality for the 45 outcomes according to the GRADE system. Only 1 (2.2%) outcome was rated as high-quality evidence, 10 (22.2%) were rated as moderate quality, 28 (62.2%) were rated as low quality, and 6 (13.3%) were rated as very low quality.

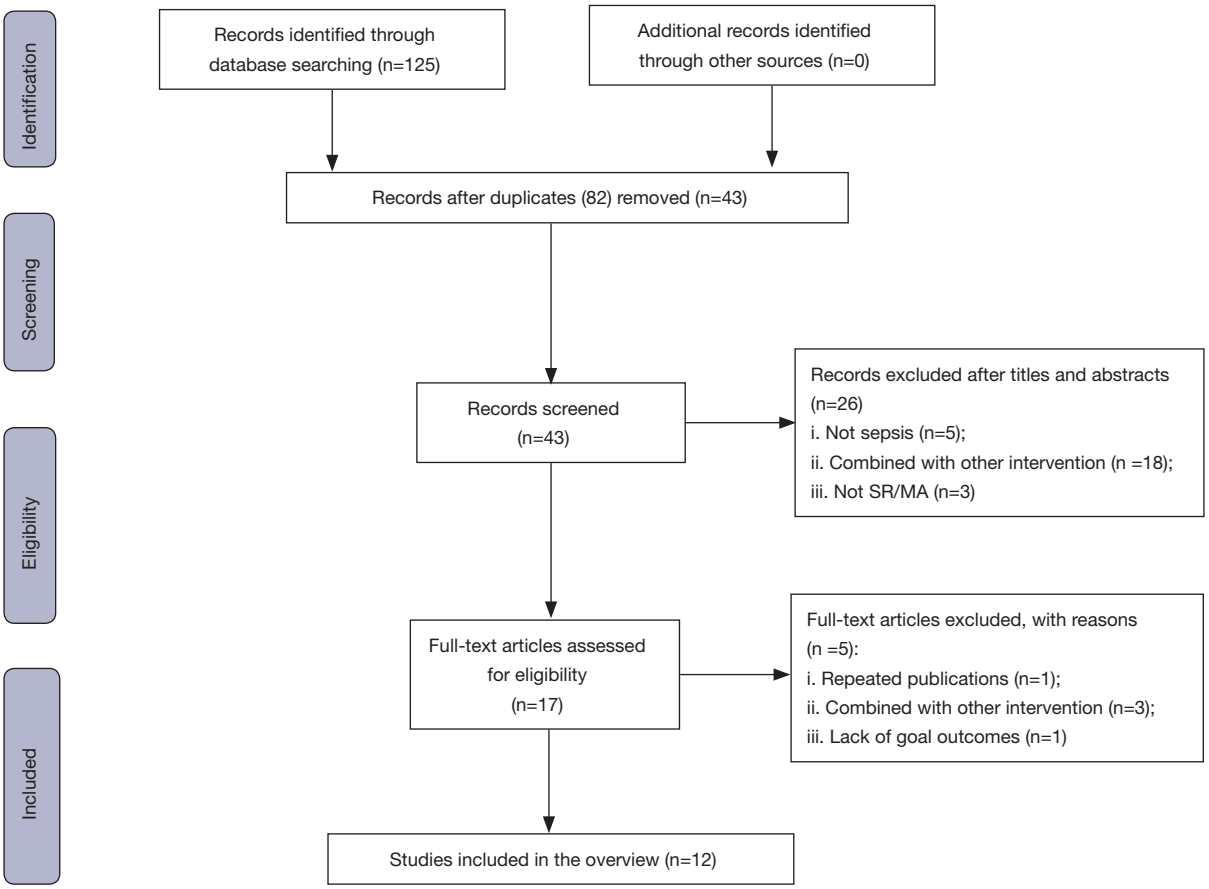

Figure 1 Study selection process for the overview.

The main factor for downgrading was the risk of bias (the included studies of all outcomes designed with a bias in random sequence generation, allocation concealment, blinding, or incomplete outcome data) and only 2 (4.4%) outcomes did not present this issue. Of 45 outcomes, evidence quality was downgraded for 17 (37.8%) due to imprecision, and for 24 (53.3%) due to inconsistency. There was no publication bias and indirectness in all outcomes. The details of the evidence quality are shown in *Table 2*.

Effectiveness of XBJ for sepsis

Twenty-eight-day mortality

A total of ten reviews (10,17,18,24-30) analyzed the 28-day mortality of XBJ for sepsis, with RCTs from 1 to 32 and participants from 21 to 2,315. Nine reviews suggested that upon comparison of the effects of XBJ plus RT *vs.* RT alone, the combined treatment had a significantly greater effect. However, one review (25) pointed out that XBJ could effectively reduce 28-day mortality at a dose of 100 mL/d, but not necessarily at 200 mL/d. According to the GRADE system, the quality of evidences for 28-day mortality was low to moderate.

APACHE II scores

Eight reviews (10,17,18,24,26-28,30), with number of RCTs from 4 to 34 and of participants from 177 to 2,838 compared the effects of XBJ plus RT treatment *vs.* RT treatment alone using the APACHE II scores, and the results revealed that the combined treatment had a better effect than RT alone. Only one (30) of them was rated high-quality evidence and the others were very low to low.

WBC

Six reviews (10,17,18,23,24,27) reported the effectiveness of XBJ for sepsis on WBC, among which 1–27 RCTs and 40–1,678 participants were included. One review (10) reported that XBJ combined with RT at doses of 400 and

Table 1 Basic characteristics of included studies

Study	N [n]	Treatment intervention [n]	Control intervention [n]	Outcome measures	Quality assessment tool	Main conclusion
Li *et al.*, 2018	16 [1,144]	XBJ + RT [581]	RT [563]	28-day mortality, mortality during treatment, APACHE II scores, WBC counts, body temperature, adverse events	Jadad Scale; Cochrane Handbook for Systematic Reviews of Interventions	Supplementation with XBJ in addition to RT may improve the 28-day mortality rate, APACHE II scores, WBC count and body temperature of sepsis patients without serious adverse events, but it may not reduce mortality during treatment, revealing a specific, remote effect of traditional Chinese medicine
Shi *et al.*, 2017	49 [3,884]	XBJ + RT [2,023]	RT [1,861]	28-day mortality, APACHE II score, PCT, WBC, CRP, NEU, temperature	Jadad Scale	XBJ could be a credible alternative for patients with sepsis and shorten the APACHE II score, WBC, CRP, NEU, temperature, and 28-day mortality. However, a need remains for larger samples, data from multi-centers, and high-quality studies to confirm the clinical efficacy of XBJ in the treatment of sepsis patients
Hou *et al.*, 2015	14 [867]	XBJ + RT [438]	RT [429]	PLT, APTT, PT, TT, FIB	Jadad Scale	XBJ injection may improve coagulopathy in patients with sepsis. High-quality and large sample clinical trials are needed for confirmation
Zhang *et al.*, 2020	15 [930]	XBJ + RT [468]	RT [462]	28-day mortality, APACHE II score, PLT, DD, TNF-α, vWF, sE-selectin, ESM-1, sTM	Cochrane Handbook for Systematic Reviews of Interventions	XBJ injection can not only effectively reduce the release of inflammatory factors, thereby improving vascular endothelial injury, reducing coagulation disorders and blocking coagulation-inflammation network; it can also increase the level of platelets, thereby repairing injured vascular endothelial cells, which has a certain value to reduce the condition of sepsis and improve the prognosis. It also provides some basis for the treatment of sepsis secondary to novel coronavirus pneumonia
Wu *et al.*, 2020	14 [938]	XBJ + RT [475]	RT [463]	28-day mortality, APACHE II score, WBC, CRP	Cochrane Handbook for Systematic Reviews of Interventions	XBJ injection can improve the clinical symptoms, significantly reduce the mortality, and has high clinical application value
Zhou *et al.*, 2016	8 [399]	XBJ + RT [202]	RT [197]	7-day mortality, 14-day mortality, 28-day mortality	Jadad Scale	Supplementation with XBJ in addition to RT may reduce relative average mortality rate, the available evidence was sufficient to support XBJ being used as an adjunctive therapy for septic shock patients

Table 1 (*continued*)

Table 1 (*continued*)

Study	N [n]	Treatment intervention [n]	Control intervention [n]	Outcome measures	Quality assessment tool	Main conclusion
Xu, 2016	8 [502]	XBJ + RT [251]	RT [251]	28-day mortality, APACHE II score, HLA-DR, $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes, $CD4^+/CD8^+$ T lymphocyte ratio	Cochrane Handbook for Systematic Reviews of Interventions	The available evidence showed that XBJ injection could improve immune dysfunction in sepsis
Li *et al.*, 2016	11 [803]	XBJ + RT [406]	RT [397]	Mortality during observation period, APACHE II score, WBC, PCT, CRP, ORR	Cochrane Handbook for Systematic Reviews of Interventions	The existing clinical evidence shows that the addition of XBJ injection on the basis of routine treatment can improve the clinical efficacy of septic shock
Sun *et al.*, 2015	13 [1,468]	XBJ + RT [756]	RT [712]	28-day mortality, APACHE II score, PLT, PT, APTT, TT, FIB, DD	Cochrane Handbook for Systematic Reviews of Interventions	XBJ injection can improve blood coagulation in patients with sepsis and also improve the prognosis of patients
Xu *et al.*, 2014	18 [1,172]	XBJ + RT [596]	RT [576]	28-day mortality	Jadad scale	Supplementation with XBJ in addition to RT can effectively improve the 28-day mortality rate of patients with sepsis
Li *et al.*, 2013	13 [1,280]	XBJ + RT [733]	RT [547]	28-day mortality, APACHE II score, PCT, WBC, CRP, PLT, PT, APTT	Jadad scale	XBJ injection has certain effect in improving the inflammatory response, coagulation function in patients with sepsis, reducing mortality and improving the APACHE II scores
Sun *et al.*, 2012	18 [1,080]	XBJ + RT [539]	RT [541]	WBC, PLT, TNF-α	Jadad scale	Supplementation with XBJ in addition to RT can reduce WBC count and TNF-α and increase the level of platelets compared to RT alone

N, number of included randomized controlled trials; n, number of participants; XBJ, Xuebijing injection; RT, routine treatment; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; WBC, white blood cells; PCT, procalcitonin; CRP, C-reactive protein; NEU, neutrophil; PLT, platelet; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; FIB, fibrinogen; DD, D-dimer; TNF-α, tumor necrosis factor-α; vWF, von Willebrand Factor; ESM, endothelial cell specific molecule; sTM, soluble thrombomodulin; HLA-DR, human leukocyte antigen-DR; ORR, overall response rate.

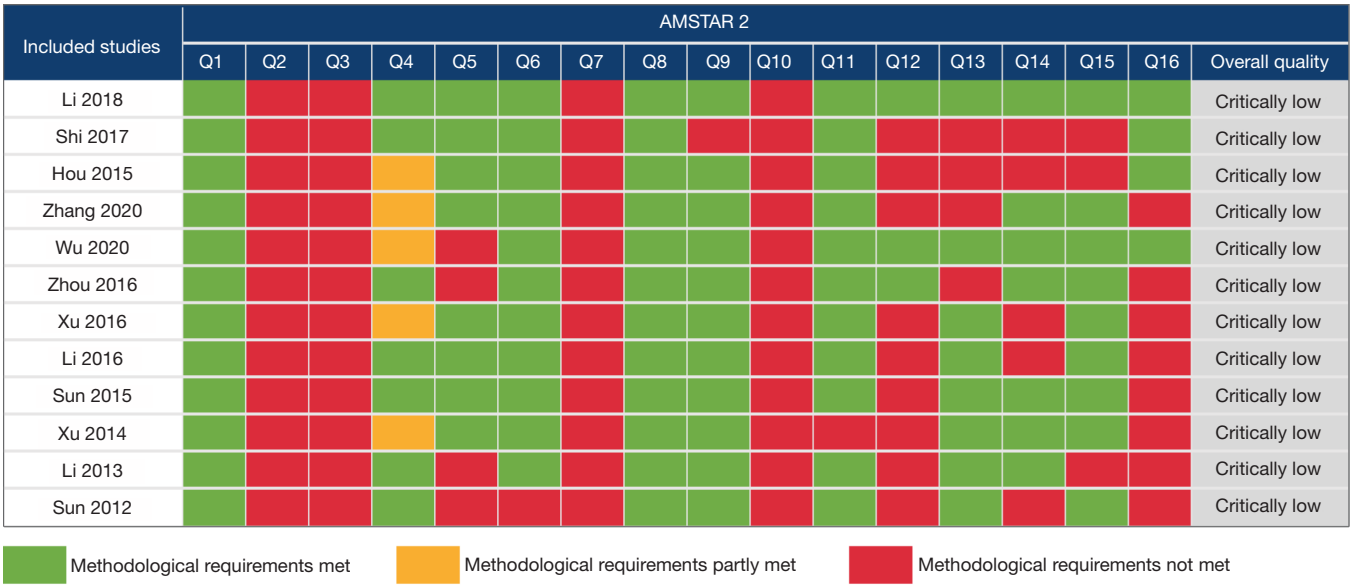

Figure 2 Methodological quality evaluation of meta-analyses (Mas) with Assessment of Multiple Systematic Reviews 2 (AMSTAR 2). Q1: did the research questions and inclusion criteria for the review include the components of population, intervention, comparison, outcome (PICO)? Q2: did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Q3: did the review authors explain their selection of the study designs for inclusion in the review? Q4: did the review authors use a comprehensive literature search strategy? Q5: did the review authors perform study selection in duplicate? Q6: did the review authors perform data extraction in duplicate? Q7: did the review authors provide a list of excluded studies and justify the exclusions? Q8: did the review authors describe the included studies in adequate detail? Q9: did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Q10: did the review authors report on the sources of funding for the studies included in the review? Q11: if meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Q12: if meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13: did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? Q14: did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Q15: if they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Q16: did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

100 mL/d worked better in improving WBC count than RT alone, but not at a dose of 200 mL/d group. The quality of evidence for WBC was very low to low.

CRP

Four MAs (17,18,24,27) reported the pooled results of XBJ plus RT *vs.* RT alone, and the number of RCTs included in the MAs ranged from 2 to 23 with participants from 306 to 1,643. Three MAs (17,18,27) with low-grade evidence indicated that combined treatment was superior to RT alone, and the reduction of the CRP was significantly higher in the XBJ plus RT group. However, one review (24) which was rated very low grade found no significant difference in CRP between two groups.

PCT

Three reviews (17,24,27) used the PCT level to compare the effects of XBJ plus RT *vs.* RT alone, and two reviews (17,27) showed that the combined treatment could significantly reduce the PCT more than RT alone, which had low quality of evidence. One MA (24), rated very low-grade evidence, analyzed 2 RCTs with 126 participants and came to the conclusion that there was no significant difference in PCT between the two groups.

Table 2 Quality of evidence in the included reviews based on GRADE criteria

Included studies	Intervention	Control	Outcomes	Effect estimate (95 % CI)	N [n]	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Li 2018	XBJ + RT	RT	28-day mortality	RR 0.62 (0.51, 0.76)	13 [934]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			APACHE II scores	MD –3.53 (–4.49, –2.54)	12 [792]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			WBC, 400 mL/d	MD –8.00 (–10.18, –5.82)	1 [40]	Serious[a]	NA	Not serious	Serious[c]	Not serious	L
			WBC, 200 mL/d	MD –2.38 (–5.01, 0.25)	3 [230]	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	VL
			WBC, 100 mL/d	MD –2.88 (–3.79, –1.96)	3 [242]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
Shi 2017	XBJ + RT	RT	28-day mortality	RR 0.51 (0.44, 0.59)	32 [2,315]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			APACHE II scores	WMD –3.70 (–4.31, –3.09)	34 [2,838]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			WBC	WMD –1.48 (–2.03, –0.94)	27 [1,678]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			PCT	WMD –1.26 (–1.63, –0.88)	19 [1,497]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			CRP	WMD –24.38 (–30.49, –18.26)	23 [1,643]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
Hou 2015	XBJ + RT	RT	PLT	MD 42.14 (22.42, 61.86)	12 [675]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			APTT	MD –4.81 (–7.86, –1.76)	14 [867]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			PT	MD –2.33 (–4.15, –0.51)	14 [867]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
Zhang 2020	XBJ + RT	RT	28-day mortality	OR 0.52 (0.38, 0.71)	8 [518]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			APACHE II scores	WMD –2.65 (–3.23, –2.08)	6 [466]	Not serious	Not serious	Not serious	Not serious	Not serious	H
			PLT	WMD 30.78 (25.65, 35.92)	5 [332]	Not serious	Not serious	Not serious	Serious[c]	Not serious	M
Wu 2020	XBJ + RT	RT	28-day mortality	RR 0.52 (0.40, 0.67)	8 [497]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			APACHE II scores	MD –5.48 (–7.52, –3.43)	9 [574]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			WBC	MD –2.26 (–3.35, –1.17)	10 [726]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			CRP	MD –37.43 (–56.70, –18.16)	7 [509]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
Zhou 2016	XBJ + RT	RT	28-day mortality	RR 0.61 (0.41, 0.90)	4 [200]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
Xu 2016	XBJ + RT	RT	28-day mortality	–	1 [21]	Serious[a]	NA	Not serious	Serious[c]	Not serious	L
			APACHE II scores	MD –2.83 (–4.82, –0.84)	4 [177]	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	VL
Li 2016	XBJ + RT	RT	28-day mortality	OR 0.33 (0.20, 0.57)	7 [372]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M

Table 2 (*continued*)

Table 2 (*continued*)

Included studies	Intervention	Control	Outcomes	Effect estimate (95 % CI)	N [n]	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
			APACHE II scores	MD –4.01 (–4.88, –3.13)	5 [273]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
			WBC	MD –4.31 (–6.73, –1.89)	2 [96]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
			CRP	MD –2.82 (–3.74, –1.91)	2 [312]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
			PCT	MD –1.42 (–1.90, –0.95)	2 [312]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
Sun 2015	XBJ + RT	RT	28-day mortality	OR 0.74 (0.56, 0.97)	5 [1,049]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			APACHE II scores	MD –3.30 (–5.38, –1.21)	5 [358]	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	VL
			PLT	MD 51.39 (45.55, 57.24)	12 [737]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			APTT	MD –3.88 (–4.77, –2.98)	12 [737]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			PT	MD –1.87 (–2.59, –1.16)	12 [737]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
Xu 2014	XBJ + RT	RT	28-day mortality, 100 mL/d	RR 1.20 (1.11, 1.29)	13 [850]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			28-day mortality, 200 mL/d	RR 1.24 (1.00, 1.54)	4 [194]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
Li 2013	XBJ + RT	RT	28-day mortality	OR 0.39 (0.27, 0.58)	8 [562]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			APACHE II scores	WMD –3.43 (–4.72, –2.15)	6 [375]	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	VL
			WBC	WMD –2.94 (–3.49, –2.38)	3 [274]	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	L
			CRP	WMD –9.81 (–21.51, 1.90)	4 [306]	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	VL
			PCT	WMD –7.25 (–16.58, 2.08)	2 [126]	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	VL
			PLT	WMD 40.63 (14.09, 67.16)	8 [519]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			APTT	WMD –4.59 (–6.69, –3.50)	8 [519]	Serious[a]	Not serious	Not serious	Not serious	Not serious	M
			PT	WMD –1.72 (–2.38, –1.06)	8 [519]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
Sun 2012	XBJ + RT	RT	WBC	WMD –1.87 (–2.92, –0.81)	9 [545]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L
			PLT	WMD 6.58 (4.01, 9.16)	7 [436]	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	L

[a], the design of the experiment with a large bias in random, allocation concealment, blinding, or incomplete outcome data; [b], the confidence interval overlaps less, the heterogeneity test P is very small, and the I^2 is larger; [c], the simple size is small, and the confidence interval is wide. CI, confidence interval; XBJ, Xuebijing injection; RT, routine treatment; RR, relative risk; MD, mean difference; WMD, weighted MD; WBC, white blood cells; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; PCT, procalcitonin; CRP, C-reactive protein; PLT, platelet; APTT, activated partial thromboplastin time; PT, prothrombin time; OR, odds ratios; H, high; M, moderate; L, low; VL, very low; NA, not applicable.

PLT

Five reviews (16,23,24,26,30) used the PLT to access the effectiveness of XBJ for sepsis, and 5–12 RCTs and 332–737 participants were included. All of them indicated that compared with the control group, PLT counts markedly increased in the treatment group. The quality of evidence for PLT was low to moderate.

APTT and PT

The APTT and PT were reported in three MAs (16,24,26) which encompassed 8–14 RCTs (519–867 participants). The pooled results demonstrated that XBJ plus RT could considerably shorten the APTT and PT when compared with RT alone. The quality of evidence for APTT was low to moderate and for PT was low.

Discussion

Main findings

In this overview, XBJ has exhibited potential effectiveness in reducing or improving the relevant outcomes, reflecting its possible clinical effectiveness on sepsis. It may be manifested in the improvement of non-endpoint outcomes: inflammation (WBC, PCT and CRP) and coagulopathy (PLT, shorting APTT and PT); the clinical endpoint: 28-day mortality, and a long-term prognosis indicator: APACHE II scores.

AMSTAR 2 and the GRADE system were used to assess the methodological quality and evidence quality of 12 MAs of XBJ for sepsis. The results for methodological quality using AMSTAR 2 showed that all of the reviews were rated as "critically low". Consistent drawbacks of methodology included the following: (I) lack of a prior protocol. Advanced registration can help to promote processing transparency and avoid post-decision bias (31). (II) Lack of explanation for the selection of the type of study for inclusion. This may lead to selection bias and lower credibility of the results. (III) Lack of a list of excluded studies. The availability of exclusion lists reduces selectivity bias and ensures research transparency. (IV) Lack of reports on sources of research funding. It is important to avoid other biases as the results of researches that receive corporate funding are more beneficial to the funder (32). Therefore, the absence of any of the above factors will reduce the credibility of the research results. We should avoid the occurrence of these problems in the future.

According to the GRADE system, this overview of 12 reviews and 45 outcomes showed that only 1 (2.2%) outcome was rated as high quality, 10 (22.2%) were rated as moderate quality, 28 (62.2%) were rated as low quality, and 6 (13.3%) were rated as very low quality. The main factors for downgrading evidence quality are as follows: (I) risk of bias, almost all the outcomes related to RCTs designed with a large bias in random sequence generation, allocation concealment, blinding, or incomplete outcome data. Due to the particularity of XBJ (a brown color liquid), blinding participants is difficult, which would require covering the bottles and transmission pipes during transfusion. (II) Imprecision, 17 (37.8%) outcomes were downgraded for small sample size and wide confidence interval, so large sample size RCTs are needed. (III) Inconsistency, 24 (53.3%) outcomes were downgraded due to inconsistency. Therefore, it is essential to perform the subgroup analysis to consider possible factors such as XBJ dose, diagnostic criteria, etc., in order to reduce inconsistencies. Despite the potential efficacy of XBJ, the strength of evidence for all outcomes is still unsatisfactory.

Interpretation to efficacy of XBJ

In this overview, the potential effectiveness of XBJ on sepsis may be manifested in the improvement of non-endpoint outcomes: inflammation (WBC, PCT and CRP) and coagulopathy (PLT, shorting APTT and PT); the clinical endpoint: 28-day mortality, and a long-term prognosis indicator: APACHE II scores.

Although the quality of evidence for most of the results was low, the efficacy of XBJ in treating sepsis was worthy of recognition. Twenty-eight-day mortality is the most appropriate endpoint in sepsis (33). In our results, only one review (25) showed that XBJ could not effectively reduce 28-day mortality at a dose of 200 mL/d. However, due to the low quality of evidence, the reliability of this result was reduced. Meanwhile, such a result suggested that it may be necessary to explore the effects of different doses of XBJ on the prognosis of patients with sepsis in future studies.

APACHE II scores were used to predict hospital mortality in septic patients (34), which consist of three parts: 12 acute physiological variables, age and chronic health status (35). Our results revealed that RT combined with XBJ could reduce the APACHE II scores and improve the prognosis of patients. But the credibility of the results is undermined by the fact that only one of the outcomes is high grade in quality and the rest are all very low to low

grade. It is suggested that more rigorous experimental design is needed to evaluate this index in the future.

WBC, PCT and CRP are all indicators of inflammation, PCT can reflect the active degree of systemic inflammation, and WBC and CRP are commonly used clinical indicators of inflammatory response. Of the 15 inflammatory outcomes, the positive outcomes were rated low, and the negative outcomes were rated very low. This suggested that positive outcomes may be more reliable, meaning that RT plus XBJ is more effective at reducing inflammation than RT alone. In addition, one review (10) also found that the dose of XBJ had an impact on the above-mentioned WBC, suggesting that subgroup analysis of XBJ dose is particularly necessary. Moreover, many reviews have indicated that XBJ could inhibit the release of pro-inflammatory cytokines such as TNF-α (23,30) and IL-6 (36) in patients with sepsis. There are some studies that have shown that XBJ could also promote the release of anti-inflammatory cytokine IL-10 in the early stage of sepsis (37,38). Further studies suggested that XBJ might play its anti-inflammatory role by down-regulating the expression of NF-κB, MAPK, and PI3K/Akt signaling pathway (39,40). More precise and comprehensive researches into the mechanism are needed.

PLT, APTT and PT are all effective indicators to reflect the coagulation function of the body, and all have strong sensitivity (41). Not only did this overview demonstrated that XBJ could improve coagulation function in patients with sepsis, but other MAs (42,43) had demonstrated this as well. XBJ reduced the release of tissue factor (44,45), increases the levels of plasma activated protein C (46) and inhibits the expression of plasminogen activator inhibitor-1 (47), thereby improving the coagulation dysfunction (12).

Inflammation (48), immunosuppression (49) and coagulation dysfunction (50) are key features in the pathogenesis of sepsis. In addition to the improvement of inflammatory response and coagulation dysfunction mentioned above, XBJ has also been reported to improve the immune function (28,51,52) of patients with sepsis. Therefore, XBJ has the effect of a multi-target treatment and a comprehensive regulation on sepsis. Over the last three decades, most of the therapeutics strategies successful in experimental sepsis failed in the clinical trials (53,54) and sepsis also remains a scientific and clinical challenge. The multi-target therapeutic advantage of XBJ is well-suited to address the critical points of the current sepsis clinical trial failure. Despite the low methodological quality and low evidence quality, it is still a good choice in the situation in which no treatment approved by the FDA is available for sepsis treatment. Moreover, the protection mechanism of XBJ is being further investigated (12,39).

In addition, it is worth nothing that XBJ is not only effective in treating sepsis, but also widely used in severe pneumonia (11), severe heat stroke (55), acute organophosphorus pesticide poisoning (56), rheumatoid arthritis (57) and other diseases. In particular, XBJ has been widely used in the treatment of COVID-19, which is the most pertinent application in the world at this moment, and its effect is remarkable (58-60). Researches on the application of XBJ to different diseases are ongoing.

Strengths and limitations

This overview is the first attempt to assess the methodological quality of SRs and MAs using the AMSTAR 2 tool and GRADE system to evaluate the quality of evidence for the efficacy of XBJ for sepsis. We conducted systematic and comprehensive searches and a reasonable literature screening, which may greatly reduce possible selection bias. Furthermore, this overview included SRs of randomized trials using strict inclusion standards, and excluded reviews with non-RCTs or observational studies in order to reduce the risk of mixed bias.

This overview still has limitations. Firstly, the evaluation process of AMSTAR 2 and GRADE is inevitably subjective and may result in bias. Secondly, the methodological quality and evidence quality of the included MAs were generally low; thus, results should be interpreted with caution. Third, we did not conduct the subgroup analysis and comparison of XBJ dose, so the effect of dose on XBJ efficacy needs further study.

Suggestions for future research

Since the methodological quality and evidence quality of MAs were generally low, the credibility of the results has been reduced, indicating that the efficacy of XBJ on sepsis is limited. We recommend that rigorous RCTs be designed, with attention to specific blinding and allocation concealment. For SRs and MAs, we suggest that subgroup analysis should be performed strictly according to consistent diagnosis and intervention, consistent treatment dose, and outcome measurement so as to reduce bias. In addition, safety evaluation of XBJ is rarely seen in RCTs, and only 2 (14,15) of the RCTs included in the 12 MRs reported adverse reactions such as skin itching and rash after the use

of XBJ. The RCTs should give more attention to reporting safety aspects.

Conclusions

In this paper, the inclusion results of MAs were extracted and analyzed systematically, suggesting that XBJ is clinically effective in the treatment of sepsis, especially in reducing inflammation, reducing mortality, improving coagulation dysfunction and prognosis. But this conclusion should be interpreted prudently, given the generally low methodological quality and low quality of evidence of the included MAs. In the future, rigorous MAs are needed following methodological requirements to provide robust evidence for definitive conclusions.

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Footnote

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

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Supplementary

Appendix 1: Details of the literature search strategy (from their inception to Sep 30, 2020)

PubMed

Search	Query	Items found
#1	((Xuebijing[Title/Abstract]) OR (Xue bi jing[Title/Abstract])) OR (XBJ[Title/Abstract])	208
#2	((((((sepsis[MeSH Terms]) OR (sepsis[Title/Abstract])) OR (severe sepsis[Title/Abstract])) OR (severe sepsis[MeSH Terms])) OR (septic shock[MeSH Terms])) OR (septic shock[MeSH Terms])) OR (septic shock[Title/Abstract])	191,603
#3	((Meta-Analysis[MeSH Terms]) OR (Meta-Analysis[Title/Abstract])) OR (Systematic Review[Title/Abstract])	275,484
#4	#1 AND #2 AND #3	13

Embase

Quick search

Search	Query	Items found
#1	sepsis:ab,ti OR 'severe sepsis':ab,ti OR 'septic shock':ab,ti	177,641
#2	xuebijing:ab,ti OR 'xue bi jing':ab,ti OR xbj:ab,ti	275
#3	'systematic review':ab,ti OR 'meta analysis':ab,ti	333,030
#4	#1 AND #2 AND #3	13

Cochrane Library

Search	Query	Items found
#1	(Xuebijing):ti,ab,kw OR (Xue bi jing):ti,ab,kw OR (XBJ):ti,ab,kw	86
#2	(sepsis):ti,ab,kw OR (severe sepsis):ti,ab,kw OR (septic shock):ti,ab,kw	12,560
#3	(systematic review):ti,ab,kw OR (meta-analysis):ti,ab,kw	25,202
#4	#1 AND #2 AND #3	2

Web of Science

Search	Query	Items found
#1	TS=(Xuebijing OR Xue bi jing OR XBJ)	347
#2	TS=(sepsis OR severe sepsis OR septic shock)	215,159
#3	TS= (Systematic Review OR Meta-Analysis)	446,963
#4	#1 AND #2 AND #3	15

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China National Knowledge Infrastructure Database

Search	Query	Items found
#1	SU=(脓毒症 + 脓毒血症 + 重症脓毒症 + 脓毒症休克 + 脓毒性休克) AND SU=(血必净) AND SU=(系统评价 + 荟萃分析 +Meta 分析 + 系统综述 + 循证评价)	23

Wanfang Data

Search	Query	Items found
#1	(主题 :“脓毒症”+“脓毒血症”+“重症脓毒症”+“脓毒症休克”+“脓毒性休克”)*(主题 :“血必净”)*(主题 :“Meta 分析”+″ 系统评价”+“荟萃分析”+“系统综述”+“循证评价”)	26

Chinese Biomedical Literature Database

Search	Query	Items found
#1	“脓毒症”[常用字段 : 智能] OR “脓毒血症”[常用字段 : 智能] OR “重症脓毒症”[常用字段 : 智能] OR “脓毒症休克”[常用字段 : 智能] OR “脓毒性休克”[常用字段 : 智能]	220,463
#2	“血必净”[常用字段 : 智能]	2,950
#3	“Meta 分析”[常用字段 : 智能] OR “系统评价”[常用字段 : 智能] OR “荟萃分析”[常用字段 : 智能] OR “系统综述”[常用字段 : 智能] OR “循证评价”[常用字段 : 智能]	198,658
#4	(“脓毒症”[常用字段 : 智能] OR “脓毒血症”[常用字段 : 智能] OR “重症脓毒症”[常用字段 : 智能] OR “脓毒症休克”[常用字段 : 智能] OR “脓毒性休克”[常用字段 : 智能]) AND (“Meta 分析”[常用字段 : 智能] OR “系统评价”[常用字段 : 智能] OR “荟萃分析”[常用字段 : 智能] OR “系统综述”[常用字段 : 智能] OR “循证评价”[常用字段 : 智能]) AND (“血必净”[常用字段 : 智能])	18

Chongqing VIP Database

Search	Query	Items found
#1	(M= 脓毒症 + 脓毒血症 + 重症脓毒症 + 脓毒症休克 + 脓毒性休克)*(M= 血必净)*(M=Meta 分析 + 系统评价 + 荟萃分析 + 系统综述 + 循证评价)	15

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Appendix 2: Characteristics of excluded studies by full text

	Author, year	Tittle	Reasons
1	Sun CL, 2012	Meta analysis of Xuebijing injection in the treatment of sepsis	Repeated publications (n=1)
2	Xu YQ, 2014	Meta analysis of randomized controlled trial of Chinese patent drug Xuebijing in the treatment of sepsis	Combined with other intervention (n=3)
3	Liu QQ, 2010	Systematic review of Xuebijing injection for the treatment of sepsis	
4	Hu J, 2010	Xuebijing injection for sepsis: a comprehensive review	
5	Zhang YL, 2010	Study on the effectiveness of Xuebijing injection in reducing sepsis mortality	Lack of goal outcomes (n=1)

https://dx.doi.org/10.21037/lcm-21-13