Systematic Review and Meta-Analysis

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Curative efficacy and safety of traditional Chinese medicine xuebijing injections combined with ulinastatin for treating sepsis in the Chinese population

A meta-analysis

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Abstract

Background: Sepsis is a clinically critical disease. However, it is still controversial whether the combined use of traditional Chinese medicine Xuebijing injections (XBJI) and western medicine can enhance curative efficacy and ensure safety compared with western medicine alone. Thus, this research consisted of a systematic review of the curative efficacy and safety of traditional Chinese medicine XBJI combined with ulinastatin for treating sepsis in the Chinese population.

Methods: A total of 8 databases were retrieved: 4 foreign databases, namely, PubMed, The Cochrane Library, Embase, and Web of Science; and 4 Chinese databases, namely, Sino Med, China National Knowledge Infrastructure (CNKI), VIP, and Wangfang Data. The time span of retrieval began from the establishment of each database and ended on August 1, 2017. Published randomized controlled trials about the combined use of traditional Chinese medicine XBJI and western medicine were included, regardless of language. Stata12.0 software was used for statistical analysis.

Results: Finally, 16 papers involving 1335 cases were included. The result of meta-analysis showed that compared with the single use of ulinastatin, traditional Chinese medicine XBJI combined with ulinastatin could reduce the time of mechanical ventilation, shorten the length of intensive care unit (ICU) stay, improve the 28-day survival rate, and decrease the occurrence rate of multiple organ dysfunction syndrome, case fatality rate, procalcitonin (PCT) content, APACKEII score, tumor necrosis factor (TNF)-α level, and interleukin (IL)-6 level.

Conclusion: On the basis of the common basic therapeutic regimen, the combined use of traditional Chinese medicine XBJI and ulinastatin was compared with the use of ulinastatin alone for treating sepsis in the Chinese population. It was found that the number of adverse events of combination therapy is not significantly increased, and its clinical safety is well within the permitted range. However, considering the limitations of this conclusion due to the low-quality articles included in the present research, it is necessary to conduct high-quality randomized controlled trials.

Abbreviations: 28-DSR = 28-day survival rate, CFR = case fatality rate, CG = Control Group, EG = Experimental Group, IL-6 = interleukin-6, ivgtt = intravenous drip, LICUS = length of ICU stay, MODS = occurrence rate of multiple organ dysfunction syndrome, PCT = procalcitonin, TMV = time of mechanical ventilation, TNF = tumor necrosis factor, USTT = Ulinastatin, XBJI = Xuebijing.

Keywords: meta-analysis, sepsis, traditional Chinese medicine, ulinastatin, xuebijing injection

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1. Introduction

Sepsis, one of multiple severe symptoms of patients with trauma, burn, shock, and infection, will induce multiple organ dysfunction syndrome (MODS), septic shock, and other more severe complications. The progression of sepsis is very fast, making it hard to predict, and its death rate is extremely high, which makes its clinical diagnosis and treatment more difficult.[1] There are approximately 20 million patients with sepsis in the world each year, and the corresponding mortality rate is 28% to 50%.[2] In addition, sepsis is closely associated with the intensive care unit (ICU) stay rate, the elongation of total days of hospital stay, and hospital mortality. Data from Australia and New Zealand have shown that the inpatient number due to sepsis accounts for more than 50% of the total number of ICU patients.[3] Some investigations have found that the treatment cost of sepsis each year is as high as $1.7 million, accounting for 40% of ICU expenses.[4] Early identification, timely diagnosis, and select effective treatment methods are the key to enhancing the success rate of sepsis treatment.

Many reports have confirmed the effectiveness of traditional Chinese medicine (TCM) Xuebijing injections (XBJI) and ulinastatin for treating sepsis in the Chinese population. The major ingredients of XBJI include Chinese angelica, salvia, Rhizoma Chuanxiong, paeonia lactiflora pall, and safflower carthamus. This formula is modified by Prof Wang Jinda from Wang Qingren's Xuefu Zhuyu Decoction based on many years of experience in Chinese and western medicine, as well as rescue experience of critically ill patients. The major effects of this formula include detoxication and tonification, elimination of bacteria and viruses, replenishment of vital energy, and invigoration of blood circulation. In addition, the formula can inhibit the role of the majority of the inflammatory mediators and endotoxins and help recover normal immune function in the body.[5] Ulinastatin, a component first found in human urine, is a kind of urinary trypsin inhibitor (UTI). This component can effectively and comprehensively inhibit the release of inflammatory factors trigged by multiple stimuli and biologically active human matter. It has been used for treating acute pancreatitis with good treatment outcomes. This treatment has inspired clinicians to use it for the treatment of inflammatory symptoms of sepsis. According to new clinical research achievements, UTI can effectively slow down the development of SIRS and MODS and show powerful protection for organs.[6]

With the development of the traditional theory of TCM in recent years, the effectiveness of TCM treatment methods has been known and recognized by clinicians and experts at home and abroad. In this research study, we selected the combined use of TCM XBJI and ulinastatin, a widely used combination therapy of Chinese and Western medicine in China.[7] To eliminate the existing controversy over drug combinations, we conducted a meta-analysis of randomized controlled trials (RCTs) in order to assess the effectiveness and safety of TCM XBJI and ulinastatin for treating sepsis in an objective manner.

2. Materials and methods

2.1. Search strategy

The selection process of this meta-analysis was implemented in strict accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). As this research is a meta-analysis of published papers, no signing of informed consent or application from an ethics committee is required. All relevant published documents were searched in eight databases, namely, PubMed, The Cochrane Library, Embase and Web of Science, Sino Med, China National Knowledge Infrastructure (CNKI), VIP, and Wangfang Data. The time span started from the establishment of each database and ended in August 2017. At the same time, abstracts, ancient books and records, meeting minutes, and nonelectronic magazines associated with the present research were retrieved manually. The keywords used were as follows: Chinese keywords were Chinese pinyin such as "Xuebijing," "Wusitading," "Nongduzheng," "Ganranxing-xiuke," "Nongduxingxiuke," while English searches combined subject terms (MeSH and EMtree) and free words, including "Sepsis," "Severe Sepsis," "Sepsis, Severe," "Pyemias," "Pyohemia," "Pyohemias," "Pyaemia," "Pyaemias," "Septicemia," "Septicemias," "Poisoning, Blood," "Blood Poisoning," "Blood Poisonings," "Poisonings, Blood," "Xuebijing," "Ulinastatin," etc. The retrieval strategy is detailed in Supplementary Table S1, http://links.lww.com/MD/C274.

2.2. Inclusion and exclusion criteria

2.2.1. Research type. Blinded or nonblinded, randomized clinical trials of TCM XBJI combined with ulinastatin, regardless of language.

2.2.2. Research objects. Patients who were diagnosed with sepsis according to the diagnostic criteria and relevant test results, regardless of whether it was caused by trauma, burn, shock, or infection, were selected as the research objects, without limiting age, gender source, the degree of illness, and time of illness. The diagnostic criteria were based on the Diagnostic Criteria Proposed by the American College of Chest Physicians/the Society of Critical Care Medicine (ACCP/SCCM) at Washington International Conference for the Definition of Sepsis in 2001,[8] the Predisposition, Infection, Response, and Organ Dysfunction (PIRO) Scoring System,[9] the Definition of Sepsis Confirmed by ACCP/SCCM (1991), and SIRS Diagnostic Criteria.[10,11] TCM diagnoses should comply with the Guideline for the Integrated Treatment of Chinese and Western medicine of Sepsis.[12]

2.2.3. Intervention measures. Experimental group included TCM XBJI + ulinastatin + basic treatment (without the limiting dosage, the times of administration, the course of disease, the interval of administration and course treatment). Control group included ulinastatin + basic treatment (without the limiting dosage, the times of administration, the course of disease, the interval of administration, and course treatment). Basic treatment included early fluid resuscitation, early active anti-infection, blood sugar control, and maintenance of homeostatic equilibrium. Mechanical ventilation was provided when sepsis resulted in acute lung injury/acute respiratory distress syndrome (ALI /ARDS), and comprehensive therapies such as the use of glucocorticoids and nutrition support were also offered when necessary.

2.2.4. Major research indicators. The evaluation indicators were as follows: time of mechanical ventilation; length of ICU stay; 28-day survival rate; occurrence rate of MODS; case fatality rate; procalcitonin (PCT); APACKEII score; tumor necrosis factor (TNF); interleukin (IL)-6.

2.2.5. Exclusion criteria. Exclusion criteria included non-RCT literatures; treatment drugs include those irrelevant to the present research; patients whose baseline data were significantly inconsistent; studies involving non-sepsis patients; incomplete case reports, reviews, animal experiments, conference papers or important data reports with no reply from the corresponding author(s); and the outcomes of the studies included involving no outcomes to be evaluated in the present research.

2.3. Data selection and extraction of relevant data

Two investigators (Xiao SH and Luo L) were asked to enter relevant search words to retrieve documents from the databases mentioned above. After a preliminary analysis of abstracts and the content of these documents, those that might be relevant for the study were selected. Then, the full text of each document was read to conduct a new round of selection according to the inclusion and exclusion criteria. Next, all the papers were re-reviewed to locate and account for deficiencies. Finally, the papers were cross-checked by the 2 investigators. In the case of disagreement, a third-party opinion was used for reference or an agreement was reached after discussion. A self-prepared

information sheet was used to summarize the literature data, and the major items included the first author, characteristics and distribution of the studied population, time of publishing, patient information (age, gender, condition, course of illness, etc.), intervention measures and controlled measures, outcomes, type of research design, etc.

2.4. Quality assessment

According to the Cochrane collaboration's tool for assessing risk of bias, domain-based risk of bias evaluation was performed from the perspectives of 6 domains[13]: whether there were implemented rules for allocation concealment and whether the method was reasonable; whether there was a program to describe randomized grouping and whether it was rigorous and correct; whether there were descriptions of dropouts and failure to follow up (including the underlying reasons), number of dropouts and failure to follow up and the processing scheme of relevant data; whether there was an implemented blind method (including its reasonability); whether there was an adopted intention to treat; whether randomization was successfully implemented. Each indicator was judged as "low risk of bias," "unclear risk of bias," and "high risk of bias."

2.5. Statistical analysis

The statistical analysis of the data collected for the meta-analysis was performed using the statistical software, Stata12.0. Numerical data were expressed as the arithmetical mean and standard deviation, and continuous variables were expressed as the weighted mean difference (WMD); for dichotomous variables, relative risk was used to standardize the efficacy analysis for effect size, and each effect size was expressed with a 95% confidence interval (95% CI). If multiple studies of the measurement data/continuous variables differed in unit, the same standard mean difference (SMD) and CI were selected after screening. The heterogeneity of the testing data was identified before meta-analysis. Heterogeneity was mainly used to judge whether study components came from the same entity. The sources of heterogeneity were methodological, statistical, and clinical heterogeneity. The judgment of heterogeneity in the primary studies mainly relied on a Chi-square distribution (X^2) Q test and I^2 index, and the inspected P value and I^2 value were introduced into the present study to judge its statistical heterogeneity. $P > .1$ and $I^2 < 50\%$ suggested no statistical heterogeneity between the listed research values. A meta-analysis was conducted on the data based on the fixed effect model. $P \leq .10$ and $I^2 \geq 50\%$ suggested statistical heterogeneity between the listed research values, and a meta-analysis was conducted on the data based on the random effect model. If clinical heterogeneity was obvious, sensitivity analysis or subgroup analysis was performed. If heterogeneity was very large, meta-analysis was not suitable, and only descriptive analysis was conducted.

2.6. Sensitivity analysis

To verify the stability of the results, sensitivity analysis was carried out to rule out studies that greatly impacted the results. No changes in the results after this process suggested that they were stable. In contrast, if the results were changed, the eliminated papers were analyzed and studied closely to identify the source(s) of heterogeneity, or a prudent conclusion or descriptive analysis was made.

2.7. Subgroup analysis

A subgroup analysis was conducted for results with large heterogeneity in the outcomes according to the information provided in the literature to identify the reasons underlying increased heterogeneity through subgroup analysis. At the same time, a suitable subgroup analysis could lower the heterogeneity of the results and increase their reliability.

2.8. Publication bias

Publication bias is very difficult to control because it is often caused by the fact that statistically significant results are more likely to be accepted and published by journals and magazines. A funnel plot is a very common method for testing publication bias.[14] Stata 12.0 software was used to test the publication bias of relevant indicators in more than 8 research articles with an Egger test, and a funnel plot was prepared accordingly.

3. Results

3.1. Search results

According to the document acquisition program, a total of 192 papers were obtained: the Cochrane Library (n = 0), PubMed (n = 1), Embase (n = 1), Web of Science (n = 1), SinoMed (n = 47), CNKI (n = 50), WanFang Data (n = 61), and VIP (n = 31). Noteexpress.2 was used to conduct duplicate checking and ultimately selected 74 papers. After reading the abstracts, irrelevant studies (n = 5), animal experiments (n = 4), and reviews (n = 12) were ruled out. Then, the entire text of these papers was obtained, and the studies that failed to meet the pre-determined inclusion criteria (n = 32), conference papers with incomplete data (n = 3), and repeated publications (n = 2) were eliminated by reading through the full article. In the end, 16 RCT studies in total[15–30] were included (see Fig. 1).

3.2. Basic characteristics and quality evaluation of the included research

Sixteen documents[15–30] involving 1355 patients (695 in the experimental group and 660 in the control group) were included

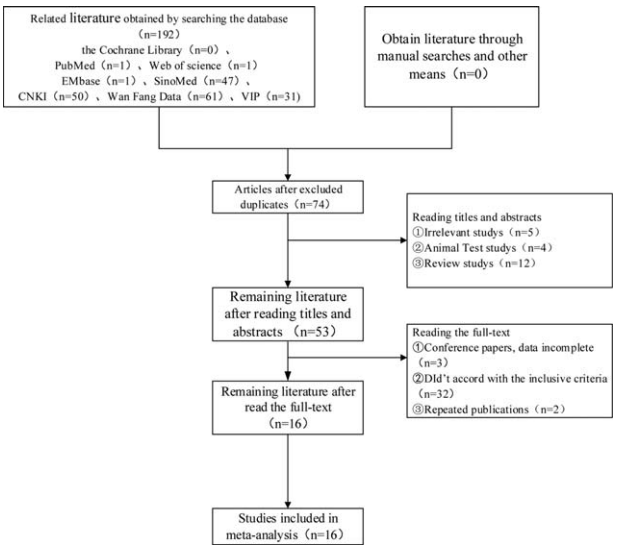

Figure 1. The flowchart of literature screening.

Table 1

Characteristics of included studies.

Ref.	Groups	Sample size	Age (median or mean or range), y	Is the baseline consistent?	Course of treatment, d	Intervention	Adverse reactions mentioned	Outcome
Mao et al[15]	EG	57	–	Yes	7	XBJI (100 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	No	①②③⑥
	CG	57	–		7	USTT (200,000 U/12 h,ivgtt)+BT	No	
Sun et al[16]	EG	20	–	Yes	10	XBJI (100 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	Yes	①②
	CG	20	–		10	USTT (300,000 U/12 h,ivgtt)+BT	Yes	
Ye and Wu[17]	EG	27	40 ± 5	Yes	7	XBJI (100 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	No	④⑤⑥⑦
	CG	23	40 ± 5		7	USTT (200,000 U/12 h,ivgtt)+BT	No	
A et al[18]	EG	15	47.1 ± 2.4	Yes	7	XBJI (50 mL/12 h,ivgtt)+USTT (300,000 U/12 h,ivgtt)+BT	Yes	①②
	CG	15	47.1 ± 2.4		7	USTT (300,000 U/12 h,ivgtt)+BT	Yes	
Zeng et al[19]	EG	27	49.20 ± 9.77	Yes	7	XBJI (50 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	Yes	⑦⑧⑨
	CG	27	45.25 ± 13.12		7	USTT (200,000 U/12 h,ivgtt)+BT	Yes	
Jiang and Mao[20]	EG	43	49.5 ± 11.2	Yes	7	XBJI (100 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	Yes	①②③④⑥⑦⑧⑨
	CG	43	49.3 ± 11.5		7	USTT (200,000/12 h, ivgtt)+BT	Yes	
Zhao and Liu[21]	EG	44	62.4 ± 11.1	Yes	7–10	XBJI (100 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	Yes	①②③⑥⑦⑧⑨
	CG	44	62.8 ± 10.5		7–10	USTT (200,000 U/12 h,ivgtt)+BT	Yes	
Zhou and Fang[22]	EG	61	43.47 ± 1.78	Yes	14	XBJI (100 mL/12 h,ivgtt)+USTT (900,000 IU/24 h,ivgtt)+BT	No	⑥
	CG	61	43.47 ± 1.78		14	USTT (900,000 IU/24 h,ivgtt)+BT	No	
Cao et al[23]	EG	135	64.3 ± 9.4	Yes	7	XBJI (100 mL/12 h,ivgtt)+USTT (100,000 U/12 h,ivgtt)+BT	No	⑥⑦
	CG	105	65.1 ± 9.1		7	USTT (100,000 U/12 h,ivgtt)+BT	No	
Li [24]	EG	40	48.2	Yes	7	XBJI (50 mL/12 h,ivgtt)+USTT (300,000 U/12 h,ivgtt)+BT	Yes	①②
	CG	40	48.2		7	USTT (300,000 U/12 h,ivgtt)+BT	Yes	
Shan [25]	EG	35	43.1 ± 9.6	Yes	7	XBJI (50 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	Yes	⑧⑨
	CG	35	41.8 ± 8.9		7	USTT (200,000 U/12h,ivgtt)+BT	Yes	
Liu et al[26]	EG	60	50 ± 6	Yes	14	XBJI (50 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	No	②⑤⑥
	CG	60	49 ± 5		14	USTT (200,000 U/12 h,ivgtt)+BT	No	
Ji et al[27]	EG	30	55.9 ± 8.3	Yes	7	XBJI (50 mL/12 h,ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	No	①②③⑦⑧⑨
	CG	30	56.4 ± 8.8		7	USTT (200,000 U/12 h,ivgtt)+BT	No	
Li [28]	EG	40	37.01 ± 10.79	Yes	7	XBJI (100 mL/12 h,ivgtt)+USTT (100,000 U/12 h,ivgtt)+BT	No	①②③⑦⑧⑨
	CG	40	36.72 ± 10.85		7	USTT (100,000 U/12 h, ivgtt)+BT	No	
Bian et al[29]	EG	26	39.2 ± 2.4	Yes	10	XBJI (50 mL/12 h, ivgtt)+USTT (100,000 U/12 h, ivgtt)+BT	No	⑨
	CG	26	38.7 ± 2.1		10	USTT (100,000 U/12 h,ivgtt)+BT	No	
Chen [30]	EG	35	33.4 ± 5.7	Yes	10	XBJI (100 mL/12 h, ivgtt)+USTT (200,000 U/12 h,ivgtt)+BT	No	⑤
	CG	34	33.0 ± 5.5		10	USTT (200,000 U/12 h, ivgtt)+BT	No	

(1) Time of mechanical ventilation; (2) length of ICU stay; (3) 28-day survival rate; (4) occurrence rate of multiple organ dysfunction syndrome (MODS); (5) case fatality rate; (6) PCT; (7) APACKEII score; (8) tumor necrosis factor (TNF); (9) IL-6.

BT = basic treatment: (early fluid resuscitation, early active anti-infection, blood sugar control and maintenance of homeostatic equilibrium, mechanical ventilation for sepsis-induced ALI/ARDS, use of glucocorticoids, and nutrition support and other comprehensive therapies where necessary), CG = control group, EG = experimental group.

in the present research, and the sample size ranged from 30 to 240 cases. The time span was 2008 to 2017. All the research was conducted in China. Eight research articles[15,16,18–21,24,25] reported adverse events, 1 research article[30] mentioned follow-up, and all the articles stated that the basic information about the patients was consistent with no statistically significant differences. The basic characteristics of these research articles are found in Table 1.

3.3. Summarization of quality and risk of bias of the included trials

According to the Cochrane system evaluator's manual and the Jada rating scale, the methodological quality evaluation forms are formulated, and all the methodological portions of the literature are evaluated by 2 independent reviewers; if a difference in evaluation arises, it is solved through discussion. The 16 documents included were low-quality research articles; 13 of them[15–17,20–22,24–30] mentioned grouping; 6 of them[15,20,25–27,29] reported the specific grouping methods (5 documents used correct grouping methods, while 1 document involved an inappropriate method); and the other research articles only analyzed grouping but failed to describe the grouping methods in detail. One document[30] mentioned information about failure to follow-up and dropout, while the rest of the 15 research articles failed to do so. All of the articles failed to mention the blinding of participants and evaluators, and 2 research articles[16,18] reported incomplete data. The summarized results of quality and risk of bias of the included trials are shown in Figures 2 and 3.

3.4. Time of mechanical ventilation (days)

Eight studies[15,16,18,20,21,24,27,28] reported results regarding the time of mechanical ventilation. These studies involved 556 cases in total (278 cases in the experimental group and 278 cases in the control group). The heterogeneity result showed low heterogeneity ($P = .098$, $I^2 = 42.0\%$). The random effect model was used. The meta-analysis result revealed that for the treatment of sepsis, the time of mechanical ventilation of the XBJI + ulinastatin group was shorter than that of the control group, showing a statistically significant difference [n = 8, SMD = -0.90, 95% CI (-1.07 to -0.72), $P < .00001$] (see Fig. 4). The result of the sensitivity analysis showed that the result remained stable (see Supplementary Figure S1, http://links.lww.com/MD/C274).

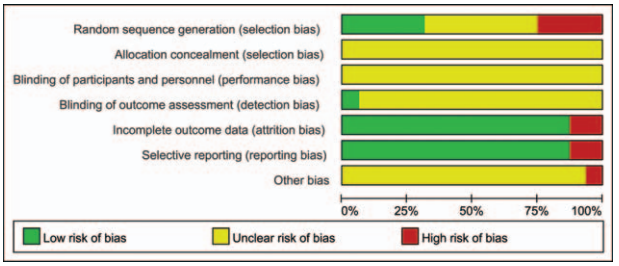

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages for all included studies.

3.5. Length of ICU stay (day)

Nine studies[15,16,18,20,21,24,26–28] reported results regarding the length of ICU stay. These studies involved 676 cases in total (338 cases in the experimental group and 338 cases in the control group). The heterogeneity result suggested low heterogeneity ($P = .193$, $I^2 = 28.3\%$). The random effect model was used. The meta-analysis result demonstrated that for the treatment of sepsis, the length of ICU stay of the XBJI + ulinastatin group was shorter than that of the control group, and there was a statistically significant difference between the 2 groups [n = 9, SMD = -0.89, 95% CI (-1.04 to -0.73), $P < .00001$] (see Fig. 5). The result of the sensitivity analysis revealed that the result was stable (see Supplementary Figure S2, http://links.lww.com/MD/C274).

3.6. Twenty-eight day survival rate

Five studies[15,20,21,27,28] reported the results of the 28-day survival rate. These studies involved 428 cases in total (214 cases in the experimental group and 214 cases in the control group). The heterogeneity result suggested no heterogeneity ($P = .878$, $I^2 = 0.0\%$), so the fixed effect model was used. The meta-analysis result demonstrated that for the treatment of sepsis, the 28-day survival rate of the XBJI + ulinastatin group was higher than that of the control group, showing a statistically significant difference between the 2 groups [n = 5, RR = 1.20, 95% CI (1.08–1.34), $P = .001$] (see Fig. 6).

3.7. Occurrence rate of MODS

Two studies[17,20] reported the results of the occurrence rate of MODS. These studies involved 136 cases in total (70 cases in the experimental group and 66 cases in the control group). The heterogeneity result suggested no heterogeneity ($P = .564$, $I^2 = 0.0\%$), so the fixed effect model was used. The meta-analysis result showed that for the treatment of sepsis, the 28-day survival rate of the XBJI + ulinastatin group was higher than that of the control group, and there was a statistically significant difference between the 2 groups [n = 2, RR = 0.63, 95% CI (0.41–0.97), $P = .038$] (see Fig. 7).

3.8. Case fatality rate

Three studies[17,26,30] reported the results of the case fatality rate. These studies involved 136 cases in total (122 in the experimental group and 117 in the control group). The heterogeneity result revealed no heterogeneity ($P = .931$, $I^2 = 0.0\%$), so the fixed effect model was employed. The meta-analysis result suggested that for the treatment of sepsis, the XBJI + ulinastatin group had a lower case fatality rate than that of the control group, and the difference between the 2 groups showed statistical significance [n = 3, RR = 0.45, 95% CI (0.29–0.70), $P < .00001$] (see Fig. 8).

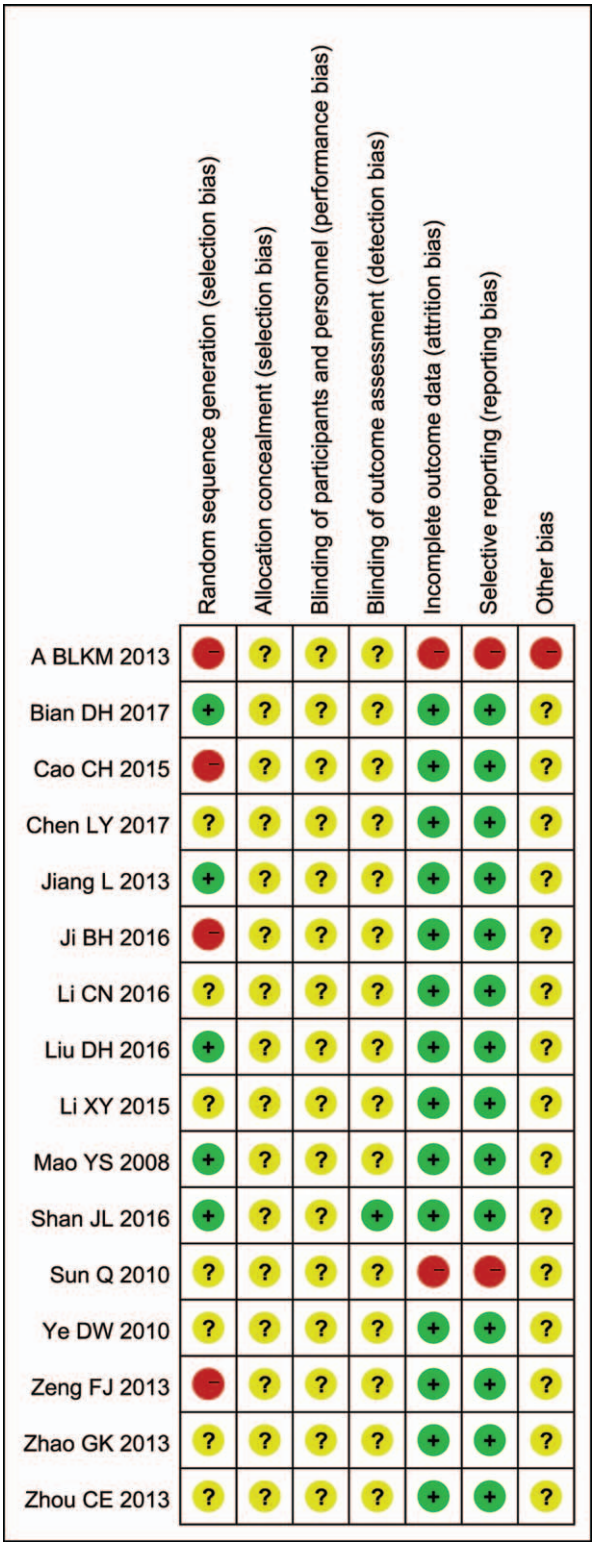

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

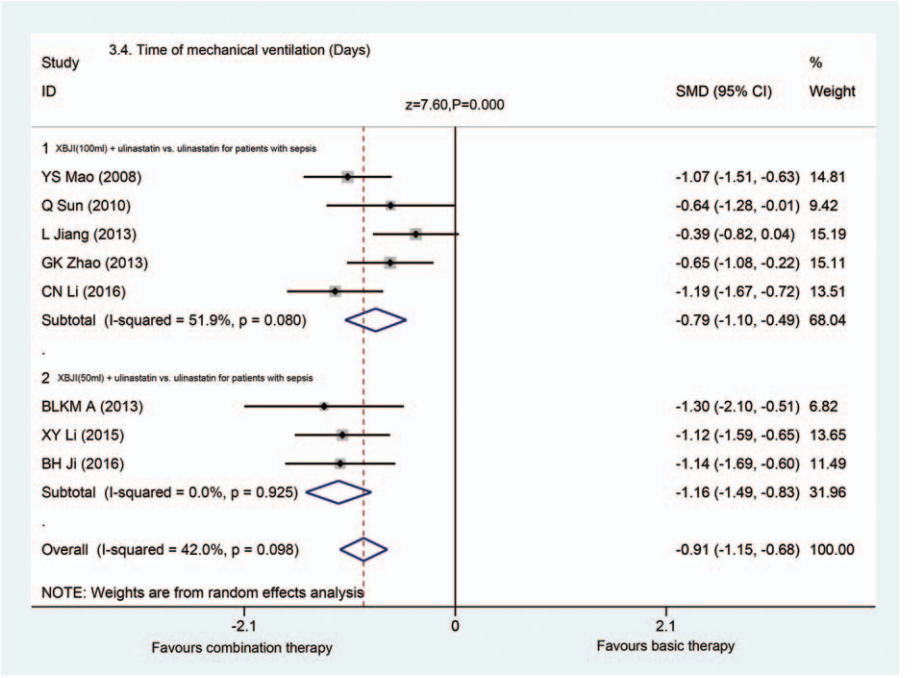

Figure 4. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of time of mechanical ventilation.

3.9. PCT (μg/mL)

Seven studies[15,17,20–23,26] reported the results of PCT. These studies involved 832 cases in total (416 in the experimental group and 416 in the control group). The heterogeneity result showed heterogeneity ($P = .107$, $I^2 = 96.4\%$), so the random effect model was employed. The meta-analysis result revealed that for the treatment of sepsis, the XBJI + ulinastatin group had a lower PCT level than that of the control group, showing a statistically significant difference [n = 7, SMD = -0.57, 95% CI (-0.77 to -0.38), $P < .00001$] (see Fig. 9). The sensitivity analysis found that the result was stable (see Supplementary Figure S3, http://links.lww.com/MD/C274).

3.10. APACKEII score (point)

Seven studies[17,19–21,23,27,28] reported the results of the APACKEII score. These studies involved a total of 662 cases (346 cases in

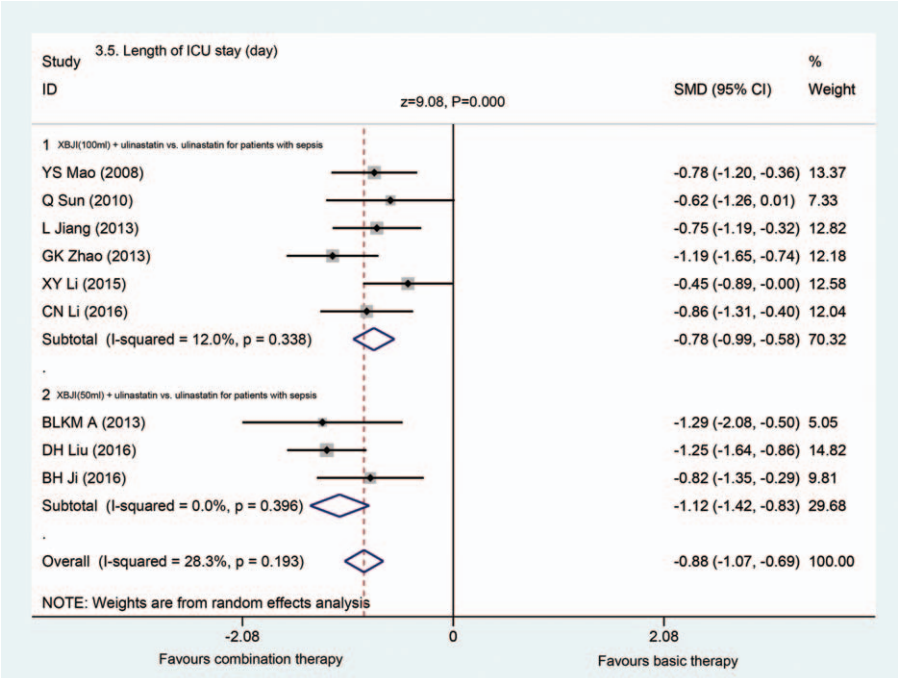

Figure 5. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of length of ICU stay.

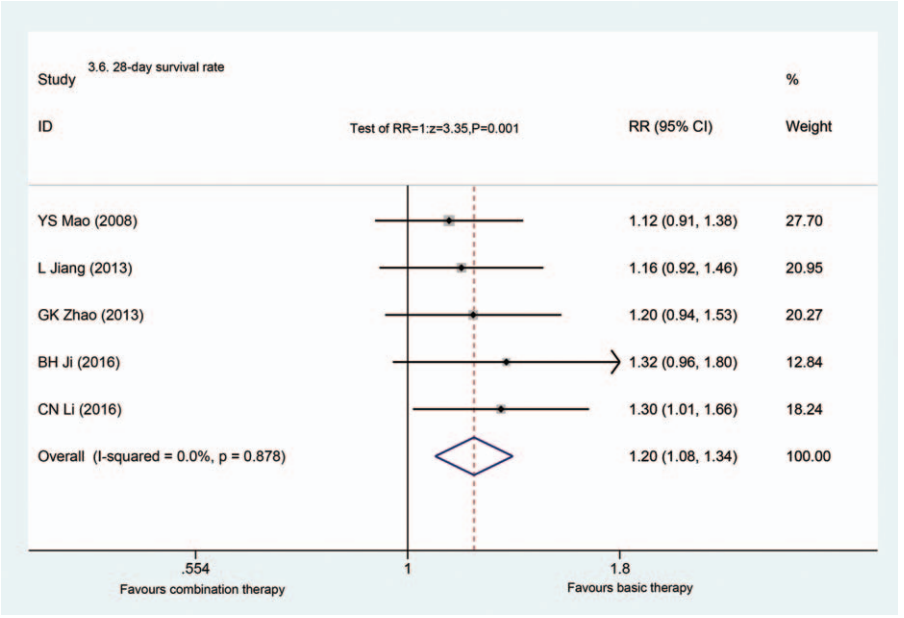

Figure 6. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of 28-day survival rate.

the experimental group and 316 cases in the control group). The heterogeneity results suggested heterogeneity ($P = .000$, $I^2 = 81.7\%$), so the random effect model was employed. The meta-analysis results showed that for the treatment of sepsis, the APACKEII score of the XBJI + ulinastatin group was lower than that of the control group, showing a statistically significant difference [n = 7, SMD = -1.16, 95% CI (-1.57 to -0.75), $P < .00001$] (see Fig. 10). The sensitivity analysis found that the result was stable (see Supplementary Figure S4, http://links.lww.com/MD/C274).

3.11. TNF-α (μg/mL)

Six studies[19–21,25,27,28] reported the results of TNF-α. These studies involved 428 cases in total, including 214 in the experimental group and 214 in the control group. The heterogeneity result suggested heterogeneity ($P < .00001$, $I^2 = 80.5\%$), so the random effect model was employed. The meta-analysis result showed that for the treatment of sepsis, the TNF-α level of the XBJI + ulinastatin group was lower than that of the control group, showing a statistically significant difference [n = 6, SMD = -1.31, 95% CI (-1.79 to -0.83), $P < .00001$] (see Fig. 11). The sensitivity analysis found that the result remained stable (see Supplementary Figure S5, http://links.lww.com/MD/C274).

3.12. IL-6 (ug/ml)

Eight studies[19–21,25,27,28] reported the results of TNF-α. These studies involved 480 cases in total (240 cases in the experimental

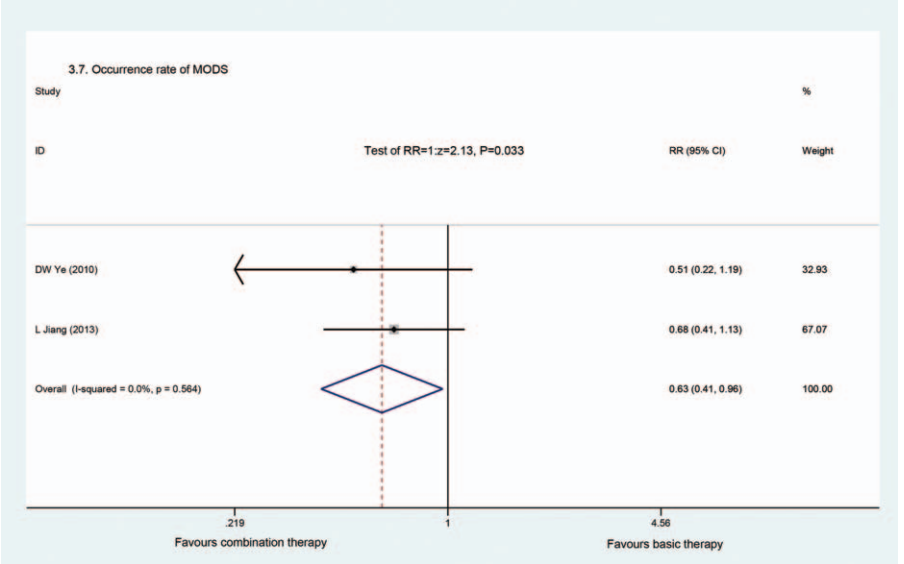

Figure 7. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of occurrence rate of MODS.

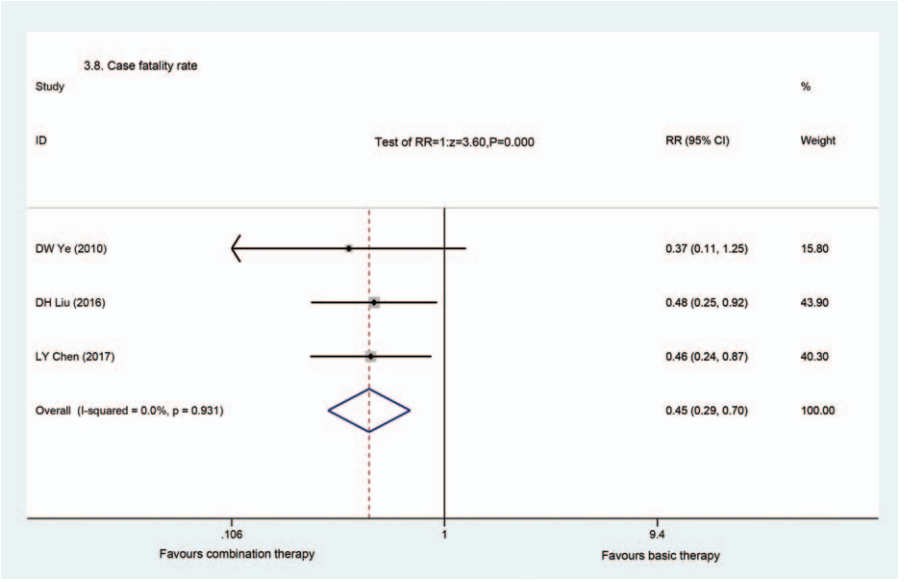

Figure 8. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of occurrence rate of case fatality rate.

group and 240 cases in the control group). The heterogeneity result suggested heterogeneity ($P=.020$, $I^2=60.1\%$), so the random effect model was employed. The meta-analysis result demonstrated that for the treatment of sepsis, the IL-6 level of the XBJI + ulinastatin group was lower than that of the control group, showing a statistically significant difference [n = 8, SMD = -1.52, 95% CI (-1.85 to -1.20), $P<.00001$] (see Fig. 12). The sensitivity analysis suggested that the result was stable (see Supplementary Figure S6, http://links.lww.com/MD/C274).

3.13. Publication bias

Stata12.0 software was used to detect publication bias of indicators whose number of documents was no smaller than 8 or $I^2 \geq 30$ in the outcomes with Egger test. $P \leq .5$ was considered to suggest publication bias. If a large publication bias was identified, the trim and filling method was employed to check whether the result was stable.[31]

Time of mechanical ventilation included the result of Egger test showed no publication bias: $P=.386$, 95% CI (-8.646638 to 3.868848).

Length of ICU stay states that the result of Egger test found no publication bias: $P=.970$, 95% CI (-5.301598 to 5.477319).

PCT stated that the result of Egger test suggested no publication bias: $P=.743$, 95% CI (-26.31368 to 20.06389).

APACKEII score stated that the result of Egger test revealed no publication bias: $P=.382$, 95% CI (-10.46285 to 4.777767).

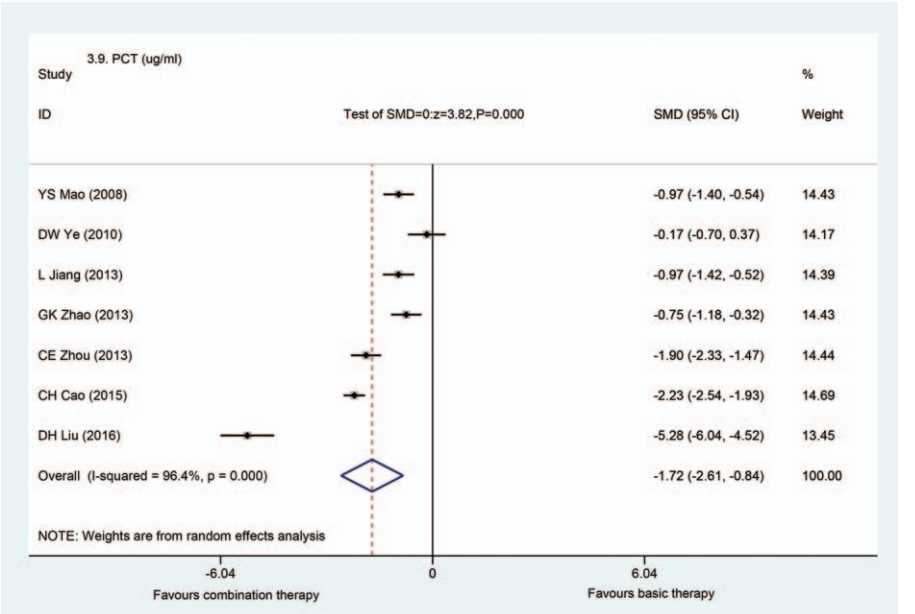

Figure 9. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of PCT level.

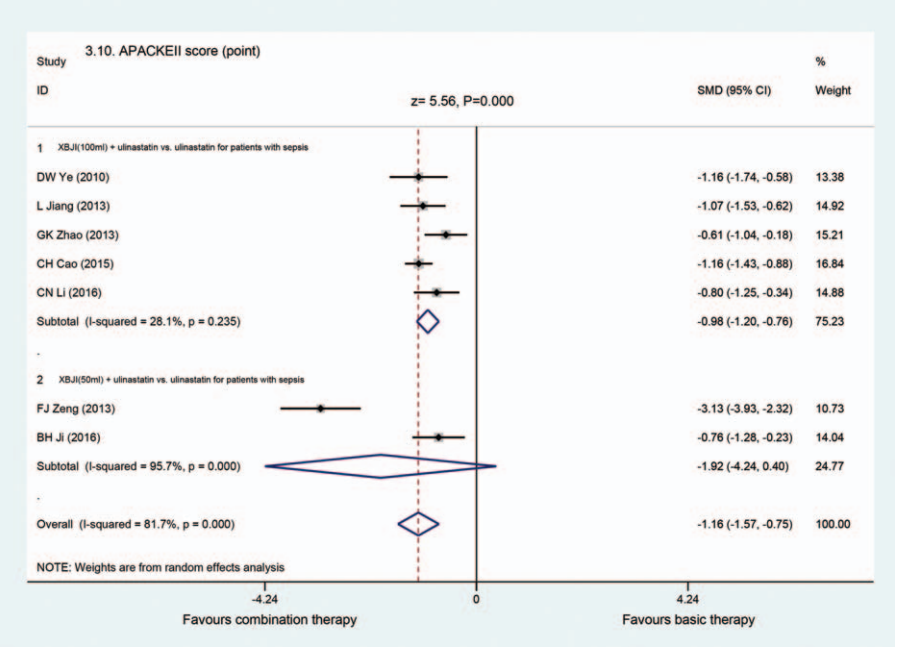

Figure 10. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of APACKEII score.

TNF-α stated that the result of Egger test demonstrated publication bias: $P = .011$, 95% CI (-18.12549 to -4.311364). The use of the trim and filling method showed result stability with no flip results.

IL-6 stated that the result of Egger test demonstrated publication bias: $P = .038$, 95% CI (-14.67149 to -0.6384177). The use of the trim and filling method revealed result stability with no flip results.

3.14. Adverse events

Eight studies reported adverse events. 6 of them reported that there was no adverse event during the course of treatment. One of them stated that there were 2 cases with itching and reddening of the skin and 1 case with phlebitis, while there were 2 cases with phlebitis, showing no statistically significant difference in adverse events ($P > .05$). All adverse events were mild reactions, no special treatment was required, and these reactions resolved spontane-

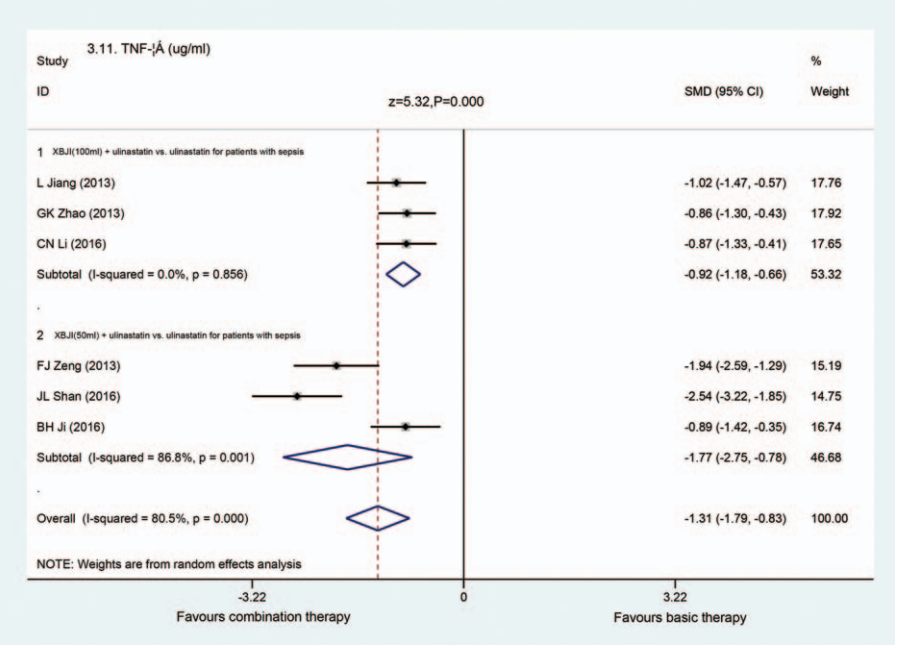

Figure 11. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of TNF-α level.

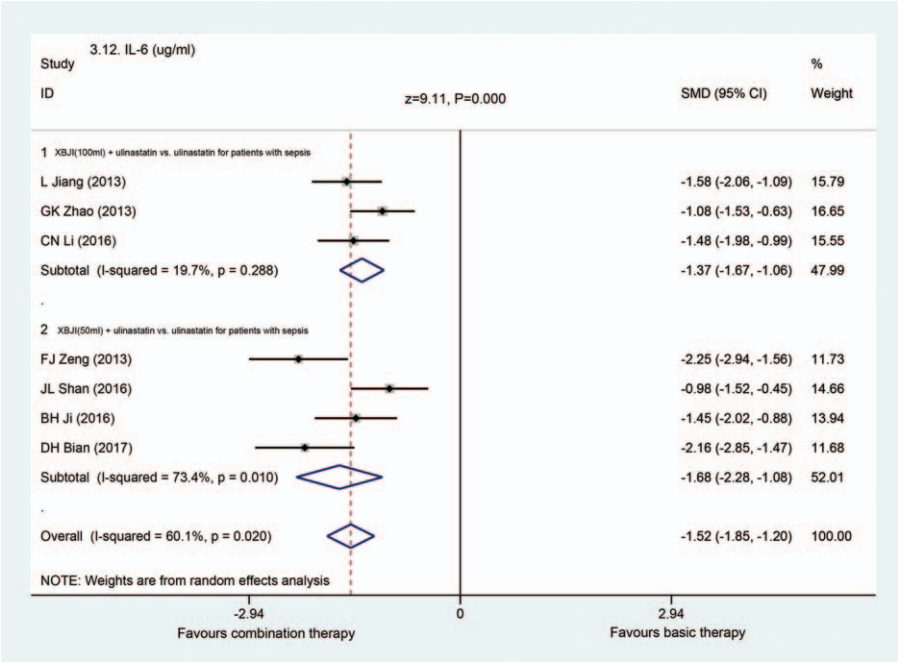

Figure 12. The comparative meta-analysis result of XBJI + ulinastatin versus ulinastatin for patients with sepsis in terms of IL-6 level.

ously after the drugs were stopped. One study reported that 2 patients suffered from rashes across the whole body after being giving ulinastatin, and such symptoms were alleviated after symptomatic treatment, with no other severe adverse reactions.

4. Discussion

MODS often occurs in patients with sepsis because of infection. Previously, anti-infection therapy was used to treat patients with sepsis by using multiple antibiotics. However, the majority of patients would suffer from MODS, bacterial drug resistance, and other adverse reactions.[32] Therefore, the combined use of TCM XBJI and ulinastatin is very common in the clinic.

XBJI mainly consists of Chinese angelica, salvia, Rhizoma Chuanxiong, paeonia lactiflora pall, and safflower carthamus. Its major functions include heat-clearing and detoxicating, as well as activating circulation to remove blood stasis. According to the relevant content of modern pharmacology, XBJI can also regulate the immune state of the body, reduce the total accumulation of endotoxins and the action of detoxicating against bacterial toxins, reduce the total quantity of oxygen free radicals in the circulatory system, inhibit the release amount of inflammatory mediators, regulate the overall microcirculation state of the body, protect and help recover vascular endothelial function, avoid platelet aggregation, and increase the total blood perfusion amount of organs. In addition, it can reduce the synthetic activity of fibroblasts by decreasing the release of mast cells to avoid inflammatory exudation and ensure normal vascular permeability when acute inflammation occurs.[33] In addition, XBJI can promote the absorption of the majority of necrosis materials and hematoma, help wounds heal, and promote the recovery of the body.

The major physical-chemical composition of ulinastatin is a glycoprotein whose relative molecular mass is 6700. It consists of 143 amino acids and mainly comes from the fresh urine of adult males. Such a substance can effectively inhibit the release and activity of multiple protein components (such as thiol enzyme, hyaluronidase, alpha-chymotrypsin, and fibrinolysin), effectively stabilize biological membranes, inhibit the release of active enzymes, reduce the generation of myocardial depressant factor (MDF), eliminate oxygen free radicals, reduce the release of multiple inflammatory factors, and effectively avoid the interactions between multiple inflammatory factors and cytokines. In addition, this substance has a powerful protective effect on vital organs of the body. XBJI and ulinastatin differ both in the major site and mechanism of action for the treatment of sepsis. The combined use of the 2 drugs can jointly block multiple sites of the overall inflammatory process and play a role in inhibiting the release of inflammatory factors, as well as have a synergistic effect of antagonizing against inflammatory factor. These 2 drugs supplement each other to directly enhance the overall prognosis of patients.

There are many therapies for the treatment of sepsis. As one of the available treatment modalities, drug therapy has been recognized by clinicians and relevant experts and scholars due to its efficacy. However, along with the development of TCM, the combination of Chinese and western medicine has been a relatively acceptable treatment method.[34] Nevertheless, there have still been many controversies about whether the combination of Chinese and western medicine will enhance the synergistic curative effect and increase adverse reactions. Therefore, this paper made a meta-analysis of the effectiveness and safety of TCM XBJI combined with ulinastatin. On the basis of the 16 articles included, 9 indicators of TCM XBJI combined with ulinastatin in treating sepsis were evaluated, including time of mechanical ventilation; length of ICU stay; 28-day survival rate; occurrence rate of MODS; case fatality rate; PCT; APACKEII score; TNF; and IL-6.

Through the research above, we can draw several conclusions. In terms of the clinical effect, for the treatment of sepsis, the combined use of TCM XBJI and ulinastatin can shorten the time of mechanical ventilation and the length of ICU stay, increase the

28-day survival rate, and decrease the occurrence rate of MODS, the case fatality rate, the PCT level, the APACKEII score, the TNF-α level, and the IL-6 level compared with the single use of ulinastatin for the treatment of sepsis. In terms of adverse reactions, 8 out of 16 research articles mentioned adverse reactions, but only 2 papers reported the occurrence of adverse reactions that were mild and alleviated or resolved after treatment.

In terms of publication bias, Egger test was carried out on 6 of the 9 indicators to detect publication bias. Except TNF-α and IL-6, there was no obvious publication bias found for the other indicators. The publication bias may be caused by the following factors[35,36]: there were only positive results in all the papers included; there were differences in the dosages of XBJI and ulinastatin; there were differences in the length of treatment; and there were direct individual differences among patients.

This systematic review also has some limitations: because of the limits of language and retrieval, there might be omissions in document retrieval and inclusion; the random allocation principle, allocation concealment, and blinding were not described in detail in some of the included documents; some studies had only a few endpoint indicators, some of which were not described in detail; and there might be certain heterogeneities between different studies, and TNF-α and IL-6 research articles had publication bias. Although the factors mentioned above may undermine the level of evidence of this meta-analysis, the selected trials are highly comparable, and the documents were selected in strict accordance with inclusion criteria. The conclusion of this research is currently only applicable to groups in China. Therefore, we hope to carry out high-quality research in areas outside China or other groups to provide more evidence to verify and improve the conclusions of this study. However, the result of the meta-analysis is stable and reliable and could provide certain reference for clinical practice and further research.

5. Conclusion

Although there are many deficiencies in this research, we can still obtain a definitive conclusion. Compared with the use of ulinastatin alone, the combined use of XBJI and ulinastatin showed an obvious synergic effect for the treatment of sepsis. Although several documents reported the occurrence of adverse events, the safety is still well within the acceptable range. The low quality of the included documents necessitates large sample size, multicenter, high-quality, clinical RCTs that attach importance to middle to long-term follow-up of patients in the future.

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Writing – original draft: Shi-Hui Xiao, Liang Luo, Hong-Ming Liu.
Writing – review & editing: Shi-Hui Xiao.

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