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Xuebijing in the treatment of patients with sepsis

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ABSTRACT

Background: There are more than 18 million patients diagnosed with sepsis every year. In China, Xuebijing (XBJ) injection is a traditional medicine that is widely used in the treatment of sepsis. However, the efficacy of XBJ in treatment of randomized controlled trials (RCTs) remains unclear. This meta-analysis was to evaluate the clinical efficacy of XBJ based on randomized case-control studies.

Methods: PubMed, Cochrane, Embase, Wanfang, CNKI, and WeiPu (VIP) databases were searched to identify all the relative randomized case-control. The latest research was done in June, 2016. Relative risks (RR), weighted mean difference (WMD) along with 95% confidence interval (95%CI) were used to analyze the main outcomes. Statistical analysis was performed using STATA 10.0 (TX, USA). The qualities of the involved articles were accessed by the Jadad scale.

Results: Forty-nine randomized case-control studies met the inclusion and exclusion criteria, with 1861 patients in the control group and 2023 patients in the XBJ group. Compared with the conventional therapy, XBJ injection could significantly reduce the APACHE-IIscore (WMD: −3.70, 95%CI: −4.31-[−3.09]), PCT (WMD: −1.26 μg/L, 95%CI: −1.63 μg/L-[−0.88 μg/L]), WBC (WMD: -1.48×10^9/L, 95%CI: -2.03×10^9/L-[-0.94×10^9/L]), CRP (WMD: −24.38 mg/L, 95%CI:−30.49 mg/L-[−18.26 mg/L]), NEU (WMD: −4.68, 95%CI: −8.32-[−1.04]), T^0(WMD: −0.50, 95%CI: −0.92-[−0.07]). The 28-day mortality of the XBJ group was significantly lower than the control group (RR: 0.51; 95%CI: 0.44–0.59).

Conclusion: XBJ injection has a significant clinical efficacy in the therapy of patients with sepsis. However, there is a need for more randomized, lager-sample size, high-quality, and multicenter studies to confirm the extract efficacy of XBJ injection.

1. Introduction

The definition of sepsis has three editions. Sepsis 1.0 and Sepsis 2.0 were published in 1992 and 2001, respectively. Sepsis 3.0 was published in the journal JAMA in 2016. Sepsis 1.0 is defined on the basis of infection and compatibility with 2 or more of the systemic inflammatory response syndrome (SIRS). Sepsis 2.0 added 21 diagnostic indicators to Sepsis 1.0. Sepsis 3.0 is defined on the basis of infection and a score equal or greater than 2 based on the sequential organ failure assessment (SOFA) [1]. The symptoms of sepsis are mostly caused by the immune system and result in aberrant coagulation, organ dysfunction, and the abnormal reaction of the immune system to different pathogenic microorganisms and toxins [2]. Every year, more than 18 million people are diagnosed with sepsis worldwide. Sepsis is a tremendous threat to people's health due to its mortality that is up to 30%–70%. The main drugs used for treating sepsis are antibiotics and glucocorticoids. The key point of success in treating sepsis is rapid and effective adjustment and control of the inflammatory reaction. However, these treatments also cause various side effects.

XBJ injection is a Traditional Chinese Medicine (TCM) that consist of *Carthamus tinctorius*, radix paeoniae rubra, ligusticum wallichii, salvia miltiorrhiza, angelica sinensis, etc. [3,4]. Based on the five TCMs, XBJ has the functions of blood-activating and stasis-dissolving, dredging sinew, scattering toxins, controlling the exaggerated inflammatory response that can have serious consequences for patients. XBJ injection has been approved by the State Food and Drug Administration (SFDA) of China, and it is widely used in the treatment of Systemic Inflammatory Response Syndrome, Multiple Organ Dysfunction Syndrome, and sepsis in clinical practices.

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In this meta-analysis, we propose to compare the clinical efficacy of XBJ and conventional therapy in the treatment of patients with sepsis.

2. Methods

2.1. Search Strategy

Cochrane, Embase, Pubmed, CNKI (China National Knowledge Infrastructure), WangFang and Weipu (VIP) databases were searched by the keywords: "Xuebijing", "XBJ", "sepsis" and so on. The search period was from the study inception to June, 2016 to identify the relevant studies. Others related articles and reference materials were also searched. All literature review was conducted by the two investigators. When disagreement occurred, a third investigator was involved until an agreement was reached.

2.2. Inclusion and Exclusion Criteria

A study was included in the analysis to determine if the pertinent literature were: (1) randomized case-control studies; (2) patients with sepsis or septic shock; (3) the treatment of the control group was conventional therapies (e.g., antibiotic therapy, nutrition supplement, etc.); (4) the therapy of the treatment group was conventional therapy and Xuebijing injection; (5) the outcome included 28-day mortality, Acute Physiology and Chronic Health Evaluation-IIscore (APACHE-IIscore), Procalcitonin (PCT), White Blood Cell (WBC), C-Reactive Protein (CRP), and Neutrophil (NEU), Temperature (T^0); and (6) only English and Chinese literature were included.

A study was excluded if it was: (1) previously published literature; (2) expert comment, conference report, systematic review, meta-analysis, or case reports; (3) the contents were theoretical or pharmaceutical analyses; (4) the treatment group did not include XBJ; (5) the data is statistically flawed; (6) the outcomes indexes were less than two. Two reviewers independently screened all studies to determine their conformance. Discrepancies were resolved by a third reviewer.

2.3. Data Extraction and Quality Assessment

The data that were extracted from previous studies consisted of two parts. The first part was the basic characteristics of the studies: the author name, year of publication, the interventions of the treatment and control groups, the sample size, the percentage of males, the age of the subjects, and the treatment period. The second part was the clinical outcomes: 28-day mortality, Acute Physiology and Chronic Health Evaluation-IIscore (APACHE-IIscore), Procalcitonin (PCT), White Blood Cell (WBC), C-Reactive Protein (CRP), Neutrophil (NEU), and Temperature (T^0). We evaluated the quality of all the studies using the Jadad Scale. The checklist consisted of five items: statement of randomization, appropriateness of randomized sequence, use and description of double blind testing method, and detail of withdrawals and dropouts. If the score was less than 3, we defined the study as low-quality and a high bias risk. If the score exceed 3, we defined the study as high-quality and low bias risk. The above review was independently conducted by two reviewers and disagreements were resolved by discussion until a consensus was reached.

2.4. Data Analysis

Chi-square and I^2 tests were used to test the heterogeneity of clinical trial results. When the Chi-square test P-value was <0.05 and the I^2 test value was $>30\%$, we determined it was heterogeneous and analysis by a random-effects model. When the Chi-square test P-value was >0.05 and the I^2 test value was $<30\%$, it was determined to be acceptable homogeneous data and assessed by a fixed-effects model. The continuous variables were expressed as the mean $\pm$ standard deviation. The categorical data are presented as frequencies and percentages. Relative risk (RR) along with 95% CI was used to analyze the 28-day mortality. Weighted mean difference (MD) and 95% CI were used to determine the Global Symptom Score (GSS), Visual Analogue Scale (VAS), Distal Motor Latency (DML), Compound Muscle Action Potential (CMAP), Motor Never Conduction Velocity (MNCV), Distal Sensory Never Latency (DSL), Sensory Nerve Action Potential (SNAP), Wrist-plam Sensory Nerve Conduction (W-P SNCV), Sensory Conduction Velocity (SCV). Two-tailed P-values less than 0.05 were considered statistically significant. All statistical analyses were performed with STATA 10.0 (TX, USA).

3. Results

3.1. Study Description

873 articles were selected from the initial searching, and 779 articles were excluded by screening the titles or abstracts. 49 articles were included in the meta-analysis and 45 articles were excluded for various reasons (e.g., repeat publication, the subject did not have sepsis, no clinical outcome data or invalid data, XBJ injection efficacy was not addressed). The basic information of the included studies is presented in Fig. 1. 1861 patients were in the control group and treated by conventional therapy. 2023 patients in the XBJ group were treated with XBJ injection along with a conventional treatment. The mean Jadad score of the included studies was 3.08 and only 14 studies had a score of 4.

3.2. 28-Day Mortality

32 articles [5-36] provided data of 28-day mortality, based on the Chi-square test $P = 0.968 > 0.05$ and $I^2 = 0.0\% < 30\%$. We selected the fixed-effects model to analyze 28-day mortality. In Fig. 2, the results show the 28-day mortality (RR: 0.51; 95%CI: 0.44–0.59) of the XBJ group was lower when compared with the control group.

3.3. APACHE-II Score

34 publications [6,8-10,12,13,16,18,19,21-26,28-45] analyzed the APACHE-II score, and we chose the random-effects model for the Chi-square test $P = 0.00 < 0.05$ and $I^2 = 71.2\% > 30\%$. Compared with the conventional therapy (Fig. 3), the XBJ injection could significantly reduce the score of APACHE-II (WMD: −3.70, 95%CI: −4.31-[−3.09]).

3.4. Procalcitonin (PCT)

19 articles [5,7,11-14,18,23,29,33,37-39,44-49] provided the result of PCT. Through the analysis of the Chi-square test $P = 0.00 < 0.05$ and $I^2 = 94.9\% > 30\%$, a random-effects model was used to analyze the

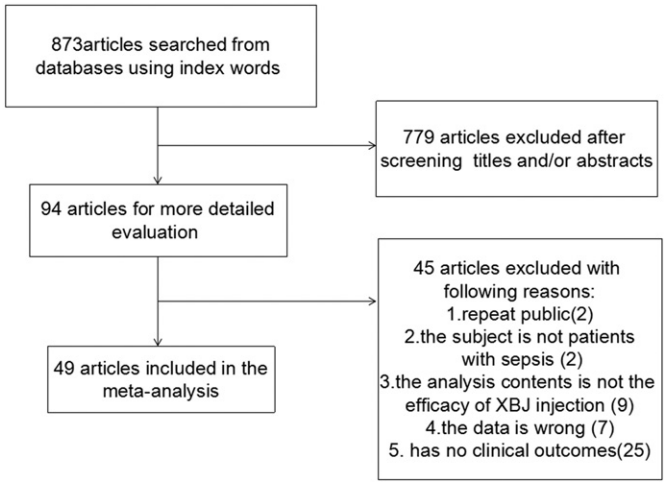

Fig. 1. The flow diagram.

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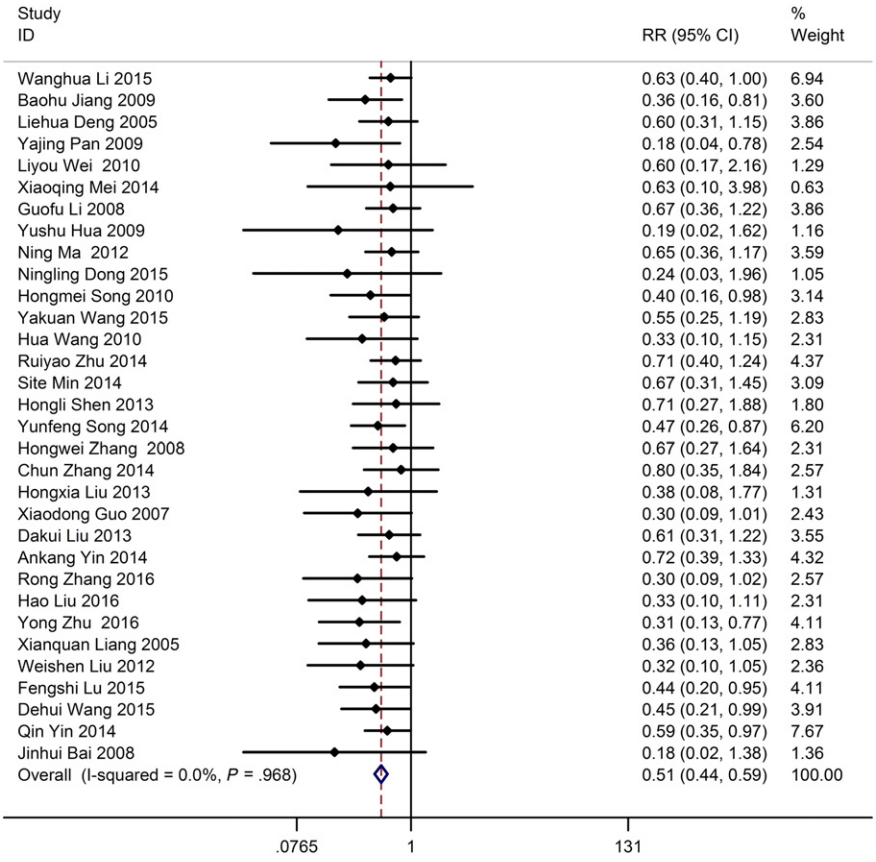

Fig. 2. Meta-analysis of 28-day mortality change.

WMD of PCT. The results (Fig. 4) show that XBJ injection could significant reduce the PCT (WMD: −1.26 μg/L, 95%CI: −1.63 μg/L-[−0.88 μg/L]).

3.5. White Blood Count (WBC)

27 articles [5,7,8,11,12,14,15,17,18,20,23-25,29,32,34,36-39,45,46,48-52] provided the result of WBC, and a random-effects model was chosen to analyze the WMD of WBC based on the Chi-square test P = 0.00 < 0.05 and I^2 = 73.6% > 30%. Compared with the conventional treatment (Fig. 5), the XBJ therapy decreased the WBC (WMD: -1.48×10^9/L, 95%CI: -2.03×10^9/L-[-0.94×10^9/L]).

3.6. C-Reactive Protein (CRP)

23 articles [8,12,14,17,18,20,23-27,29,33,37-39,42,45,47-49,52,53] provided the result of CRP. Through the analysis of the Chi-square test P = 0.00< 0.05 and I^2 = 95.9% > 30%, a random-effects model was used to analyze the WMD of CRP. XBJ injection could shorten the CRP (WMD: −24.38 mg/L, 95%CI:−30.49 mg/L-[−18.26 mg/L]) compared with the conventional treatment (Fig. 6).

3.7. Neutrophile (NEU)

14 publications [5,7,11,12,15,17,18,20,32,43,45,49-51] analyzed the NEU, and we chose a random-effects model for the Chi-square test P = 0.00< 0.05 and I^2 = 97.8% > 30%. Compared with the conventional therapy (Fig. 7), the XBJ injection could significantly reduce NEU (WMD: −4.68, 95%CI: −8.32-[−1.04]).

3.8. Temperature (T^0)

13 articles [5,11,12,14,15,17,24,25,34,36,46,49,50] analyzed the T^0, and a random-effects model was chosen for the Chi-square test P = 0.00< 0.05 and I^2 = 97.81% > 30%. XBJ therapy could significantly shorten T^0 (WMD: −0.50, 95%CI: −0.92-[−0.07]) compared with the conventional therapy (Fig. 8).

4. Discussion

In previous studies many scholars have analyzed the different treatments of sepsis. Li Q et al. [54] found that a treatment group (i.e., XBJ plus ulinastatin) could reduce the level of IL-6 and PCT, shorten the average length of hospitalization, and duration of mechanical ventilation. However, the TNF-α of the experimental and control groups had no statistical differences. Zhou GS et al. [55] reported that XBJ and ulinastatin could shorten the average length of hospitalization, the duration of mechanical ventilation, and the APACHEIIscore when compared with a single use of ulinastain or XBJ or conventional therapy. Compared with only using XBJ, XBJ and ulinastain could reduce the mortality. Compared with the ulinastain, ulinastain and XBJ could shorten the level of IL-6. Compared with conventional therapy, XBJ and ulinastatin could significantly shorten the level of IL-6 and PCT. Xu YQ et al. [56] included 18 RCT studies to analyze the mortality of XBJ and conventional therapy, the results showed that XBJ combined with conventional therapy could significantly improve the 28-day survival rate. Sun CL et al. [57] made a conclusion that XBJ could significantly shorten the level of WBC, PCT, and TNF-α. Hou SY et al. [58] reported that compared with a placebo, the XBJ injection significantly improved platelets; shortened the time of activated partial thromboplastin, prothrombin, and thrombin. However, there was no significant difference of fibrinogen between the two groups.

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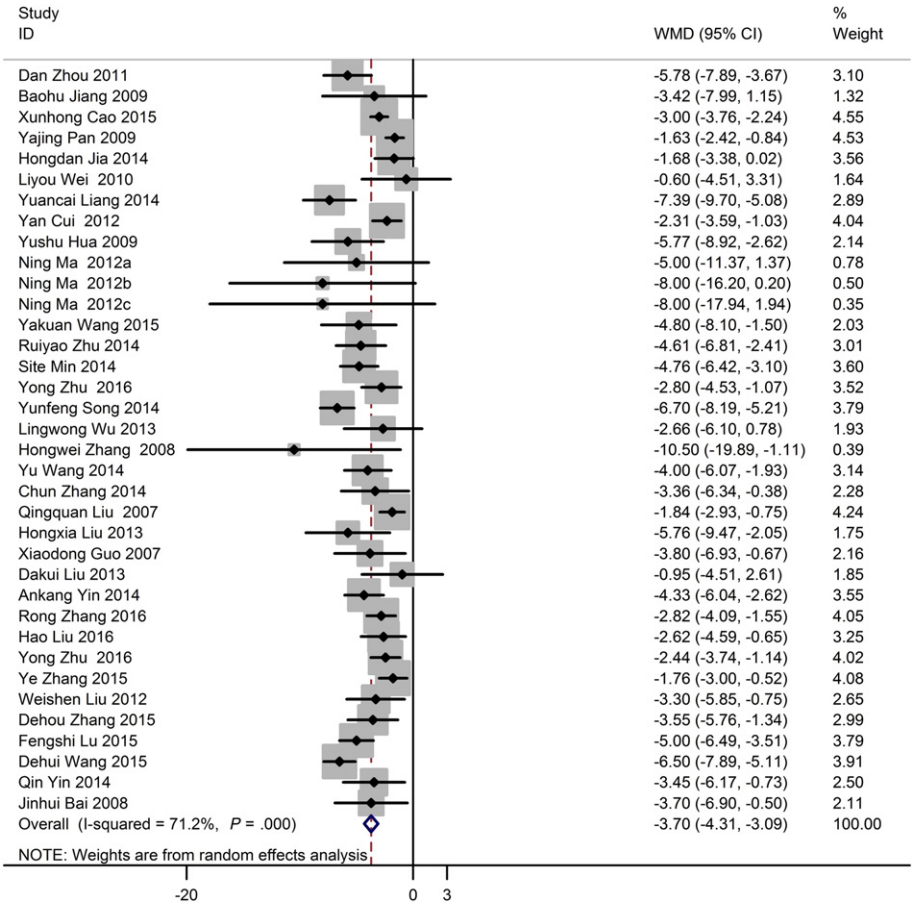

Fig. 3. Meta-analysis of APACHE-II SCORE change.

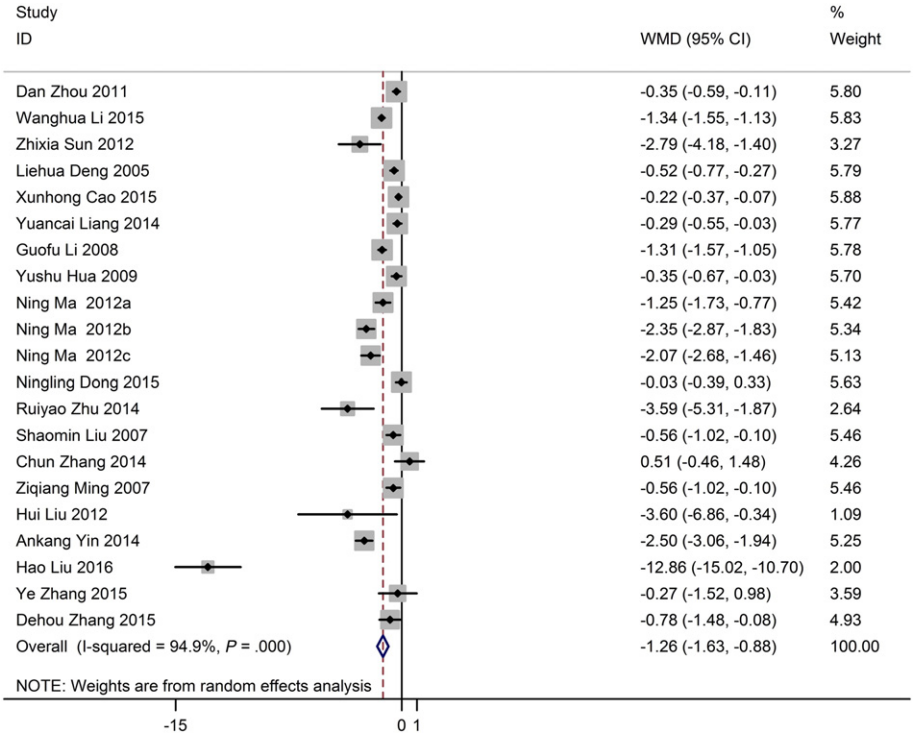

Fig. 4. Meta-analysis of Procalcitonin (PCT) change.

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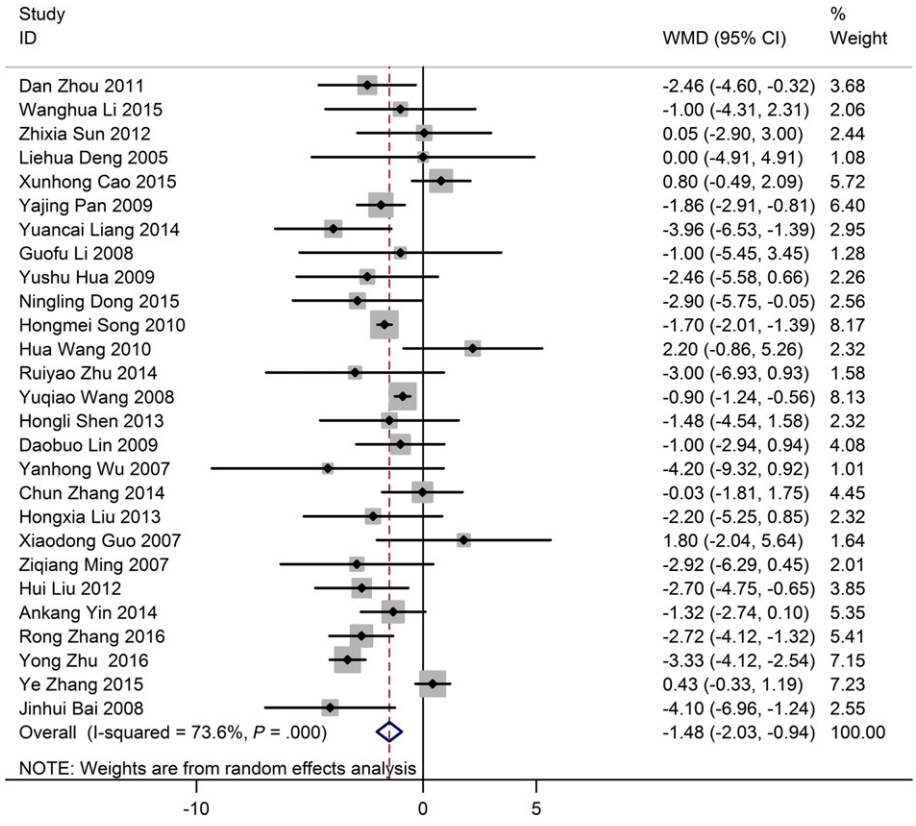

Fig. 5. Meta-analysis of White Blood Count (WBC) change.

In this meta-analysis, we found that compared with conventional therapy, XBJ combined with conventional therapy could significantly decrease the APACHE-IIscore (WMD: −3.70, 95%CI: −4.31-[−3.09]), PCT (WMD: −1.26 μg/L, 95%CI: −1.63 μg/L-[−0.88 μg/L]), WBC (WMD: -1.48×10^9/L, 95%CI: -2.03×10^9/L-[-0.94×10^9/L]), and this conclusion is in agreement with the previous studies. XBJ combined with conventional therapy also could significantly reduce the CRP (WMD: −24.38 mg/L, 95%CI: −30.49 mg/L-[−18.26 mg/L]), NEU

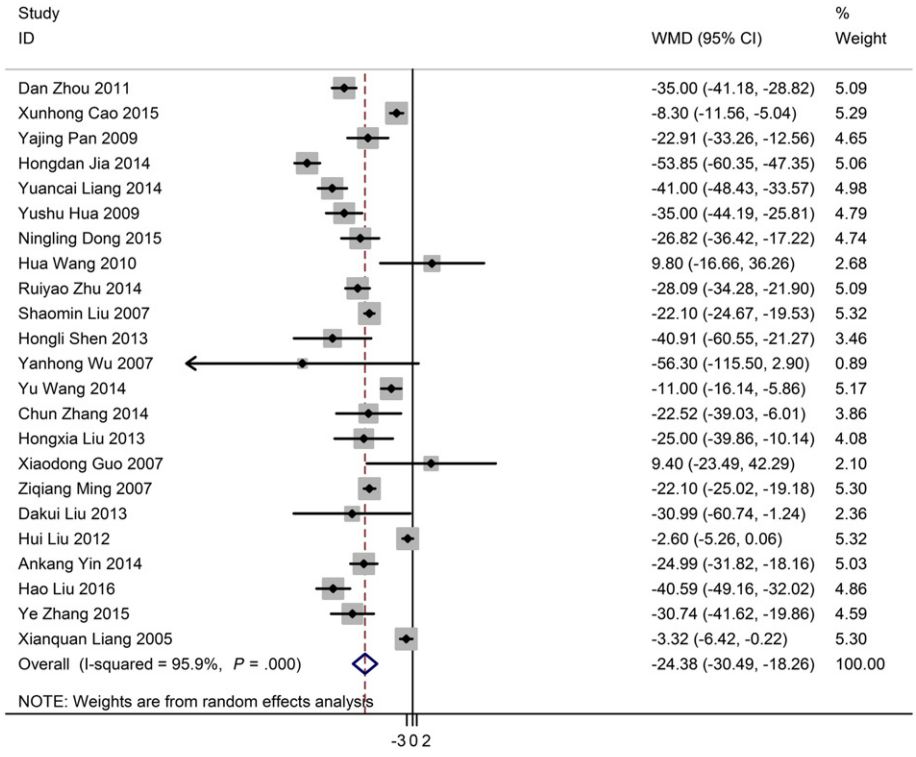

Fig. 6. Meta-analysis of C-Reactive Protein (CRP) change.

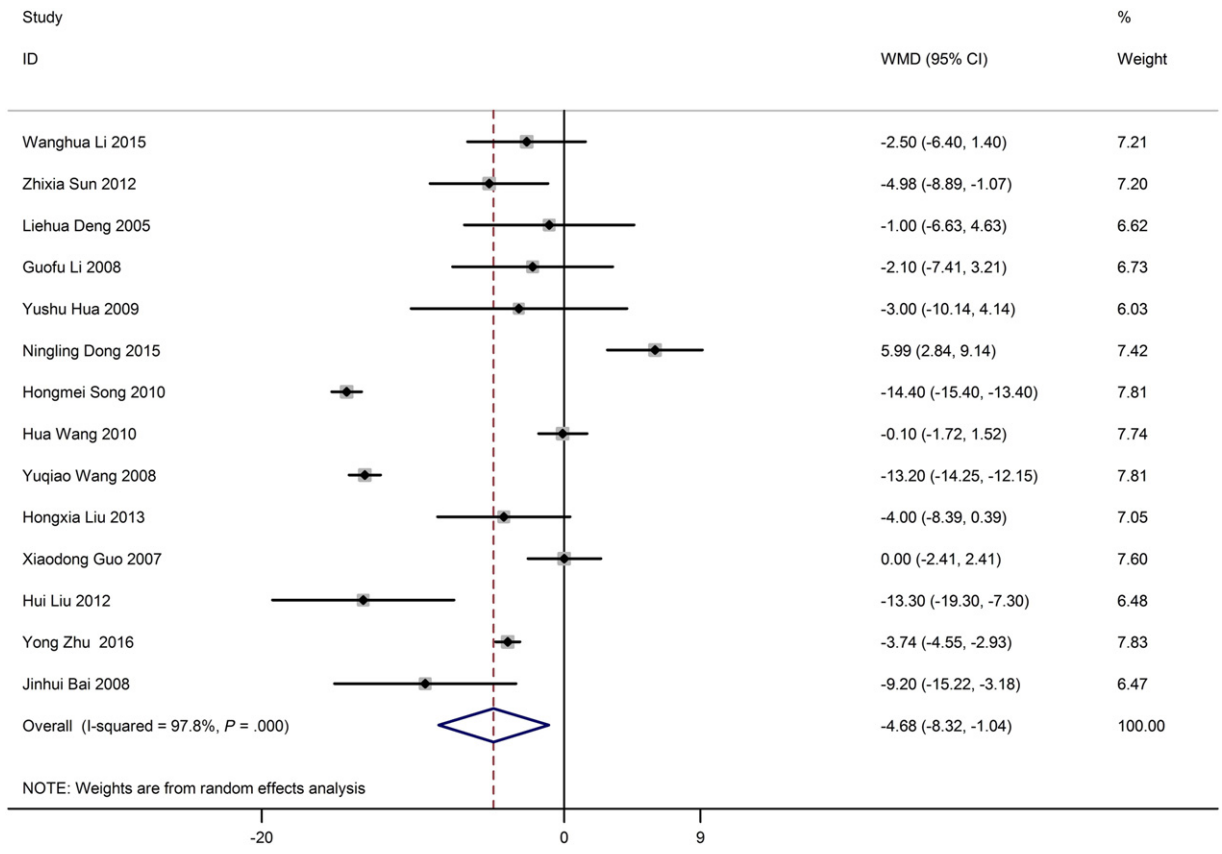

Fig. 7. Meta-analysis of Neutrophile (NEU) change.

(WMD: −4.68, 95%CI: −8.32-[−1.04]), T^0(WMD: −0.50, 95%CI: −0.92-[−0.07]). The 28-day mortality (RR: 0.51; 95%CI: 0.44–0.59) has not been analyzed in the previous meta-analysis.

The limitations of our study are as follows: (1) randomized case-control studies are included; (2) different doses of XBJ might result in bias; (3) differences may exist in the inclusion criteria and exclusion

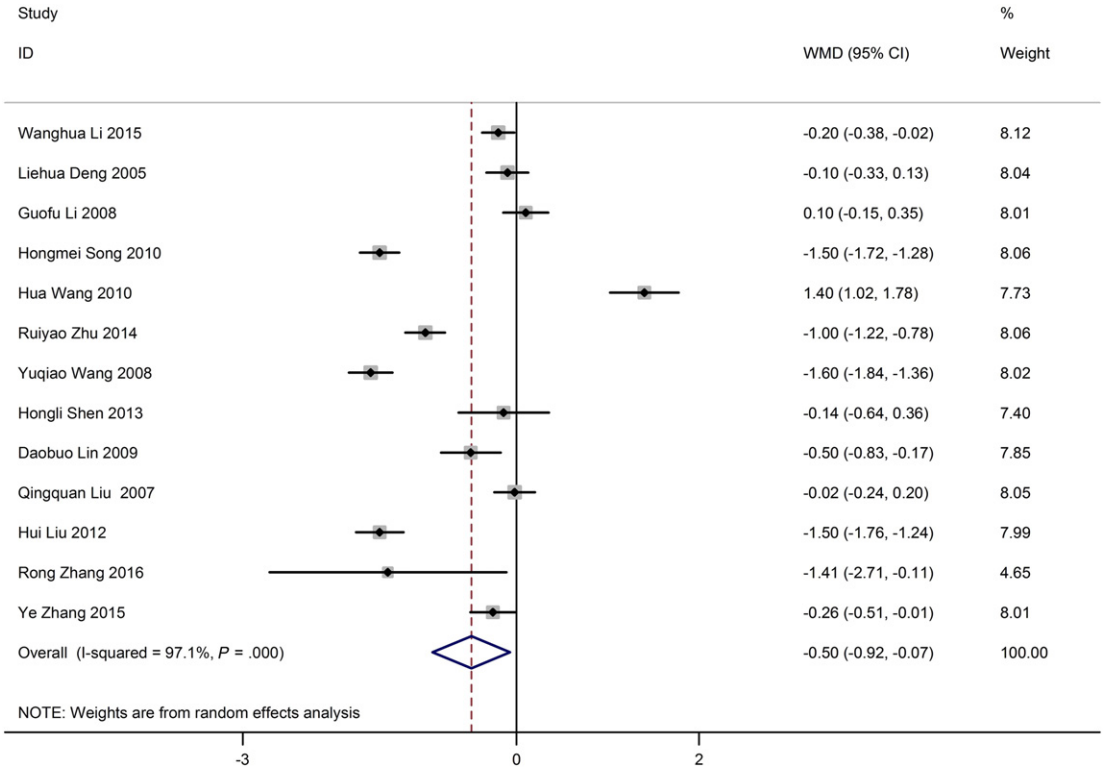

Fig. 8. Meta-analysis of Temperature (T^0) change.

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criteria for patients; (4) different patients with previous diseases and treatments were unavailable; (5) several trials with low quality were included in our study; and (6) pooled dates were used for analysis, and individual patients' data were unavailable. Therefore we were limited to conduct a more comprehensive analysis.

In conclusion, we included forty-nine randomized case-control studies with the main Jadad score of 3.08 in the meta-analysis. The findings indicate that XBJ could be a credible alternative for patients with sepsis and shorten the APACHE-IIscore, WBC, CRP, NEU, T^0, and 28-day mortality. However, a need remains for larger samples, data from multicenters, and high quality studies to confirm the clinical efficacy of XBJ in the treatment of sepsis patients.

Conflict of Interests

All authors declare that they have no conflict of interests.

Acknowledgments

None.

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