



Research Article

Could Xuebijing Injection Reduce the Mortality of Severe Pneumonia Patients? A Systematic Review and Meta-Analysis

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Background and Aim. Xuebijing injection (XBJ) is a Chinese traditional medicine preparation, mainly made from *Carthamus tinctorius* flowers (Honghua in Chinese), *Paeonia lactiflora* roots (Chishao), *Ligusticum chuanxiong* rhizomes (Chuanxiong), *Salvia miltiorrhiza* roots (Danshen), and *Angelica sinensis* roots (Danggui). It can reduce inflammation and regulate blood coagulation and immune function. XBJ has been used in severe pneumonia patients in China. Whether it can reduce the mortality of patients is still controversial. This study aimed to analyze the effectiveness of XBJ in the treatment of severe pneumonia. **Methods.** Databases including PubMed, Cochrane Library, Web of Science, Embase, CNKI, WanFang, and VIP were searched, from inception to February 2020, to identify randomized controlled trials (RCTs) about XBJ combined with western medicine treatment in treating severe pneumonia. Literature screening, data extraction, and methodological quality assessment were carried out by two researchers back-to-back. RevMan 5.3 software was used for statistical analysis. **Results.** A total of 21 articles involving 2072 patients were included. The meta-analysis showed that treatment combined with XBJ has better efficiency compared with western medicine treatment alone. It could also decrease 28-day mortality; shorten the length of intensive care unit (ICU) stay time and mechanical ventilation time; and reduce the levels of C-reactive protein (CRP), procalcitonin (PCT), white blood cell (WBC), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and D-dimer in the serum of patients. The incidence of adverse reactions did not increase significantly. **Conclusion.** XBJ combined with western medicine treatment has significant clinical efficacy and no obvious adverse reactions. A dose of 100 ml bid is recommended to reduce 28-day mortality. The conclusion needs to be further verified with larger-sample size and higher-quality RCTs.

1. Introduction

Severe pneumonia is mainly manifested as respiratory failure, usually accompanied by systemic inflammation, which can occur with septic shock, multiple organ failure, diffuse intravascular coagulation, and so on. Severe pneumonia has become one of the main causes of death in hospitalized patients in intensive care unit (ICU), with long hospital stay and high mortality [1–3]. At present, the conventional western medicine treatment mainly involves antibiotics, mechanical ventilation, vasoactive drugs, nutritional support, and so on. However, there is no specific drug [4]. The treatments mentioned above

cannot curb the progress of the body's inflammatory storm, which may be one of the reasons for the high mortality rate of patients with severe pneumonia.

In recent years, Chinese medical workers have used Xuebijing injection (XBJ) with the functions of promoting blood circulation and removing blood stasis to treat severe pneumonia and have achieved good clinical results. In the treatment of COVID-19, XBJ is one of the most frequently used traditional Chinese medicine preparations in China, and it has shown significant effects on severe patients.

Systematic reviews of XBJ in the treatment of severe pneumonia were published in 2012, 2014, and 2015,

respectively, in Chinese journals [5–7], all of which confirmed the effectiveness of XBJ in the treatment of severe pneumonia. However, whether XBJ could reduce the mortality of severe pneumonia patients is still controversial. In the past five years, more studies have been published on mortality, length of hospital stay, and duration of mechanical ventilation in severe pneumonia treated with XBJ. Therefore, this systematic review and meta-analysis, based on the currently published related randomized controlled trials (RCTs), is going to provide further evidence for clinical treatment of XBJ.

2. Materials and Methods

2.1. Registration. The registration number of PROSPERO is CRD42020173729.

2.2. Research Type. The research included blinded or non-blinded RCTs of XBJ combined with western medicine treatment. The language was limited to Chinese or English.

2.3. Research Objects. Adult patients with severe pneumonia were included; the diagnostic criteria must meet any of the following for severe pneumonia: (1) “Guidelines for the Diagnosis and Treatment of Community-Acquired Pneumonia in Chinese Adults” developed by the Respiratory Branch of Chinese Medical Association in 2016 [8]; (2) “Guidelines for Diagnosis and Treatment of Community-Acquired Pneumonia” made by the Respiratory Branch of Chinese Medical Association in 2006 [9]; (3) “Adult Community-Acquired Pneumonia (CAP) Guidelines for Diagnosis and Treatment” issued by the American Thoracic Society/American Society of Infectious Diseases (AST/IDSA) in 2007 [10]; (4) “Guidelines for the Management of Adults with Community-Acquired Pneumonia. Diagnosis, Assessment of Severity, Antimicrobial Therapy, and Prevention” formulated by the American Thoracic Society in 2001 [11].

2.4. Intervention Measures. The control group was given conventional western treatments such as anti-infectives, phlegm reduction medicines, mechanical ventilation, nutritional support, and so on. In the experimental group, adjuvant treatment was added with XBJ on the basis of conventional western treatment. In order to reduce the heterogeneity of the analysis of results, this study chose the literature with an intervention course of 7 days and observation index data on the 7th day.

2.5. Outcomes. One or more outcome indicators of the following must be involved: primary outcomes: (1) effective rate, (2) 28-day mortality; secondary outcomes: (1) length of intensive care unit (ICU) stay time, (2) duration of mechanical ventilation; (3) C-reactive protein (CRP), (4) procalcitonin (PCT), (5) white blood cells (WBC), (6) tumor necrosis factor- α (TNF- α), (7) interleukin-6 (IL-6), (8) D-dimer, (9) adverse reactions.

2.6. Exclusion Criteria. Exclusion criteria include the following:

- (1) Republished studies.
- (2) Unclear diagnostic criteria for severe pneumonia.
- (3) Nonadult studies.
- (4) Combination with other critically ill patients (tumor, pulmonary fibrosis, tuberculosis, secondary respiratory failure in other systems, etc.).
- (5) Combination with other proprietary Chinese medicines with effects of regulating blood coagulation or anti-inflammation.

2.7. Retrieval Strategy. The English databases of PubMed, Cochrane Library, Web of Science, and Embase, as well as the Chinese databases of CNKI, WanFang, and VIP, were retrieved to look up all the RCTs that used XBJ for severe pneumonia by the computer since the databases were established until February 2020. The search strategy for English databases was “pneumonia [Title/Abstract] AND Xuebijing [Title/Abstract].” The search strategy for Chinese databases was (“zhong zheng fei yan (han yu pin yin) [Title/Abstract]” OR “zhong zheng fei bu gan ran (han yu pin yin) [Title/Abstract]”) AND “xue bi jing (han yu pin yin) [Title/Abstract].”

2.8. Data Extraction. Two researchers read and screened the literature according to the inclusion and exclusion criteria back-to-back. After being extracted, the data was cross-checked. If there were differences, a third researcher joined the discussion. Extracted data included author, year of publication, region, sample size, age distribution, baseline characteristics, intervention dose, course of treatment, method of randomization, allocation concealment, blind method, data integrity, and outcomes.

2.9. Quality Assessment. The bias risk assessment tool for RCTs recommend by Cochrane Handbook 5.1.0 was used for quality evaluation, which included random sequence generation, allocation concealment, blinding method, incomplete outcome data, selective reporting, and other bias. Two researchers conducted a back-to-back bias risk assessment and then cross-checked the results. In case of disagreement, a third researcher joined the discussion.

2.10. Statistical Analysis. Meta-analysis was performed using RevMan 5.3 and Stata 16.0 statistical software. Outcomes were expressed as risk ratio (RR) for dichotomous variables and mean difference (MD) or standardized mean difference (SMD) for continuous variables together with 95% confidence intervals (CIs). Chi-square distribution (X^2) Q test and I^2 index were introduced to judge the heterogeneity of the research results. $P > 0.1$ and $I^2 < 50\%$ indicated that there was no statistical heterogeneity between the results and a fixed-effect model was used for meta-analysis. $P \leq 0.1$ and $I^2 \geq 50\%$ indicated that there was statistical heterogeneity

between the results and a random effect model was used for meta-analysis. If there was obvious clinical heterogeneity, subgroup meta-analysis or descriptive analysis was conducted. Inverted funnel chart and Egger's test were used to detect publication bias where there were more than 10 trials in the meta-analysis.

3. Results

3.1. Description of Included Studies. A total of 705 studies were obtained in the initial examination. After screening, 21 studies that met the criteria were finally included [12–32], involving 2072 patients, 1030 in the experimental group and 1042 in the control group. There were 20 papers [13–32] in Chinese and 1 paper [12] in English. There were two PhD theses. [13, 14] All research was conducted in China. The screening process is shown in Figure 1, and the risk of bias of the included trials is shown in Figure 2. The characteristics of the included studies are presented in Table 1.

3.2. Primary Outcomes

3.2.1. Effective Rate. A total of 11 studies reported effective rate of treatment [14–24], and the evaluation criteria adopted by these studies were basically the same. Significantly effective rate was reported as follows: within 7 days, clinical symptoms such as cough, sputum, fever, and dyspnea were completely relieved, positive signs of lung examination disappeared, the shadow area of lungs on the X-ray was absorbed by more than 50%, laboratory examination was completely normal, and pathogen test turned negative in sputum specimens. Effective rate was reported as follows: within 7 days, the above clinical symptoms were partially relieved, signs of lung examination improved, shadow area of lungs on the X-ray absorbed was <50%, laboratory examination was significantly improved, and pathogen in sputum specimens was partially cleared or replaced. Invalid rate was reported as follows: within 7 days, no clinical symptoms were improved, positive signs of lung examination did not improve or worsen, the shadow area of lungs on the X-ray had no obvious absorption or had aggravation, there was no improvement or aggravation in the laboratory examination, and the examination of the sputum pathogen did not turn negative. Effective rate = (significantly effective cases + effective cases)/number of cases. According to the dosage of XBJ, studies were divided into two subgroups of 50 ml bid and 100 ml bid.

There were 7 studies in the 50 ml bid subgroup [14–20]. Heterogeneity was detected between these trials ($P = 0.06$, $I^2 = 50\%$), so random effect model was adopted. Meta-analysis results showed that the effective rate of XBJ group was higher than the control group (RR = 1.20, 95% CI [1.08, 1.32], $P = 0.0004$). There were 4 studies in the 100 ml bid subgroup [21–24]. No heterogeneity was detected between these trials ($P = 0.53$, $I^2 = 0\%$). Meta-analysis of random effect model result showed that the effective rate of XBJ group was higher than the control group (RR = 1.22, 95% CI [1.10, 1.35], $P = 0.0002$), as shown in Figure 3. Therefore, the results of the two subgroups showed that, regardless of

whether the dose was 50 ml bid or 100 ml bid, the effective rate of the XBJ group was significantly higher than that of the control group, as shown in Figure 3. Figure 4 shows the funnel chart of the treatment efficiency of the XBJ group and the control group. The symmetry is poor, and the data is to the right, indicating that there may be selectivity and publication bias. Egger's test showed that $\beta_1 = 1.91$, SE of $\beta_1 = 0.601$, $z = 3.18$, and $\text{Prob} > |z| = 0.0015$ ($P = 0.0015$), which also meant that there may be selectivity and publication bias.

3.2.2. 28-Day Mortality. A total of 5 studies reported a 28-day mortality rate [12, 13, 21, 25, 26]. No heterogeneity was detected between these trials ($P = 0.79$, $I^2 = 0\%$). Meta-analysis results of the fixed-effect model showed that the 28-day mortality in XBJ group was significantly lower than the control group (RR = 0.63, 95% CI [0.50, 0.81], $P = 0.0003$), as shown in Figure 5. Among them, the dose of XBJ used in four studies was 100 ml bid [12, 13, 21, 26], and only one study used 50 ml bid [25].

3.3. Secondary Outcomes

3.3.1. ICU Stay Time. Five studies reported ICU stay time [12, 16, 25, 26, 28]. Heterogeneity was detected between these trials ($P = 0.0005$, $I^2 = 80\%$). The sample size of Song et al.'s study [12] was found to be significantly larger than that of other studies, and heterogeneity may have come from the difference of sample size. When subgroup analysis was carried out according to the sample size, the heterogeneity decreased significantly. Meta-analysis results showed that the ICU stay time of XBJ group was shorter than that of the control group (RR = -1.33, 95% CI [-2.23, -0.44], $P = 0.004$), as shown in Figure 6. Large sample size may better reflect the response of the population, so larger-sample research needs to be carried out.

3.3.2. Duration of Mechanical Ventilation. A total of 5 studies reported duration of mechanical ventilation [12, 16, 26, 28, 29]. Heterogeneity was detected between these trials ($P < 0.00001$, $I^2 = 90\%$). The sample size of Song et al.'s study [12] was found significantly larger than that of other studies, and heterogeneity may have come from the difference of sample size. When subgroup analysis was carried out according to the sample size, the heterogeneity decreased significantly. Meta-analysis results showed that duration of mechanical ventilation of the XBJ group was shorter than that of the control group (RR = -1.97, 95% CI [-2.53, -1.42], $P < 0.00001$), as shown in Figure 7. Large sample size may better reflect the response of the population, so larger-sample research needs to be carried out.

3.3.3. CRP. A total of 9 studies reported CRP level in plasma [13, 18, 19, 22–24, 27, 30, 31]. Heterogeneity was detected between these trials ($P < 0.00001$, $I^2 = 91\%$). Male proportion of subjects in Kong's study [18] was found to be significantly higher than that of other studies, and heterogeneity may

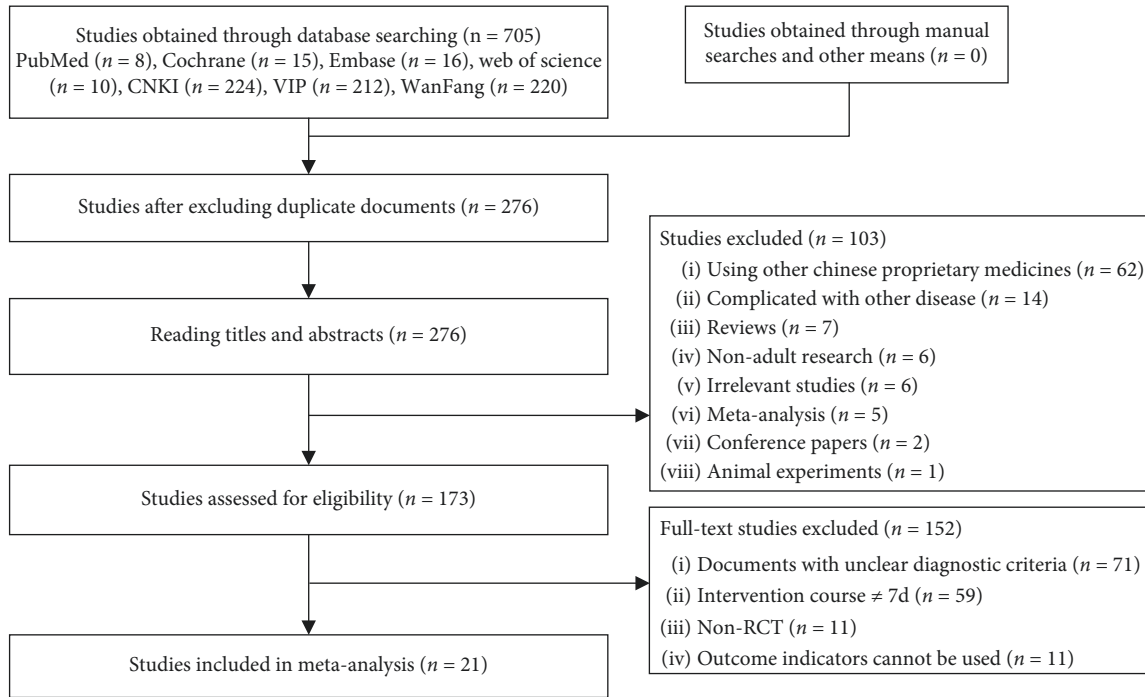


FIGURE 1: Flowchart of literature screening.

Author (Year)	Zhu et al. 2014	Yu et al. 2016	Yu 2018	Yu et al. 2017	Yang et al. 2018	Wang et al. 2019	Wang et al. 2013	Wang 2019	Song et al. 2019	Sheng et al. 2019	Lu 2012	Liu 2019	Kong 2015	Jing 2017	Ji 2010	Gong et al. 2010	Fu et al. 2011	Du 2018	Diao et al. 2017	Cheng et al. 2012	Che et al. 2018	
Random sequence generation (selection bias)	+	?	?	?	+	+	+	+	+	?	?	+	+	+	?	?	?	+	+	?	+	+
Allocation concealment (selection bias)	+	?	?	?	?	?	?	?	+	?	?	?	?	+	?	?	?	?	?	?	?	?
Blinding of participants and personnel (performance bias)	?	?	?	?	?	?	?	?	+	?	?	?	?	+	?	?	?	?	?	?	?	?
Blinding of outcome assessment (detection bias)	?	?	?	?	?	?	?	?	+	?	?	?	?	?	?	?	?	?	?	?	?	?
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other bias	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?

FIGURE 2: Evaluation of literature quality.

have come from the difference in gender composition. When subgroup analysis was carried out according to the gender, the heterogeneity decreased significantly. Meta-analysis results showed that the CRP level of the XBJ group was lower than that of the control group (MD = -12.06, 95% CI [-15.31, -8.08], $P < 0.00001$), as shown in Figure 8. Therefore, when Xuebijing is used to treat severe pneumonia, gender may be an influencing factor in the change of CRP level.

3.3.4. PCT. Seven studies reported PCT level in plasma [14, 15, 18, 20, 23, 25, 27]. Heterogeneity was detected between these trials ($P = 0.004$, $I^2 = 68%$). When subgroup analysis was carried out according to the dose of XBJ, the heterogeneity decreased significantly. There were 5 studies in

the 50 ml bid subgroup [14, 15, 18, 20, 25]. No heterogeneity was detected between these trials ($P = 0.25$, $I^2 = 26%$). Meta-analysis results showed that the PCT level of the XBJ group was lower than that of the control group (MD = -0.36, 95% CI [-0.64, -0.09], $P = 0.009$). There were 2 studies in the 100 ml bid subgroup [23, 27]. No heterogeneity was detected between the two trials ($P = 0.20$, $I^2 = 39%$). Meta-analysis results showed that the PCT level of the XBJ group was lower than that of the control group (MD = -1.04, 95% CI [-1.54, -0.54], $P < 0.0001$). Therefore, the results of the two subgroups showed that, regardless of whether the dose was 50 ml bid or 100 ml bid, the PCT level of the XBJ group was lower than that of the control group, as shown in Figure 9. Accordingly, when Xuebijing is used to treat severe pneumonia, the dose of XBJ may be an influencing factor in the change of PCT level.

TABLE 1: Characteristics of included studies.

Study ID	Sample size T/C	Gender (men%) T/C	Mean age (years) T/C	Diagnostic criteria	Randomization method	Blinding method	Intervention		Course (d)	Follow- up time (d)	Outcome indicators
							C	T			
Song et al. [12]	334/341	67.1/68.6	58.7/58.1	America 2007 [10]	Interactive web response system	Double blinded	BT	BT + XBJ 100 ml bid	7	28	2, 3, 4, 11
Jing [13]	30/30	60.0/66.7	61.5/62.1	America 2007	Allocation sequence, assigned random number by system	Double blinded	BT	BT + XBJ 100 ml bid	7	28	2, 5, 11
Liu [14]	29/35	65.5/60.0	71.8/77.7	China 2016 [8]	Random number table	Unstated	BT	BT + XBJ 50 ml bid	7	—	1, 6, 7, 8, 9
Wang [15]	34/34	64.7/58.8	75.2/75.6	China 2016	Random number table	Unstated	BT (Biapenem 0.3 g q8 h) BT (Cefoperazone sulbactam 3.0 g q12 h + Levofloxacin 0.5 g qd)	BT + XBJ 50 ml bid	7	—	1, 6, 11
Wang et al. 2019 [16]	49/49	57.1/61.2	54.8/53.3	China 2016	Draw method	Unstated	BT + XBJ 50 ml bid	BT + XBJ 50 ml bid	7	—	1, 3, 4, 11
Yang and Xu [17]	98/98	63.3/66.3	57.4/53.6	America 2007	Random number table	Unstated	BT	BT + XBJ 50 ml bid	7	—	1
Kong [18]	34/34	82.4/85.3	48.9/50.6	America 2007	Interactive web response system	Double blinded	BT	BT + XBJ 50 ml bid	7	—	1, 5, 6, 7
Cheng et al. [19]	40/40	62.5/52.5	—	America 2001 [11]	Unstated	Unstated	BT	BT + XBJ 50 ml bid	7	—	1, 5, 7
Lu [20]	23/23	65.2/60.9	71.04/69.3	America 2001	Unstated	Unstated	BT	BT + XBJ 50 ml bid	7	—	1, 6, 7, 11
Yu and Ma [21]	30/30	76.7/70.0	52.1/54.5	China 2006 [9]	Unstated	Unstated	BT	BT + XBJ 100 ml bid	7	28	1, 2, 8, 9
Yu [22]	38/38	57.9/52.6	65.9/67.1	America 2007	Unstated	Unstated	BT	BT + XBJ 100 ml bid	7	—	1, 5, 7
Che et al. [23]	60/60	—	—	America 2007	Random number table	Unstated	BT	BT + XBJ 100 ml bid	7	—	1, 5, 6
Fu and Ge [24]	34/34	70.6/64.7	69.6/67.8	America 2001	Unstated	Unstated	BT	BT + XBJ 100 ml bid	7	—	1, 5, 7
Sheng et al. [25]	21/21	81.0/61.9	43.6/44.3	China 2016	Unstated	Unstated	BT	BT + XBJ 50 ml bid	7	28	2, 3, 6
Zhu and Liu [26]	22/21	72.7/66.7	68.3/64.6	America 2007	Random number table	Unstated	BT	BT + XBJ 100 ml bid	7	28	2, 3, 4
Gong et al. [27]	16/14	56.3/78.6	57.0/59.0	China 2006	Random number table	Unstated	BT	BT + XBJ 100 ml bid	7	—	5, 6, 8
Ji [28]	19/21	—	—	China 2006	Unstated	Unstated	BT	BT + XBJ 100 ml bid	7	—	3, 4

TABLE 1: Continued.

Study ID	Sample size T/C	Gender (men%) T/C	Mean age (years) T/C	Diagnostic criteria	Randomization method	Blinding method	Intervention		Course (d)	Follow- up time (d)	Outcome indicators
							C	T			
Yao et al. [29]	23/23	73.9/65.2	45.6/44.8	America 2007	Unstated	Unstated	BT	BT + XBJ 100 ml bid	7	—	4, 8, 9
Diao et al. [30]	50/50	—	—	America 2007	Random number table	Unstated	BT	BT + XBJ 50 ml bid	7	—	5, 7, 8, 9
Wang et al. [31]	16/16	—	—	America 2001	Random number table	Unstated	BT	BT + XBJ 50 ml bid	7	—	5, 7
Du [32]	30/30	60.0/53.3	58.6/57.9	America 2007	Random number table	Unstated	BT	BT + XBJ 50 ml bid	7	—	8

Note. T: intervention group; C: control group; BT: basic treatment including rational antibiotic treatment, early fluid resuscitation, mechanical ventilation, use of glucocorticoids, nutrition support, maintenance of homeostatic equilibrium, and other comprehensive therapies. Outcome indicators: 1, effective rate; 2, 28-day mortality; 3, ICU stay time; 4, duration of mechanical ventilation; 5, CRP; 6, PCT; 7, WBC; 8, TNF- α ; 9, IL-6; 10, D-dimer; 11, adverse reactions.

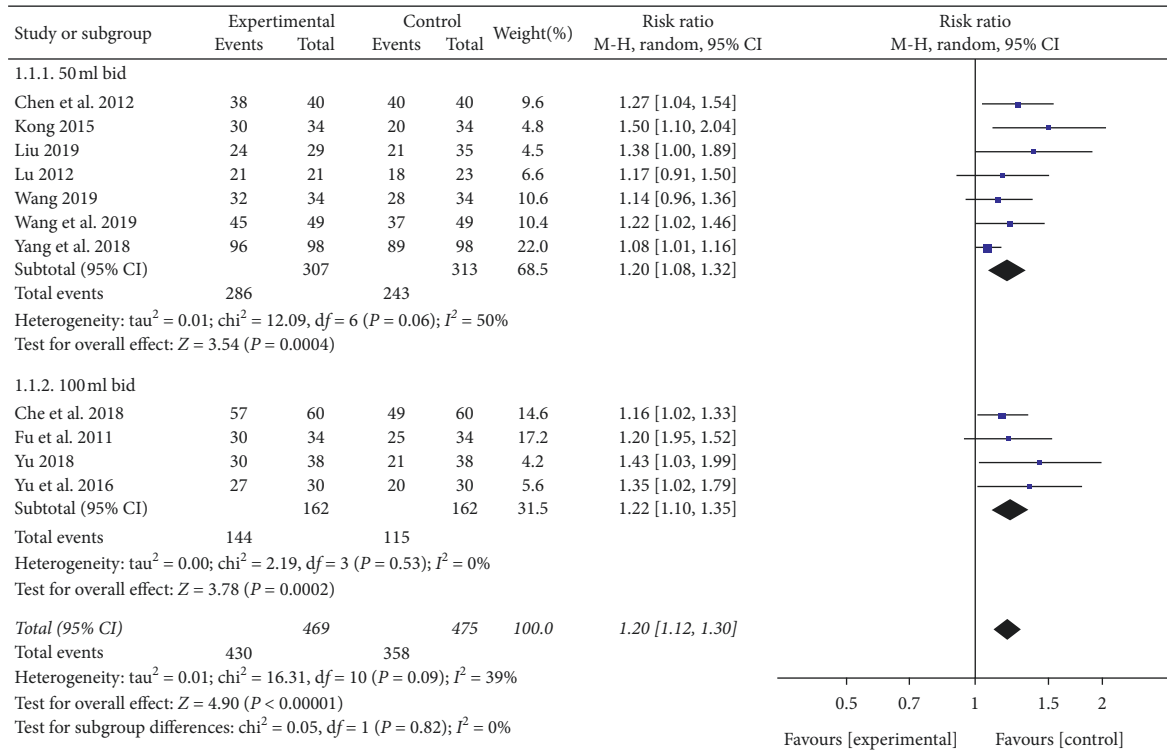


FIGURE 3: Effect of XBJ on effective rate in patients with severe pneumonia.

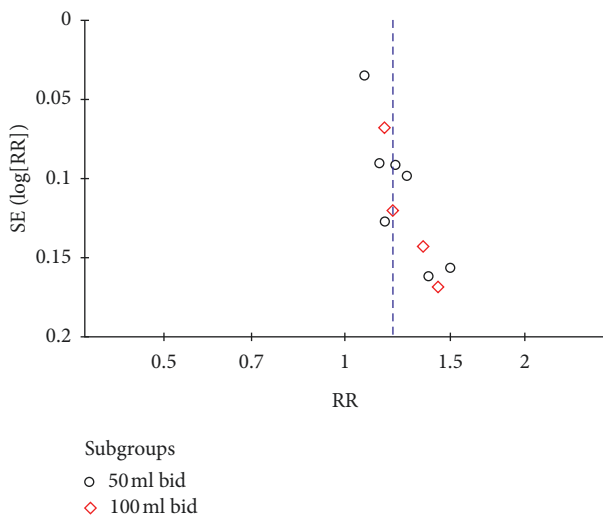


FIGURE 4: Funnel chart of the effectiveness of XBJ in treating severe pneumonia.

3.3.5. *WBC*. A total of 8 studies reported WBC level in plasma [14, 18–20, 22, 24, 30, 31]. No heterogeneity was detected between these trials ($P = 0.78$, $I^2 = 0\%$). Meta-analysis results of the fixed-effect model showed that the level of WBC in the XBJ group was significantly lower than that of the control group (MD = -2.47, 95% CI [-3.27, -1.66], $P < 0.00001$), as shown in Figure 10.

3.3.6. *TNF-α*. Six studies reported the serum TNF-α level [14, 21, 27, 29, 30, 32]. Heterogeneity was detected between

these trials ($P < 0.00001$, $I^2 = 86\%$). Heterogeneity between the six studies which cannot be reduced by subgroup analysis may be due to the influence of multiple factors such as sample size, age and gender composition, and treatment dose. Hence, descriptive analysis was conducted. The 6 studies, respectively, showed that the TNF-α level of the XBJ group was lower compared with the control group with statistical significance indicating that XBJ combined with basic treatment could reduce the level of TNF-α in patients with severe pneumonia.

3.3.7. *IL-6*. A total of 4 studies have reported the serum IL-6 level [12, 14, 29, 30]. Heterogeneity was detected between these trials ($P < 0.00001$, $I^2 = 91\%$). Heterogeneity between the four studies which cannot be reduced by subgroup analysis may be due to the simultaneous influence of multiple factors such as sample size, age and gender composition, and treatment dose. Hence, descriptive analysis was conducted. The four studies, respectively, showed that the IL-6 level of the XBJ group was lower compared with the control group with statistical significance indicating that XBJ combined with basic treatment could reduce the level of IL-6 in patients with severe pneumonia.

3.3.8. *D-Dimer*. Four studies reported the serum D-dimer level [15, 16, 25, 27]. Heterogeneity was detected between these trials ($P < 0.10$, $I^2 = 52\%$), so random effect model was adopted. Meta-analysis result showed that the level of D-dimer was lower compared with the control group (SMD = -0.79, 95% CI [-1.19, -0.39], $P = 0.0001$), as shown

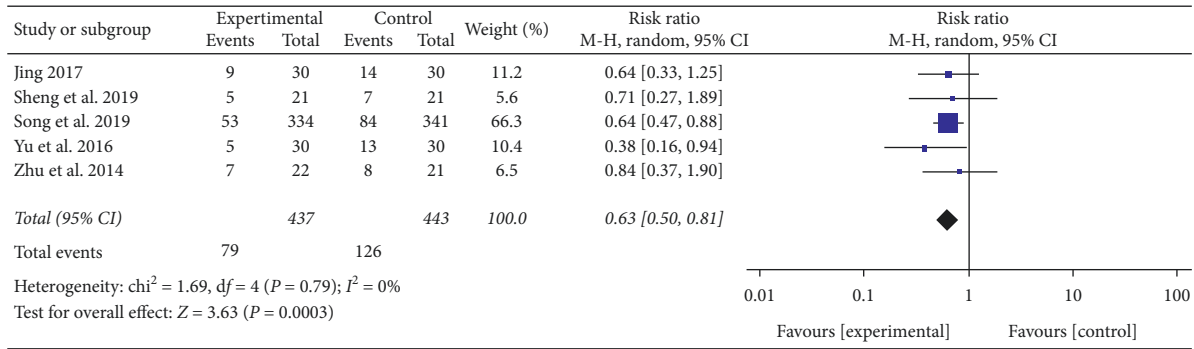


FIGURE 5: Effect of XBJ on 28-day mortality in patients with severe pneumonia.

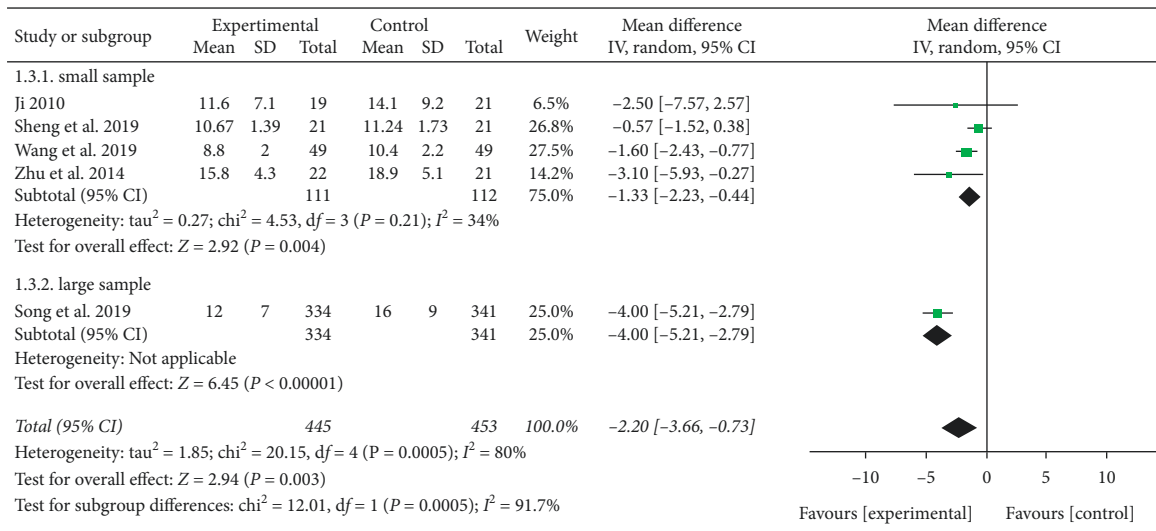


FIGURE 6: Effect of Xuebijing on ICU stay time in patients with severe pneumonia.

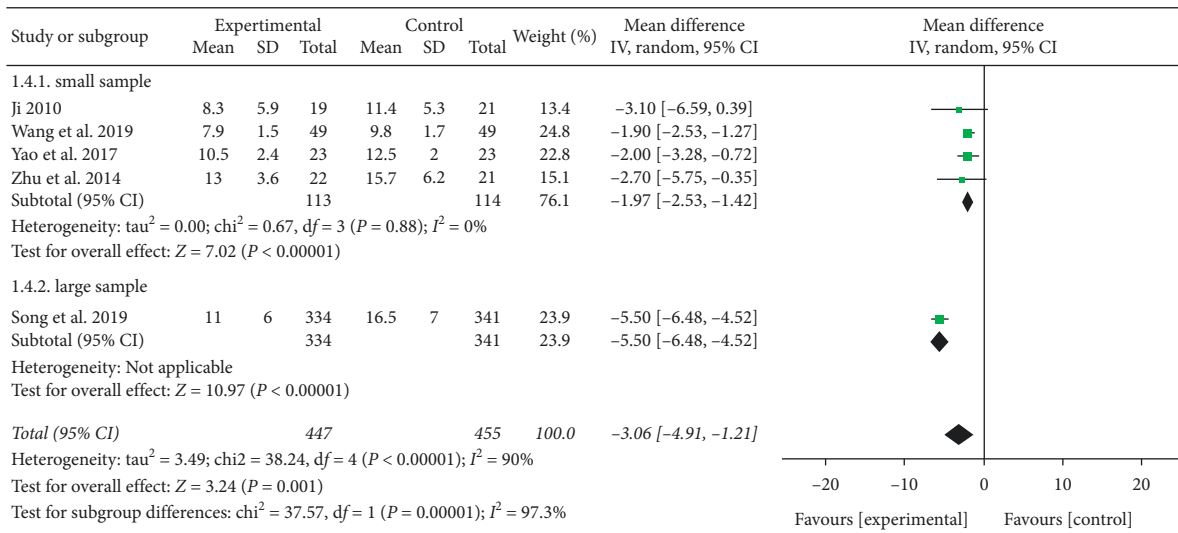


FIGURE 7: Effect of Xuebijing on mechanical ventilation time in patients with severe pneumonia.

in Figure 11. In addition, Liu Xinyan’s study found that the platelet level of the XBJ group was significantly lower than that of the control group after treatment [14]. The study of

Gong et al. found that the time of thromboplastin in the XBJ group was significantly shorter than that of the control group after treatment [27].

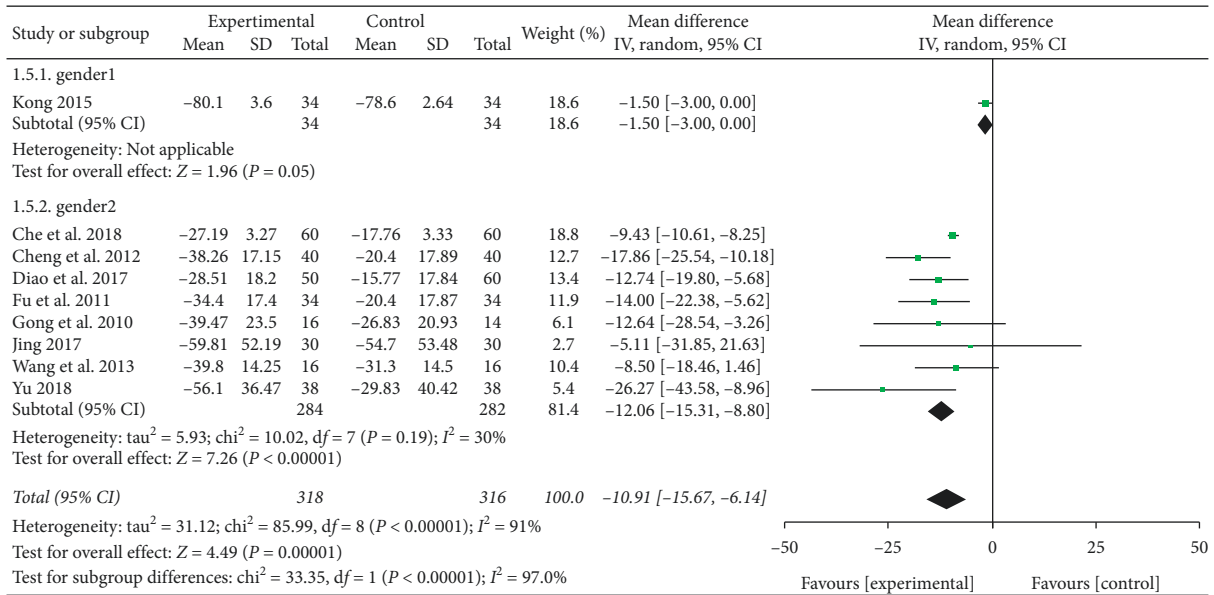


FIGURE 8: Effect of XBJ on the level of CRP in patients with severe pneumonia.

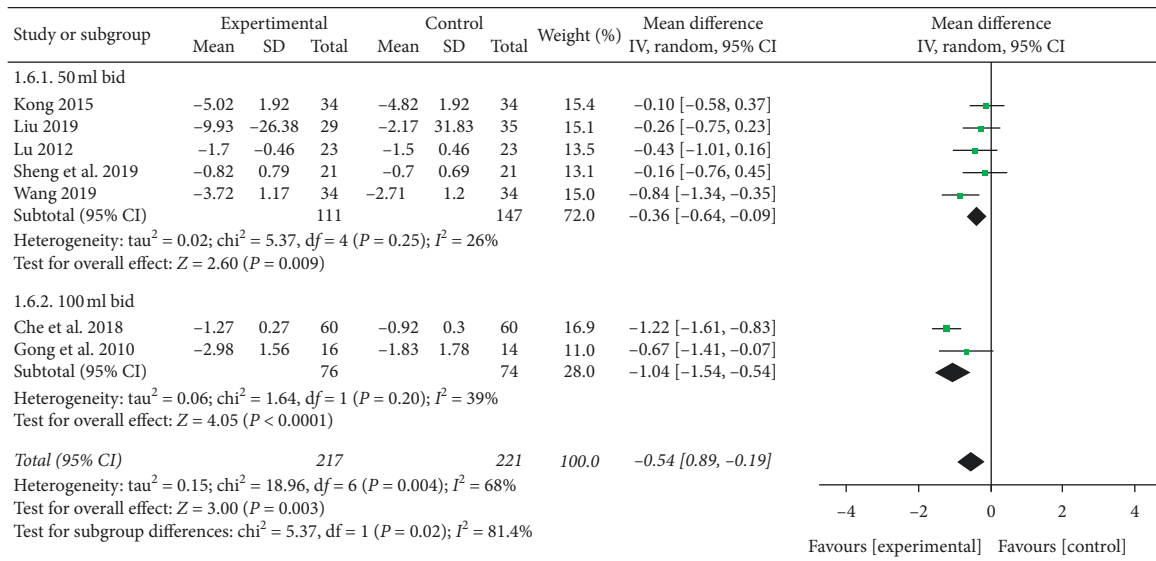


FIGURE 9: Effect of XBJ on the level of PCT in patients with severe pneumonia.

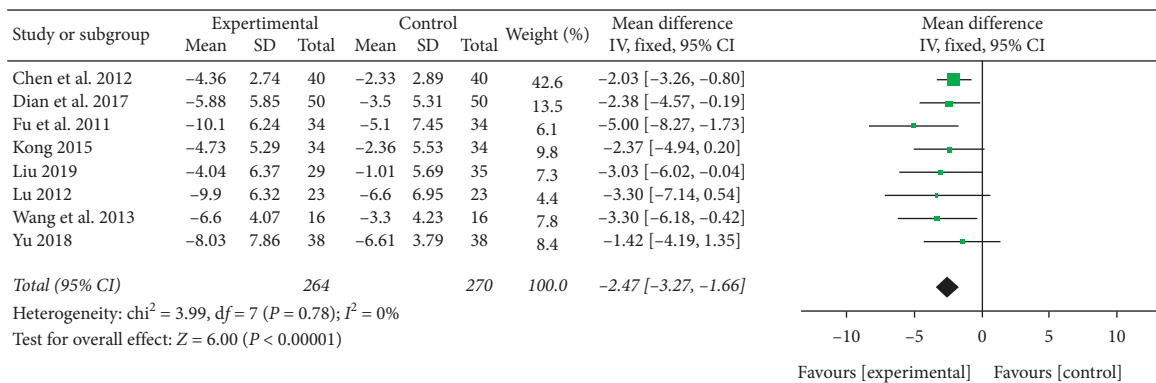


FIGURE 10: Effect of XBJ on the level of WBC in patients with severe pneumonia.

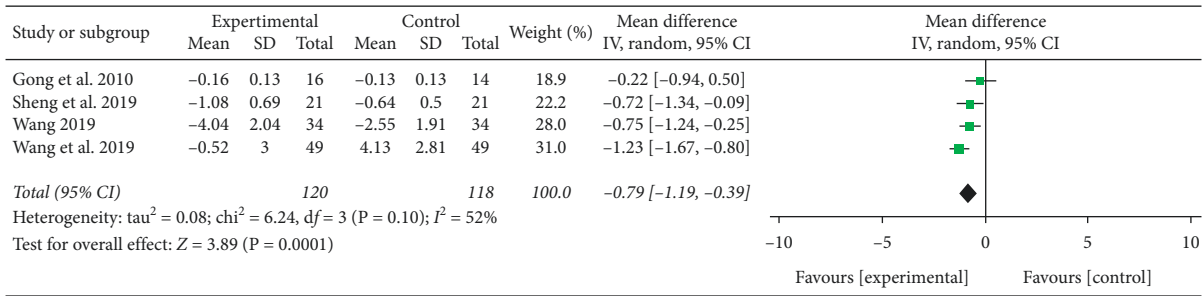


FIGURE 11: Effect of XBJ on the level of D-dimer in patients with severe pneumonia.

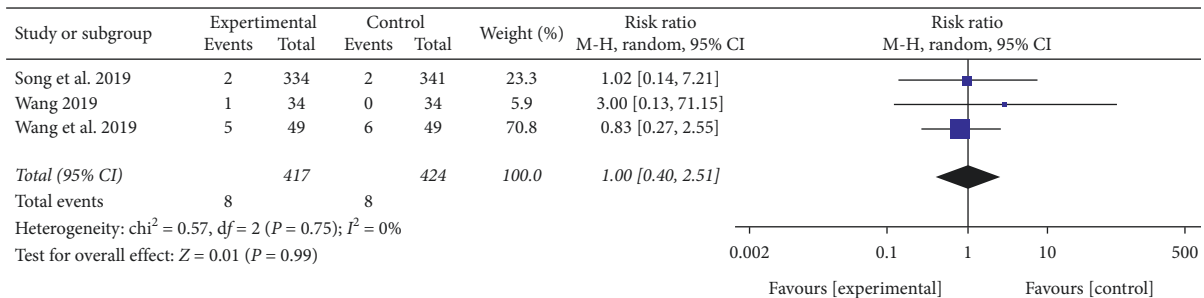


FIGURE 12: Meta-analysis of adverse reactions of XBJ in patients with severe pneumonia.

3.3.9. Adverse Reactions. A total of 5 studies reported adverse reactions [12, 13, 15, 16, 20], of which Jing [13] and Lu [20] did not find any adverse reactions. No heterogeneity was detected between these trials ($P = 0.75$, $I^2 = 0\%$). Meta-analysis results of the fixed-effect model showed that there was no significant difference in adverse reactions between the two groups (RR = 1, 95% CI [0.40, 2.51], $P = 0.99$), as shown in Figure 12.

4. Discussion

4.1. The Main Findings of This Study Compared to Previous Studies. Compared with the previous meta-analyses, the quality of the included literature has improved. All the studies included in this paper used 7-day intervention courses. The drug instructions for Xuebijing do not clearly stipulate the course of treatment. In clinical practice, the course of treatment is mostly 7 days, sometimes extended to 14 days. However, in the evaluation of efficacy, the observation time is usually 7 days, so studies of 7-day treatment courses containing observation data on the 7th day were included. Thus, heterogeneity of the study results could be controlled. This study shows that XBJ combined with conventional western treatment of severe pneumonia is effective and could reduce the level of inflammation reaction, which is consistent with the results of previous meta-analyses [5–7].

However, whether XBJ could reduce the mortality of patients with severe pneumonia has been controversial. Our study found that XBJ in the treatment of severe pneumonia could improve 28-day mortality of patients. However, meta-analyses conducted by Bai et al. [5] and Zhu et al. [6] both

reported that there was no difference in the mortality between XBJ group and control group in treating severe pneumonia. There are two main reasons for their results. On the one hand, the mortality was observed only during the patient's hospitalization but was not followed up after the patients were discharged. It is speculated that XBJ must still have a therapeutic effect after the course of treatment. On the other hand, this may be related to the dosage of XBJ. In Zhu's study, three articles reported mortality, and the dosage of XBJ used was 50 ml bid. In Bai's study, two articles reported mortality; one article used 50 ml bid and the other used 100 ml bid. The dosage of XBJ used in both studies was lower compared with this research.

In this research, 5 articles reported 28-day mortality [12, 13, 21, 25, 26], four of which used XBJ at a dose of 100 ml bid [12, 13, 21, 26], and only one used XBJ at a dose of 50 ml bid [25]. In addition, Wang et al. (50 ml bid) [16], Liu (50 ml bid) [14], and Gong et al. (100 ml bid) [27] reported that the mortality was not statistically different from that of the control group. Similarly, they observed the mortality only during the patient's hospitalization, but did not follow up to observe the 28-day mortality. Simultaneously, dosage of XBJ used in their studies was 50 ml bid, 50 ml bid, and 100 ml bid, respectively. Therefore, this research shows that XBJ may have a delayed treatment effect, and in order to reduce the 28-day mortality rate of patients with severe pneumonia, the recommended dose of XBJ should be 100 ml bid for at least 7 days.

Different from previous studies, this research also conducted a meta-analysis of ICU stay time, duration of mechanical ventilation, and adverse reactions of patients with severe pneumonia, finding that XBJ could shorten the

ICU stay time and the duration of mechanical ventilation and have no increased adverse reactions. This provides a further evidence-based basis for the clinical use of XBJ in the treatment of severe pneumonia.

4.2. Other Findings. This study also found that XBJ could shorten thromboplastin time, reduce levels of serum D-dimer and platelets, and correct coagulopathy of patients [14, 16, 25, 27]. Many studies have found that, in severe infections, the inflammatory factors in patients could activate blood coagulation factors and start the blood coagulation process, leading to the body's microcirculation disorders, thereby exacerbating the occurrence of multiple organ failure [33, 34]. This has been recorded a long time ago in the ancient Chinese medicine books. "WenYiLun" says "Evil heat has long been restrained, but there is no way to vent, so it stayed in the meridians and became stasis." "YiLinGaiCuo" states that "poison burnt its blood, blood was burnt, and its blood must coagulate." They explain the relationship between inflammation and coagulation [35].

Xuebijing, an intravenous preparation, was approved by the China Food and Drug Administration (China FDA) in 2004. Xuebijing is prepared from a combination of *Carthamus tinctorius* flowers (Honghua in Chinese), *Paeonia lactiflora* roots (Chishao), *Ligusticum chuanxiong* rhizomes (Chuanxiong), *Salvia miltiorrhiza* roots (Danshen), and *Angelica sinensis* roots (Danggui). It has the functions of anti-inflammation, antioxidation, improving blood coagulation, improving microcirculation, regulating immune function, etc. [36]. The mechanism of XBJ in the treatment of severe pneumonia may be to improve the patient's microcirculation and organ function by suppressing the excessive inflammatory response and correcting the coagulation disorder.

4.3. Defects and Deficiencies. Some of the literature included in this study is of low quality. In addition, there are still some clinical trials with small sample size and inadequate design. All of the studies were conducted in China. The subjects were basically Chinese. Larger-sample size, multiregion, and multicenter clinical RCTs are required to verify whether XBJ has the same effect on people in different regions or people of different ethnicities.

Abbreviations

XBJ:	Xuebijing injection
RCTs:	Randomized controlled trials
RRs:	Risk ratios
CIs:	Confidence intervals
CNKI:	China National Knowledge Infrastructure
ICU:	Intensive care unit
CRP:	C-reactive protein
PCT:	Procalcitonin
WBC:	White blood cell
TNF:	Tumor necrosis factor
IL:	Interleukin.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Juan Wang reviewed the literature, collected the data, and drafted the manuscript. Jia Zhu designed the study. Jie Guo reviewed the literature and collected the data. Qian Wang provided critical comments and revised the manuscript. All authors made intellectual contribution to the manuscript and approved the submission.

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