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Review Article

Efficacy and safety of Xuebijing combined with ulinastatin in the treatment of sepsis complicated by acute lung injury: a meta-analysis

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Abstract: Objective: To evaluate the efficacy and safety of Xuebijing injection combined with ulinastatin in patients with sepsis complicated by acute lung injury. Methods: PubMed, Web of Science, the Cochrane Library, VIP Database, China National Knowledge Infrastructure and Wanfang Database were searched from inception to January 2026. Two reviewers independently screened studies, extracted data and assessed the risk of bias using the revised Cochrane Risk-of-Bias Tool for Randomized Trials, Version 2, for randomized controlled trials (RCTs) and the Risk Of Bias In Non-randomized Studies of Interventions tool for the retrospective study. Meta-analyses were performed using R version 4.2.0. Results: Thirteen studies involving 1,158 patients (670 in the combination therapy group and 488 in the control group) were included. Compared with control therapy, Xuebijing plus ulinastatin significantly reduced TNF-α, IL-6, HMGB-1, PCT and CRP levels; improved the oxygenation index; reduced the extravascular lung water index and Acute Physiology and Chronic Health Evaluation II score and shortened mechanical ventilation duration (all $P < 0.05$). The total effective rate (RD 0.179, 95% CI 0.101-0.257; NNT = 5.6; $P < 0.001$) and 28-day survival rate (RD 0.118, 95% CI 0.002-0.234; NNT = 8.5; $P = 0.047$) were significantly higher in the combination group, whereas the incidence of adverse events did not differ significantly between groups (RD -0.004, 95% CI -0.049-0.042; $P = 0.881$). Sensitivity analyses supported the robustness of the findings. Conclusion: Xuebijing combined with ulinastatin may reduce inflammation, improve lung function and disease severity, shorten mechanical ventilation duration and increase response and survival rates without increasing adverse events. Owing to heterogeneity in treatment regimens and inclusion criteria, these findings require validation in large-scale, multicenter RCTs.

Keywords: Xuebijing, ulinastatin, sepsis, acute lung injury, efficacy, safety

Introduction

Acute lung injury (ALI) is a severe complication of sepsis. Its primary pathophysiology involves disruption of the pulmonary capillary endothelial and alveolar epithelial barriers, driven by an uncontrolled systemic inflammatory response and excessive activation of innate immunity [1, 2]. Clinically, patients typically present with progressive hypoxemia and impaired gas exchange. Those who deteriorate rapidly may develop acute respiratory distress syndrome (ARDS), leading to prolonged mechanical ventilation, prolonged intensive care unit (ICU) stay and increased mortality [3]. Therefore, suppressing inflammation and preserving lung structural integrity and function are essential for improving outcomes [4].

Ulinastatin, a broad-spectrum protease inhibitor, exhibits anti-inflammatory, anti-apoptotic and multi-organ protective effects. In ALI, it primarily suppresses excessive neutrophil activation and reduces the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Clinical evidence indicates that ulinastatin improves oxygenation and shortens the duration of mechanical ventilation [5].

Xuebijing injection, a traditional Chinese medicine preparation derived from herbs such as Carthami Flos, Paeoniae Radix Rubra and Ligustici Chuanxiong Rhizoma, is traditionally used to clear heat, remove toxins and promote blood circulation. Its active components help modulate inflammation and neutralize endotox-

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ins and have shown benefits in sepsis and associated organ injury [6, 7].

In recent years, several clinical studies have investigated the combination of Xuebijing and ulinastatin in patients with sepsis-induced ALI. Preliminary findings suggest that these two agents may exert synergistic anti-inflammatory effects, potentially enhancing overall treatment efficacy [8].

Nevertheless, three critical research gaps remain. First, most available studies are small, single-center randomized controlled trials (RCTs) with considerable variation in dosing regimens, treatment durations and outcome measures, resulting in inconsistent conclusions. Second, existing meta-analyses have largely focused on the general sepsis population or evaluated monotherapy; none has specifically assessed combination therapy in patients with sepsis-associated ALI or ARDS. This gap is clinically significant because ALI represents a more severe, organ-specific phenotype in which anti-inflammatory and vasoprotective therapies may be especially beneficial. Third, since Xuebijing is predominantly used in China, the relevant evidence has not been well integrated into the international literature, which limits the generalizability of the current findings.

Given these gaps, we conducted a systematic review and meta-analysis of both Chinese- and English-language literature to evaluate the efficacy and safety of Xuebijing combined with ulinastatin in sepsis-associated ALI, aiming to provide evidence to inform clinical decision-making.

Methodology

Search strategy

We systematically searched PubMed, Web of Science, the Cochrane Library, the VIP Database, China National Knowledge Infrastructure and Wanfang Database from their inception to January 2026. The search combined Medical Subject Headings and free-text terms for the key concepts: Xuebijing, ulinastatin, sepsis, acute lung injury and randomized controlled trials. No language restrictions were applied. The complete search strategies for all databases are provided in **Appendix 1**. This meta-analysis was registered with PROSPERO (CRD420261383278).

Inclusion and exclusion criteria

Studies were included if they met all of the following criteria: (1) RCTs; (2) enrolled patients diagnosed with sepsis according to Sepsis-3 criteria and complicated by ALI based on the Berlin definition or equivalent consensus criteria; (3) compared Xuebijing injection combined with ulinastatin with ulinastatin alone, Xuebijing alone, or conventional therapy alone; (4) reported at least one outcome of interest, including inflammatory markers, lung function indices, disease severity scores, duration of mechanical ventilation, ICU length of stay, mortality, or adverse events; and (5) were published in Chinese or English.

Studies were excluded if they met any of the following criteria: (1) non-randomized designs; (2) enrollment of patients with other severe organ dysfunction, severe liver or kidney failure, heart failure, malignancy, or autoimmune disease; (3) co-interventions involving additional anti-inflammatory or lung-protective agents that were not balanced between groups; (4) duplicate publications, incomplete data, or unavailable full text; or (5) animal or in vitro studies.

Literature screening and data extraction

Two reviewers independently screened the titles and abstracts and subsequently assessed the full texts of potentially eligible studies for final inclusion. Disagreements were resolved through discussion or consultation with a third senior reviewer. Two reviewers independently extracted data using a standardized form that included study characteristics (first author, year, sample size and age), diagnostic criteria, intervention and control regimens, pre- and post-treatment outcome data (means, standard deviations and sample sizes) and information for risk-of-bias assessment (randomization, allocation concealment, blinding and completeness of outcome data).

Quality assessment

Two reviewers independently assessed the risk of bias in each included study. For the 12 RCTs, we used the revised Cochrane risk-of-bias tool

for Randomized Trials, Version 2 (RoB 2.0) [9], which evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Each domain and the overall risk of bias were judged as low risk, some concerns, or high risk. For the single retrospective study, we applied the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [9], which covers seven domains: confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result. Each domain and the overall judgment were rated as low, moderate, serious, or critical risk of bias. Disagreements were resolved through discussion or by consulting a third reviewer. Inter-rater agreement was assessed using the kappa statistic.

Statistical analysis

All meta-analyses were performed using R version 4.2.0. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. A fixed-effect model was used when $I^2 < 50\%$ and $P > 0.10$; otherwise, a random-effects model was applied. Subgroup analyses were prespecified for outcomes with substantial heterogeneity ($I^2 \geq 50\%$) to explore potential sources of heterogeneity, including treatment duration (> 7 days vs. ≤ 7 days) and subgroup type (ulinastatin alone, Xuebijing alone, conventional therapy alone, or dose-comparison). The "Xuebijing alone" subgroup refers to studies where the control group received Xuebijing without ulinastatin, allowing assessment of the incremental effect of adding ulinastatin to Xuebijing; the "dose-comparison" subgroup refers to studies comparing different doses of Xuebijing in the intervention group. Sensitivity analyses included: (1) leave-one-out analyses for outcomes with $I^2 \geq 50\%$; (2) reanalysis using a fixed-effect model for all primary continuous outcomes to assess the impact of the between-study variance assumption. Publication bias was planned to be assessed using Egger's regression test when at least 10 studies were available; however, as no outcome included 10 or more studies, Egger's test was not performed for most outcomes. For the overall response rate (n = 4), exploratory analyses including Egger's test and trim-and-fill were conducted with caution and the results were interpreted with this limitation in mind. For continuous outcomes, we calculated mean differences (MD) with 95% confidence intervals (CIs) when all studies used the same units; otherwise, standardized mean differences (SMD) were used. For the APACHE II score specifically, SMD was preferred over MD because the reported standard deviations varied considerably across studies (ranging from 2.8 to 9.1), reflecting heterogeneity in case mix and baseline disease severity, which precluded direct pooling of mean differences. For dichotomous outcomes, we calculated risk differences (RDs) with 95% CIs as the primary effect measure. For key efficacy outcomes (i.e., overall response rate and 28-day survival rate), we also derived the number needed to treat (NNT) from the RD when the RD was positive and statistically significant.

Results

Literature search and screening results

The initial database search retrieved 40 records. After removing 6 duplicates and 1 ineligible record, the remaining records underwent full-text screening and studies with incomplete data, inconsistent interventions, no control group, or other inconsistencies were excluded. Thirteen studies (one retrospective study [10] and 12 RCTs [11-22]) ultimately met the eligibility criteria. The study selection process is detailed in **Figure 1**.

Characteristics of included studies

The 13 included studies, all conducted in China, enrolled a total of 1,158 patients (670 in the combination group and 488 in the control group). Control regimens consisted of conventional therapy alone in 1 study [21] and conventional therapy plus ulinastatin in 11 studies [11-20], with one dose-comparison study [14] included as a separate subgroup. Conventional therapy typically included anti-infective treatment, fluid resuscitation, mechanical ventilation and maintenance of electrolyte balance. The combination group received Xuebijing injection combined with ulinastatin in addition to the same control regimen. Sample sizes ranged from 40 to 140 patients and treatment duration ranged from 5 to 14 days. Xuebijing dosing varied (50 mL twice daily, 100 mL twice daily, or 100 mL four times daily), as did ulinastatin dos-

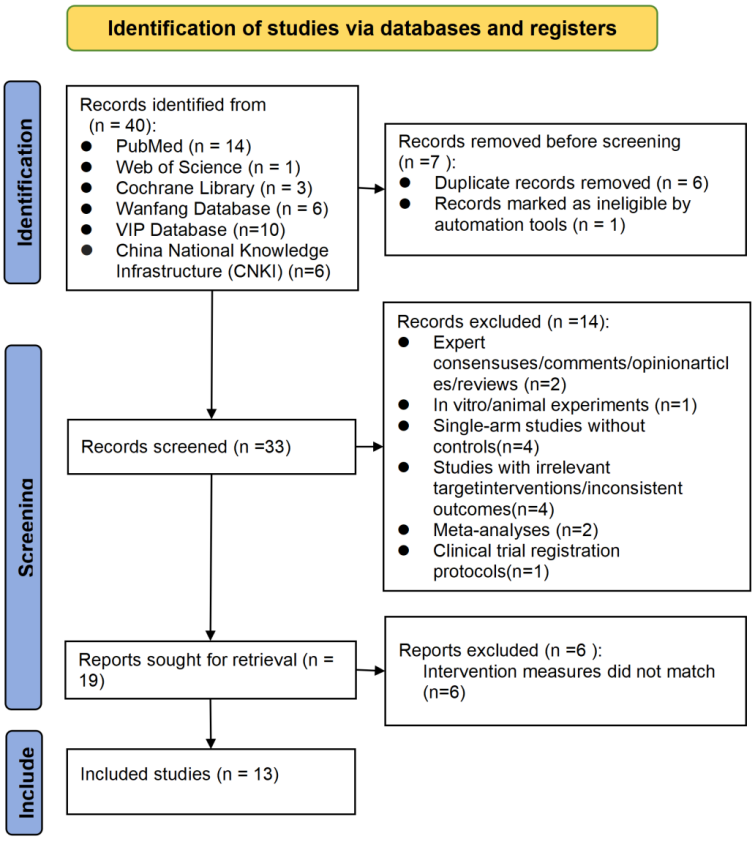

Figure 1. Flowchart of the literature search and study selection.

ing (100,000 U one to three times daily, 200,000 U every 12 h, or 300,000 U every 8 h).

Reported outcomes were as follows: inflammatory markers (TNF-α: 6 studies; IL-6: 3; HMGB-1: 3; PCT: 5; CRP: 4), oxygenation index (5 studies), extravascular lung water index (ELWI) (3 studies), APACHE II scores (7 studies [10-13, 15, 18, 22]), duration of mechanical ventilation (5 studies [10, 12, 13, 15, 16]), overall response rate (4 studies [11, 12, 14, 19]), 28-day mortality (3 studies [13, 15, 16]) and adverse events (5 studies [11-14, 18]). For Li et al. (2020) [13], the three dose subgroups (low, medium, high) were merged as a single study in the analysis. Detailed characteristics are provided in **Table 1**.

Quality assessment of included studies

The risk-of-bias assessments are summarized in **Table 2**. Of the 12 RCTs evaluated with RoB 2.0, four [14, 16, 18, 19] were judged to have a low overall risk of bias and the remaining eight [11-13, 15, 17, 20-22] were judged as having some concerns, mainly due to lack of blinding of participants and outcome assessors. No RCT was classified as having a high risk of bias. Common methodological limitations included inadequate reporting of allocation concealment and blinding, which are often difficult to implement in intensive care settings. The single retrospective study [10] was assessed using ROBINS-I and was judged to be at moderate risk of bias, primarily owing to potential confounding and possible deviations from intended interventions.

Meta-analysis results

For outcomes with substantial heterogeneity, subgroup analyses were performed where applicable and the results are summarized in **Table 3**.

(1) Inflammatory markers: Six studies reported TNF-α levels. Combination therapy significantly reduced TNF-α levels compared with the control group (SMD -4.85, 95% CI -6.76 to -2.95, P < 0.001). Subgroup analysis by treatment duration showed no significant subgroup difference (> 7 days: SMD -4.84, 95% CI -7.18 to -2.51; ≤ 7 days: SMD -5.05, 95% CI -12.72 to 2.62; P for subgroup difference = 0.961). When stratified by control type, the effect was largest in the conventional-treatment-alone subgroup (SMD -20.15, 95% CI -22.84 to -17.46) and smallest in the Xuebijing-alone subgroup (SMD -1.01, 95% CI -1.36 to -0.66; P for between-subgroup difference < 0.001). The subgroup analyses are shown in **Figure 2A** and **2B**. After excluding two outlier studies, the pooled SMD was -1.08 (95% CI -1.33 to -0.82, I^2 = 0%).

Three studies reported IL-6 levels. Combination therapy significantly reduced IL-6 levels (MD -39.25, 95% CI -51.98 to -26.51, P < 0.001) (**Figure 2C**). Leave-one-out analysis identified one study as the primary source of heterogeneity; after its removal, the pooled MD was -33.57 (95% CI -37.64 to -29.49, I^2 = 0%).

Table 1. Basic characteristics of the included studies

No.	Study	Journal	Study design	Sample size by group	Interventions	Treatment duration	Main outcome measures
1	Yang et al. (2025) [10]	Northwest Pharmaceutical Journal	Retrospective study	31/49	Control group: ulinastatin 300,000 U bid + conventional treatment; Experimental group: Xuebijing 50 mL bid + ulinastatin 300,000 U bid + conventional treatment	5 d	Inflammatory markers (HMGB-1, TRAF-6, MCP-1), APACHE II score, mechanical ventilation duration, renal injury indicators (SCr, Cys-C)
2	Li et al. (2025) [11]	Clinical Misdiagnosis and Mistherapy	RCT	20/20	Control group: ulinastatin 300,000 U q8h + conventional treatment; Experimental group: Xuebijing 100 mL bid + ulinastatin 300,000 U q8h + conventional treatment	14 d	Inflammatory markers (PCT, HMGB-1, MCP-1), APACHE II score, total effective rate, coagulation function index
3	Gong et al. (2022) [12]	China Pharmacy	RCT	60/60	Control group: ulinastatin 400,000 U tid + conventional treatment; Experimental group: Xuebijing 100 mL bid + ulinastatin 400,000 U tid + conventional treatment	7 d	Inflammatory markers (IL-1β, IL-18, endotoxin), oxygenation index, APACHE II score, total effective rate
4	Li et al. (2020) [13]	China Pharmacy	RCT	Low dose 29/medium-dose 30/high dose 30 vs. control 26	Control group: ulinastatin 300,000 U q8h + conventional treatment; Experimental group: low-dose Xuebijing 50 mL bid/ medium-dose 100 mL bid/high-dose 100 mL qid + ulinastatin 300,000 U q8h + conventional treatment	7 d	Inflammatory markers (IL-6, TNF-α, hs-CRP), oxygenation index, ELWI, APACHE II score, mechanical ventilation duration, adverse events
5	Zheng et al. (2024) [14]	Journal of Translational Medicine	RCT	70/70	The control group received ulinastatin 100,000 U 1-3 times/d + conventional treatment; Experimental group: Xuebijing 50 mL bid + ulinastatin 100,000 U 1-3 times/d + conventional treatment	14 d	Inflammatory markers (hs-CRP, TNF-α, PCT), HMGB-1/TLR4/NF-κB signaling pathway indicators, and total effective rate, adverse events
6	Liu et al. (2021) [15]	Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care	RCT	35/35	Control group: ulinastatin 200,000 U q12h + conventional treatment; Experimental group: Xuebijing 100 mL q12h + ulinastatin 200,000 U q12h + conventional treatment	5 d	Oxygenation index, PA-aO_2, pulmonary vascular permeability index, 28-day survival rate, and duration of mechanical ventilation
7	Zhang et al. (2018) [16]	Clinical Focus	RCT	30/30	Control group: ulinastatin 200,000 U q8h + conventional treatment; Experimental group: Xuebijing 50 mL q12h + ulinastatin 200,000 U q8h + conventional treatment	6 d	Inflammatory markers (PCT, CRP, BNP), invasive ventilation time, EICU length of stay, and 28-day mortality
8	Wang et al. (2023) [17]	Journal of Medical Theory and Practice	RCT	Conventional-dose group, 41; medium-dose group, 41; high-dose group, 41	Control group: ulinastatin 200,000 U tid + conventional treatment; Experimental group: ulinastatin 200,000 U tid + conventional treatment + Xuebijing 200 mL/d; Experimental group: ulinastatin 200,000 U tid + conventional treatment + Xuebijing 400 mL/d	14 d	Inflammatory markers (CRP, IL-10, IL-18, PCT), respiratory function indices (RFI, MVV, FEV1), and 14-day mort, adverse eventsality

9	He et al. (2024) [18]	Journal of North Pharmacy	RCT	33/32	The control group received ulinastatin 200,000 U bid (adjusted to 100 000 U after 3 days) + conventional treatment; Experimental group: Xuebijing 50 mL bid (adjustable to 3 times/d) + ulinastatin 200,000 U bid + conventional treatment	14 d	Clinical symptom relief time, APACHE II score, hemodynamic parameters, inflammatory markers (TNF-α, CRP, PCT)
10	Chen et al. (2017) [19]	Journal of Emergency in Traditional Chinese Medicine	RCT	30/30	Control group: ulinastatin (dose unclear) + conventional treatment; Experimental group: Xuebijing (unspecified dose) + ulinastatin + conventional treatment	14 d	Blood gas indices, inflammatory markers (hs-CRP, TNF-α, PCT), and total effective rate, adverse events
11	Zhou et al. (2013) [20]	Modern Journal of Integrated Traditional Chinese and Western Medicine	RCT	61/51	Control group: conventional treatment; Experimental group: Xuebijing 100 mL/d + ulinastatin 900,000 U/d + conventional treatment	14 d	Inflammatory cytokines (IL-6, TNF-α, PCT), T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD4^+/CD8^+$), adverse events
12	Zhou et al. (2013) [21]	American Journal of Translational Research	RCT	56/53	Control group: conventional treatment; Experimental group: Xuebijing 100 mL/d + ulinastatin 900,000 U/d + conventional treatment	14 d	Inflammatory cytokines (IL-6, TNF-α, PCT), T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD4^+/CD8^+$)
13	Zhen et al. (2019) [22]	International Journal of Clinical and Experimental Medicine	RCT	32/32	Control group: ulinastatin 200,000 U q4h + conventional treatment; Experimental group: Xuebijing 50 mL q12h + ulinastatin 200,000 U q4h + conventional treatment	7 d	Blood gas indexes (PaO_2, oxygenation index), inflammatory markers (TNF-α, IL-6, IL-8, CRP, PCT), mechanical ventilation duration, ELWI, adverse events

Note: Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; bid, twice daily; BNP, B-type natriuretic peptide; $CD3^+$, cluster of differentiation 3-positive T cells; $CD4^+$, cluster of differentiation 4-positive T cells; $CD8^+$, cluster of differentiation 8-positive T cells; CRP, C-reactive protein; Cys-C, cystatin C; d, day(s); EICU, emergency intensive care unit; ELWI, extravascular lung water index; FEV1, forced expiratory volume in 1 second; HMGB-1, high-mobility group box 1; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; mL, milliliter(s); MVV, maximal voluntary ventilation; NF-κB, nuclear factor-κB; PaO_2, arterial partial pressure of oxygen; $PA\text{-}aO_2$, alveolar-arterial oxygen partial pressure difference; PCT, procalcitonin; q4h, every 4 hours; q8h, every 8 hours; q12h, every 12 hours; qid, four times daily; RCT, randomized controlled trial; RFI, respiratory function index; SCr, serum creatinine; tid, three times daily; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRAF-6, tumor necrosis factor receptor-associated factor 6; U, unit(s).

Table 2. Risk-of-bias assessment of the included studies

Part A. Randomized controlled trials assessed using RoB 2.0

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Li et al. (2025) [11]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Gong et al. (2022) [12]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Li et al. (2020) [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zheng et al. (2024) [14]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Liu et al. (2021) [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhang et al. (2018) [16]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Wang et al. (2023) [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
He et al. (2024) [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chen et al. (2017) [19]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Zhou et al. (2013) [20]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Zhou et al. (2013) [21]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Zhen et al. (2019) [22]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns

Part B. Retrospective study assessed using ROBINS-I

Study	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported results	Overall risk of bias
Yang et al. (2025) [10]	Moderate	Low	Low	Moderate	Low	Low	Low	Moderate

Note: Abbreviations: RoB 2.0, revised Cochrane Risk-of-Bias Tool for Randomized Trials, Version 2; ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions.

Table 3. Subgroup analyses for outcomes with substantial overall heterogeneity (I^2 > 50%)

Outcome	Subgroup variable	Subgroup	Studies (n)	Pooled effect estimate (95% CI)	I^2 (%)	P for subgroup difference
PCT	Treatment duration	> 7 days	3	-0.96 (-1.28, -0.63)	0.0	0.449
		≤ 7 days	2	-1.69 (-3.56, 0.18)	94.6	
CRP	Treatment duration	> 7 days	2	-0.73 (-1.09, -0.37)	0.0	0.557
		≤ 7 days	2	-1.10 (-1.49, -0.71)	0.0	
TNF-α	Treatment duration	> 7 days	4	-4.84 (-7.18, -2.51)	98.4	0.961
		≤ 7 days	1	-5.05 (-7.60, -2.50)	98.7	
TNF-α	Control group type	Ulinastatin alone	4	-2.80 (-4.55, -1.06)	96.4	< 0.001
		Xuebijing alone	1	-1.01 (-1.36, -0.66)	-	
		Conventional therapy alone	1	-20.15 (-22.84, -17.46)	-	
Oxygenation index	Control group type	Ulinastatin alone	4	3.43 (1.72, 5.13)	96.7	0.001
		Dose-comparison	1	0.39 (-0.05, 0.82)	-	

Note: "Subgroup type" classifies comparisons as: ulinastatin alone, Xuebijing alone (incremental effect of adding ulinastatin), conventional therapy alone, or dose-comparison (different Xuebijing doses within the combination group). "-" indicates not applicable because only one study was included and I^2 was not calculated. Outcomes with fewer than five studies, including IL-6, HMGB-1, and ELWI, were not subjected to subgroup analysis; instead, sensitivity analyses were performed as reported in the text. Abbreviations: CI, confidence interval; CRP, C-reactive protein; ELWI, extravascular lung water index; HMGB-1, high-mobility group box 1; IL-6, interleukin-6; PCT, procalcitonin; TNF-α, tumor necrosis factor-α.

Three studies reported high-mobility group box 1 (HMGB-1) levels. Combination therapy significantly reduced HMGB-1 levels compared with control therapy (SMD -0.78, 95% CI -1.03 to -0.52, P < 0.001), with no observed heterogeneity (I^2 = 0%) (**Figure 2D**).

Five studies reported procalcitonin (PCT) levels. Combination therapy significantly reduced PCT levels compared with control therapy (SMD -1.26, 95% CI -1.88 to -0.64, P < 0.001). In the subgroup analysis by treatment duration, the point estimate was larger in the ≤ 7-day subgroup (SMD -1.69, 95% CI -3.56 to 0.18; I^2 = 94.6%) than in the > 7-day subgroup (SMD -0.96, 95% CI -1.28 to -0.63; I^2 = 0%), but the between-subgroup difference was not significant (P = 0.449) (**Figure 2E**). After excluding one study from the ≤ 7 days subgroup, the pooled SMD was -0.89 (95% CI -1.13 to -0.65, I^2 = 0%).

Four studies reported C-reactive protein (CRP) levels. Combination therapy significantly reduced CRP levels compared with control therapy (SMD -0.90, 95% CI -1.16 to -0.63, P < 0.001). In the subgroup analysis by treatment duration, the effect did not differ significantly between the > 7-day subgroup (SMD -0.73, 95% CI -1.09 to -0.37) and the ≤ 7-day subgroup (SMD -1.10, 95% CI -1.49 to -0.71; P for subgroup difference = 0.557) (**Figure 2F**).

Pulmonary function indices: Five studies reported oxygenation index data. Combination therapy significantly improved the oxygenation index compared with control therapy (SMD 2.15, 95% CI 1.32 to 2.98, P < 0.001) (**Figure 3A**). Subgroup analysis by control group type showed that the effect was greater in the ulinastatin-alone subgroup (SMD 3.43, 95% CI 1.72 to 5.13) than in the conventional-therapy-alone subgroup (SMD 0.39, 95% CI -0.05 to 0.82; P for subgroup difference = 0.001). **Figure 3B** presents a sensitivity analysis excluding one outlier study, which yielded consistent results (SMD 1.81, 95% CI 1.14 to 2.49, I^2 = 0%).

ELWI was reported in three studies. Combination therapy was associated with a significant reduction in ELWI compared with control therapy (SMD 3.80, 95% CI 1.39 to 6.22, P = 0.002), indicating greater reduction in pulmonary edema in the combination group (**Figure 3C**). The positive SMD reflects the definition of the effect size as (mean_control - mean_intervention)/pooled SD.

(3) Disease severity: APACHE II scores were reported in seven studies [10-13, 15, 18, 22]. Pooled analysis showed that combination therapy was associated with a significantly greater reduction in APACHE II scores compared with control therapy (SMD 1.07, 95% CI 0.84 to 1.30, P < 0.001), with substantial heterogene-

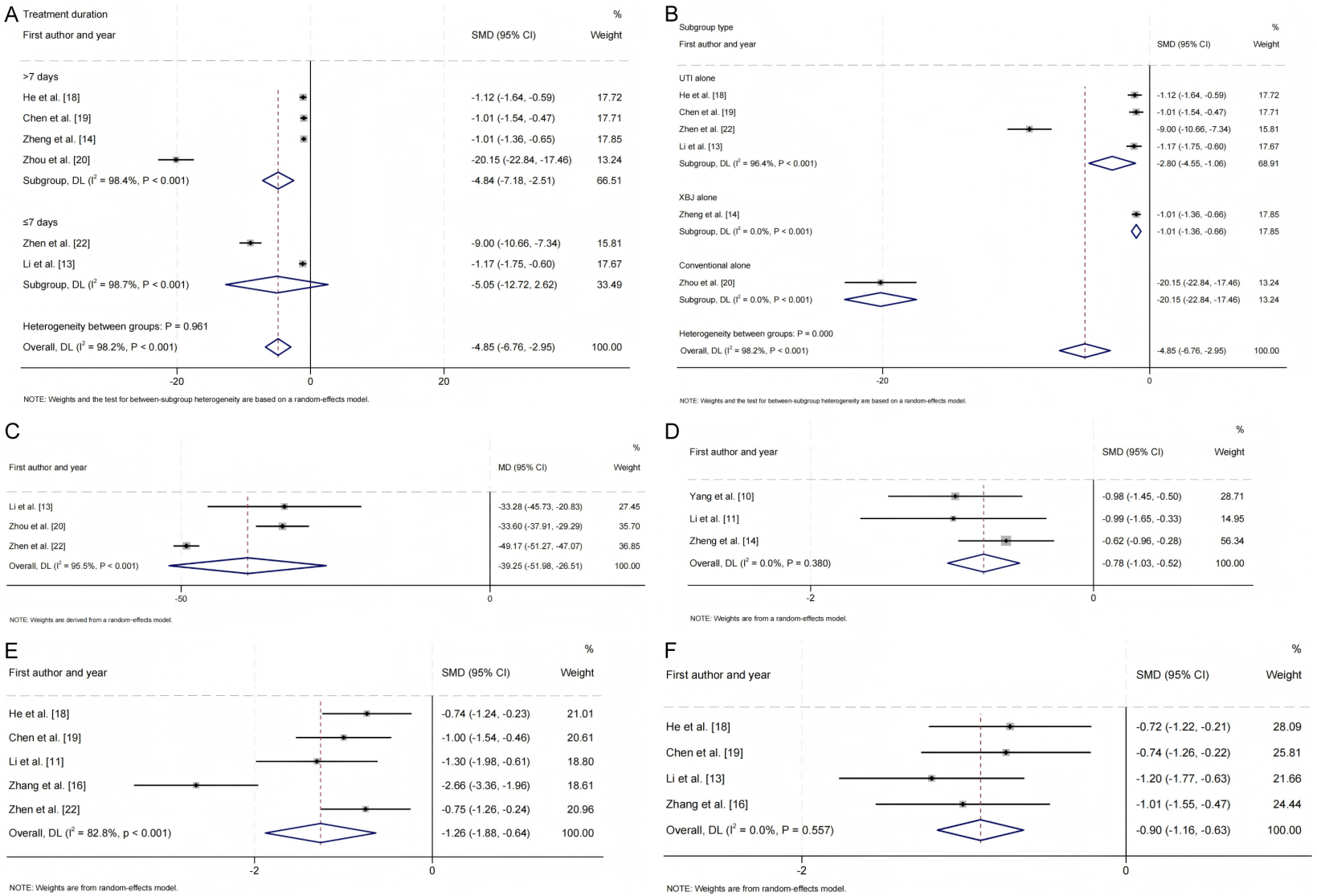

Figure 2. Forest plots for the meta-analysis of inflammatory marker levels. Note: (A) Subgroup analysis of TNF-α by treatment duration (≤ 7 days vs. > 7 days). (B) Subgroup analysis of TNF-α by control group type (ulinastatin alone, Xuebijing alone, or conventional therapy alone). (C) Forest plot of IL-6 levels. (D) Forest plot of HMGB-1 levels. (E) Subgroup analysis of PCT levels by treatment duration. (F) Subgroup analysis of CRP levels by treatment duration. Squares represent study-

specific effect sizes, with sizes proportional to study weights. Horizontal lines indicate 95% CIs. Diamonds indicate pooled estimates. The I^2 statistic quantifies heterogeneity. For panels with subgroup analyses (A, B, E, F), subgroup estimates are shown as diamonds. NOTE: Weights and the test for between-subgroup heterogeneity are based on a random-effects model. Abbreviations: CI, confidence interval; CRP, C-reactive protein; HMGB-1, high-mobility group box 1; IL-6, interleukin-6; MD, mean difference; PCT, procalcitonin; SMD, standardized mean difference; TNF-α, tumor necrosis factor-α; UTI, ulinastatin; XBJ, Xuebijing.

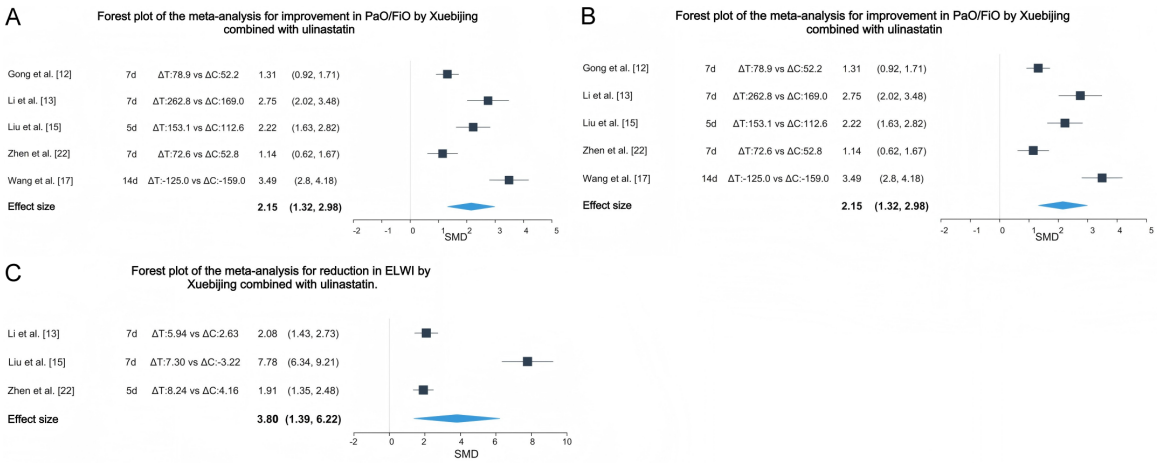

Figure 3. Forest plots for the meta-analysis of pulmonary function-related indices. Note: A. Overall and subgroup analyses for improvement in oxygenation index (PaO_2/FiO_2) by subgroup type. B. Sensitivity analysis for oxygenation index with exclusion of an outlier study. C. Sensitivity analysis for ELWI with exclusion of an outlier study. Squares represent study-specific effect sizes, with sizes proportional to study weights. Horizontal lines indicate 95% CIs. Diamonds indicate pooled estimates. I^2 values are shown for heterogeneity assessment. Abbreviations: CI, confidence interval; ELWI, extravascular lung water index; FiO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; SMD, standardized mean difference.

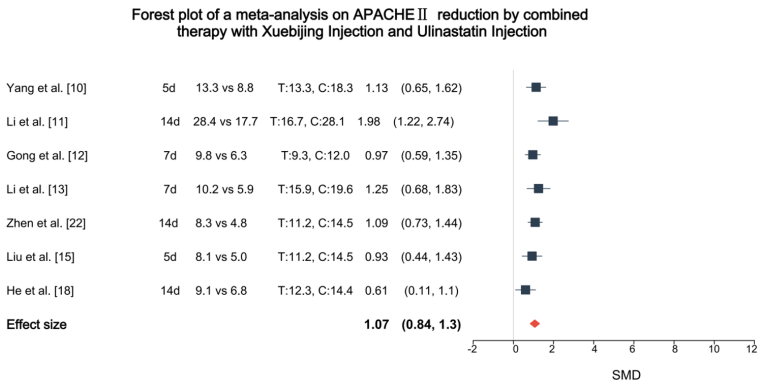

Figure 4. Forest plot of the meta-analysis of APACHE II scores. Note: SMD values were calculated as (mean-control-mean-treatment)/pooled SD; therefore, positive SMD values favor the combination therapy group. Squares indicate study-specific effect sizes (area proportional to study weight). Horizontal lines represent 95% confidence intervals. The diamond indicates the pooled standardized mean difference (SMD) with its 95% confidence interval. The I^2 statistic quantifies heterogeneity (85.2%, $P < 0.001$). Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; d, day(s); SMD, standardized mean difference; T, treatment group; C, control group.

ity (I^2 = 85.2%) (**Figure 4**). The positive SMD reflects the definition of the effect size as (mean control-mean intervention)/pooled SD, whereby positive values favor the intervention.

(4) Prognostic indicators: Five studies reported the duration of mechanical ventilation. Com bination therapy significantly shortened the duration of mechanical ventilation compared with control therapy (MD -78.9 hours, 95% CI -104.3 to -53.4, $P < 0.001$) (**Figure 5A**).

(5) Overall response rate: The overall response rate was reported in four studies [11, 12, 14, 19]. Combination therapy significantly increased the overall response rate compared with control therapy (RD 0.179, 95% CI 0.101 to 0.257; NNT = 5.6; $P < 0.001$), with no observed heterogeneity (I^2 = 0%) (**Figure 5B**). As the forest plot in **Figure 5B** presents RDs, the RD was used as the primary effect measure for this outcome.

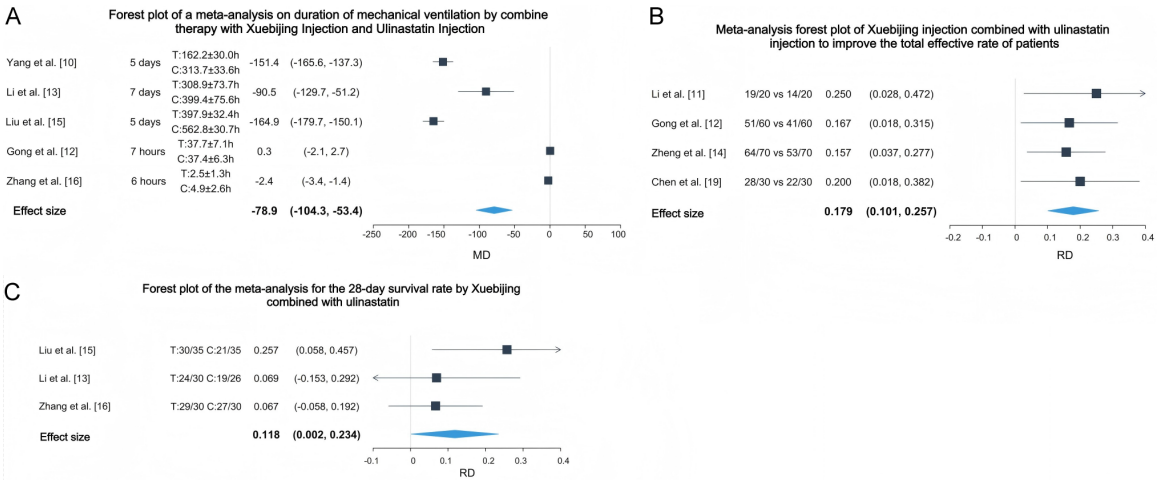

Figure 5. Forest plots for the meta-analysis of prognostic indicators. Note: A. Duration of mechanical ventilation (MD, hours). B. Overall response rate (RD). C. 28-day survival rate (RD). In each panel, squares indicate study-specific effect sizes, with sizes proportional to study weights. Horizontal lines represent 95% CIs. Diamonds indicate pooled estimates. Fixed-effect or random-effects models were used as indicated by the I^2 statistic. Abbreviations: CI, confidence interval; MD, mean difference; RD, risk difference.

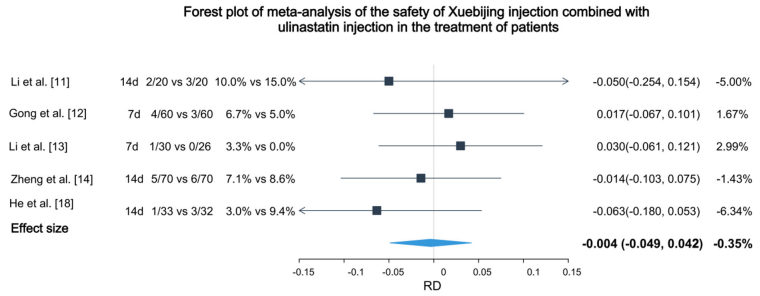

Figure 6. Forest plot for the meta-analysis of safety outcomes. Note: The forest plot shows the RD with 95% CIs. Squares represent individual studies, with sizes proportional to study weights. The diamond indicates the pooled RD. I^2 = 0% indicates no observed heterogeneity. Abbreviations: CI, confidence interval; RD, risk difference.

(6) 28-day survival rate: The 28-day survival rate was reported in three studies [13, 15, 16]. Combination therapy significantly improved 28-day survival compared with control therapy (RD 0.118, 95% CI 0.002 to 0.234, P = 0.047; NNT = 8.5), with low heterogeneity (I^2 = 25.4%) (**Figure 5C**).

Safety analysis

Five studies [11-14, 18] reported adverse events, most commonly gastrointestinal or skin-related reactions, including nausea, vomiting, abdominal distension, diarrhea, rash and pruritus. No serious adverse events were reported. Pooled analysis showed no significant difference between groups (RD -0.004, 95% CI -0.049 to 0.042, P = 0.881; I^2 = 0%, P for heterogeneity = 0.735) (**Figure 6**). These results suggest that combination therapy does not increase the risk of adverse events.

Sensitivity analysis results

Leave-one-out analyses showed that for APACHE II scores, PCT levels and CRP levels, the pooled SMDs remained statistically significant and directionally consistent when any single study was excluded (APACHE II: SMD range, 1.10 to 1.71; I^2 range, 72%-88%; PCT: SMD range, -2.31 to -1.70; CRP: SMD range, -2.32 to -1.51), with all 95% CIs excluding zero (**Figure 7A-C**).

Additional analyses supported the robustness of the findings. Reanalysis using a fixed-effect model yielded estimates for all primary continuous outcomes that were consistent in direction and statistical significance with the random-effects model estimates (Supplementary Table 1). For the overall response rate, the fixed-effect model yielded a consistent RD of 0.179 (95% CI 0.101 to 0.257; P < 0.001), with an NNT of 5.6 (95% CI 3.9 to 9.9).

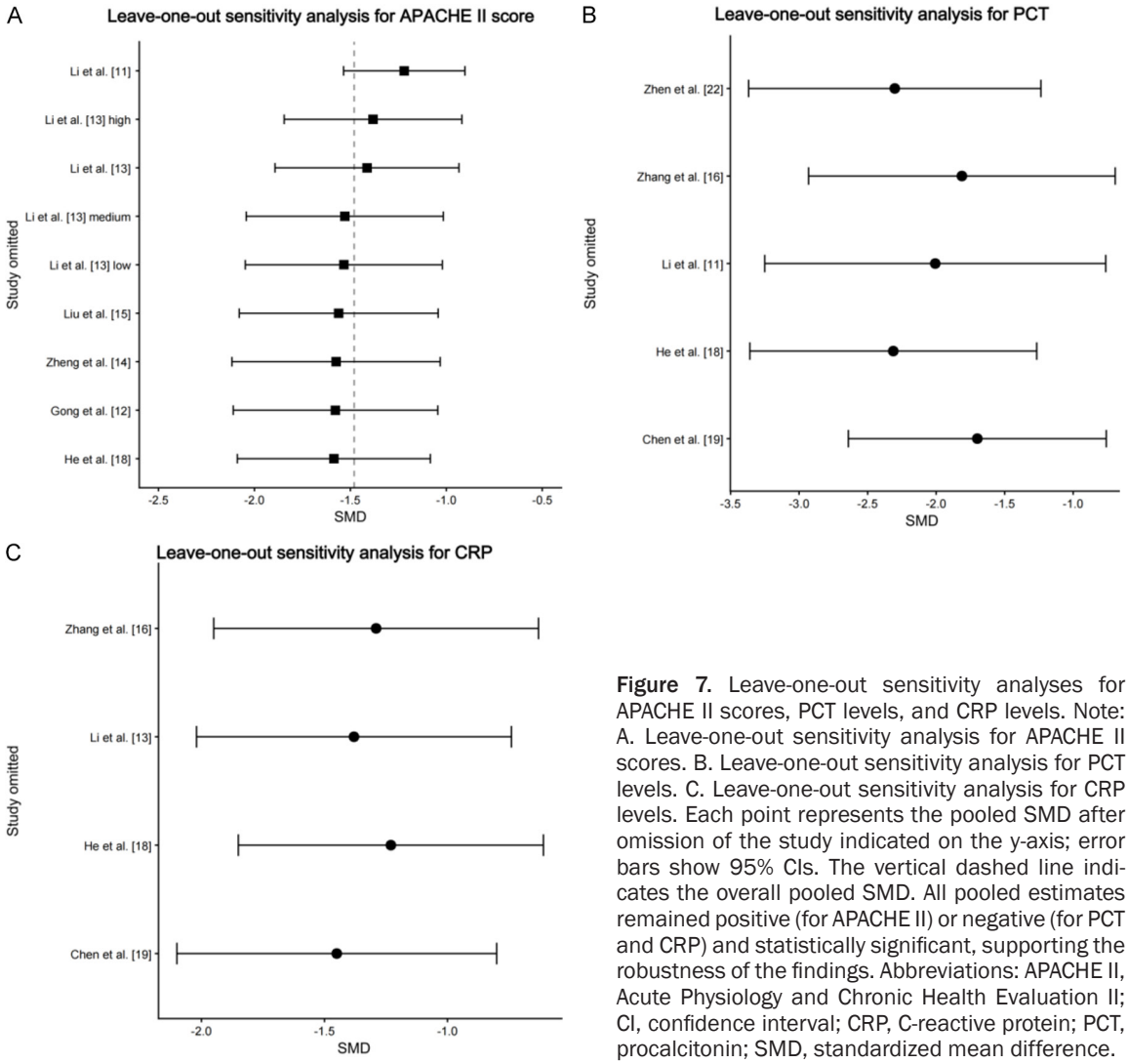

Figure 7. Leave-one-out sensitivity analyses for APACHE II scores, PCT levels, and CRP levels. Note: A. Leave-one-out sensitivity analysis for APACHE II scores. B. Leave-one-out sensitivity analysis for PCT levels. C. Leave-one-out sensitivity analysis for CRP levels. Each point represents the pooled SMD after omission of the study indicated on the y-axis; error bars show 95% CIs. The vertical dashed line indicates the overall pooled SMD. All pooled estimates remained positive (for APACHE II) or negative (for PCT and CRP) and statistically significant, supporting the robustness of the findings. Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; CRP, C-reactive protein; PCT, procalcitonin; SMD, standardized mean difference.

Publication bias

Publication bias was assessed for the overall response rate (n = 4 studies) using Egger's regression test, which suggested potential small-study effects (P = 0.009) (**Figure 8**). Trim-and-fill analysis imputed two hypothetical missing studies, yielding a corrected RD of 0.179 (95% CI 0.101 to 0.257), which remained statistically significant. However, because Egger's test has limited reliability with fewer than 10 studies, these results should be interpreted cautiously.

Discussion

Sepsis-induced ALI remains a life-threatening condition characterized by high morbidity and mortality, with limited effective treatment options [23]. Xuebijing injection, a traditional Chinese medicine formulation, exhibits anti-inflammatory, detoxifying and immunomodulatory properties, while ulinastatin effectively suppresses inflammatory responses and protects organ function. The combination of these two agents has attracted increasing interest in sepsis research [24]. However, the evidence remains inconsistent across studies and the overall reliability of this evidence is uncertain, underscoring the need for rigorous quality assessment of the existing literature.

Using the RoB 2.0 tool, four RCTs were assessed as having a low risk of bias, while eight were judged as having some concerns. The single retrospective study was rated as having a moderate risk of bias using the ROBINS-I tool. Although the overall quality was generally ac-

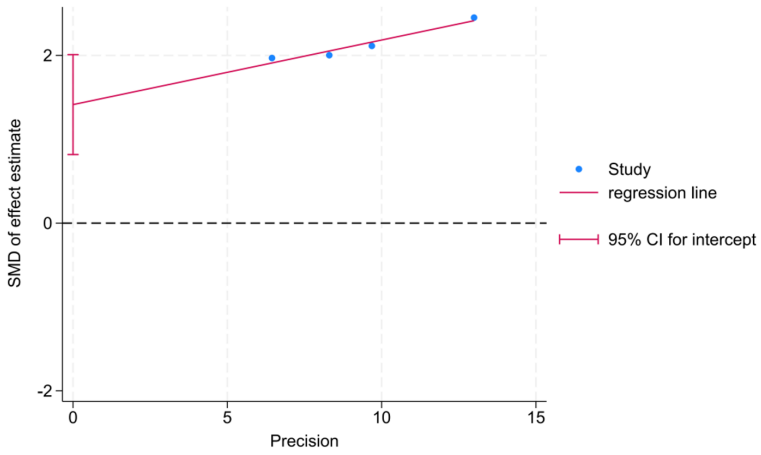

Figure 8. Egger's regression plot for publication bias assessment of the overall response rate. Note: Each point represents a single study. The vertical line indicates the pooled risk difference (RD) on the log scale. The diagonal lines represent pseudov-95% confidence limits around the pooled estimate in the absence of publication bias. The y-axis shows the standardized mean difference (SMD) of the effect estimate. Asymmetry may suggest small-study effects or publication bias (Egger's test P = 0.009). Given the limited number of studies (n = 4), the results of Egger's test should be interpreted with caution. Abbreviations: CI, confidence interval; RD, risk difference, SMD, standardized mean difference.

ceptable, certain methodological limitations were identified.

Among the low-risk RCTs, Liu et al. [15] and Wang et al. [17] employed rigorous randomization methods (random number tables or drawing lots), reported no loss to follow-up and focused on objective, clinically meaningful outcomes such as survival rates and respiratory function indices, thereby effectively minimizing bias.

Among the studies with some concerns, Li et al. [11] and Zheng et al. [14] described adequate random sequence generation and had balanced baseline characteristics but did not report blinding or allocation concealment. To some extent, this limitation is inherent to the intensive care setting, where patients are often clinically unstable and require close monitoring and highly individualized treatment. Additionally, investigational drugs frequently differ in appearance and administration from standard therapies, making blinding challenging. Gong et al. [12] described adequate random sequence generation but did not report allocation concealment or blinding and Zhou et al. [21] did not specify the randomization method, both of which increased the risk of selection bias.

The primary methodological limitations identified in the included RCTs pertained to the frequent lack of blinding and allocation concealment, as well as incomplete documentation of patient dropouts or withdrawals in some studies. These deficiencies are inherently linked to the challenges of managing critically ill patients within ICUs and highlight the practical difficulties of implementing rigorous trial designs in such complex clinical settings.

Future research should prioritize enhanced methodological rigor. Where feasible, single-blind or double-blind study designs should be adopted, along with strict enforcement of allocation concealment procedures. Additionally, comprehensive reporting of patient attrition, including details of dropouts and withdrawals, should be ensured. For individual studies, such as that conducted by Yang et al. [10], efforts should be intensified to control key confounding variables and increase sample sizes, thereby achieving an optimal balance between scientific validity and clinical relevance. The ultimate goal is to generate higher-quality evidence to guide the clinical application of Xuebijing in combination with ulinastatin.

Several recent meta-analyses and systematic reviews have evaluated the efficacy of ulinastatin alone, Xuebijing alone, or their combination in the treatment of sepsis. An extensive umbrella review by Cao and Han assessed ulinastatin, with or without thymosin α1 or Xuebijing, in relation to sepsis outcomes. This review confirmed the anti-inflammatory benefits of these interventions but emphasized the need to carefully consider the interactions between ulinastatin and concomitant therapies to fully evaluate the efficacy of ulinastatin [5]. Among meta-analyses focusing specifically on combination therapy, Zheng et al. [25], Xiao et al. [26] and Chen et al. [27] consistently reported that the combination of Xuebijing and ulinastatin was superior to ulinastatin monotherapy

or standard care; however, Chen et al. cautioned against the limited methodological quality of the included studies. More recently, a network meta-analysis by Liu et al. investigated the dose-response relationship of Xuebijing in sepsis, demonstrating that a daily dose of 100 mL improved activated partial thromboplastin time and CRP levels, while higher doses were associated with greater reductions in APACHE II scores [28]. An editorial by Unger and Clissold addressed the potential and challenges of introducing Xuebijing to the U.S. market, emphasizing the need for rigorously designed RCTs to satisfy regulatory requirements [29].

Notably, the sepsis-focused studies mentioned above did not specifically target the ALI/ARDS subpopulations; rather, most enrolled general sepsis cohorts without restricting inclusion based on pulmonary involvement. This distinction is critical, as ALI represents a more severe, organ-specific phenotype in which the anti-inflammatory and microvascular protective effects of combination therapy are most likely to yield clinical benefit. Furthermore, a meta-analysis conducted by Dai et al. [23] specifically examined the use of Xuebijing in ALI, reporting improvements in the oxygenation index and reductions in mortality; however, this analysis did not evaluate Xuebijing combined with ulinastatin.

This study contributes to the existing literature in four significant ways. First, to our knowledge, it is the first meta-analysis to specifically synthesize evidence on the combination of Xuebijing and ulinastatin in patients with sepsis-associated ALI, thereby providing more precise guidance for intensivists managing this high-risk population. Second, it provides the first quantitative estimate of the 28-day survival benefit associated with this combination in the ALI population (RD 0.118, 95% CI 0.002 to 0.234, P = 0.047; NNT = 8.5), an outcome not consistently reported in previous meta-analyses of general sepsis populations. Third, comprehensive subgroup and sensitivity analyses, along with an updated risk-of-bias assessment, substantially enhance the methodological rigor and transparency of the findings. Fourth, by systematically incorporating studies published in Chinese, the analysis enhances the generalizability of conclusions regarding a therapeutic regimen predominantly used in China.

The combination therapy significantly reduced circulating levels of TNF-α, IL-6, PCT, CRP and HMGB-1 compared with those in the control groups. These agents exert synergistic anti-inflammatory effects by modulating complementary molecular pathways.

TNF-α and IL-6 are pivotal pro-inflammatory cytokines released early in the septic response. Their excessive elevation contributes to pulmonary capillary endothelial and alveolar epithelial injury, resulting in pulmonary edema, impaired gas exchange and hypoxemia. Elevated concentrations of these cytokines have been correlated with an increased risk of progression from ALI to ARDS [30]. In the present meta-analysis, combination therapy reduced IL-6 levels by a mean of 39.25 ng/L.

Ulinastatin, a broad-spectrum protease inhibitor, attenuates upstream inflammatory signaling by binding to the active sites of trypsin and kallikrein, thereby inhibiting excessive neutrophil activation and lysosomal enzyme release. This binding attenuates Toll-like receptor 4 (TLR4)/myeloid differentiation primary response protein 88 signaling and reduces NF-κB p65 nuclear translocation, ultimately downregulating the transcription of TNF-α and IL-6 [8]. Furthermore, Li et al. [31] demonstrated in animal models that ulinastatin activates the extracellular signal-regulated kinase 5/Mer tyrosine kinase signaling pathway, enhancing macrophage-mediated clearance of apoptotic neutrophils and thus indirectly mitigating inflammation.

Xuebijing exerts its effects through distinct mechanisms. Cui et al. [32] demonstrated that several of its constituents, including quercetin, ferulic acid and paeoniflorin, interact with the Ser455 residue of ATP citrate lyase, inhibiting its enzymatic activity and reducing acetyl-CoA production. This reduction in acetyl-CoA influences MYB acetylation and nuclear translocation, leading to downregulation of retinoic acid-inducible gene I expression, suppression of sustained NF-κB activation and decreased synthesis of TNF-α and IL-6. Additionally, tanshinone IIA, another component of Xuebijing, binds to the extracellular domain of TLR4, blocking endotoxin binding and further inhibiting NF-κB nuclear translocation. Consistent with these findings, Ren et al. [33] demonstrat-

ed in a murine model of sepsis that Xuebijing alleviated ALI by inhibiting alveolar epithelial cell apoptosis via the cAMP/PKA signaling pathway, further supporting the multi-target protective effects of this preparation.

The lower PCT and CRP levels observed with combination therapy may be attributed to the inhibitory effect of ulinastatin on bacterial endotoxin-induced PCT synthesis in hepatic and pulmonary tissues [34], together with its suppression of neutrophil activity, which may also modulate CRP release.

HMGB-1 is released later in sepsis but persists longer and has been associated with multi-organ dysfunction. In the present study, patients receiving combination therapy exhibited lower HMGB-1 levels. Xuebijing likely contributes by inhibiting the TLR4/NF-κB pathway, thereby attenuating downstream inflammatory responses triggered by HMGB-1 [15]. Ulinastatin may act by stabilizing lysosomal membranes, limiting passive HMGB-1 release from necrotic cells and suppressing active HMGB-1 secretion from activated macrophages. Enhanced macrophage phagocytic activity, as reported by Li et al. [31], may facilitate the clearance of HMGB-1 originating from necrotic cells.

The oxygenation index reflects both the severity of lung injury and the efficiency of gas exchange, which in turn influence the duration of mechanical ventilation, ICU length of stay and mortality. Across five studies reporting this outcome [12, 13, 15, 17, 22], patients receiving combination therapy consistently demonstrated greater improvement than those in the control groups. This advantage likely results from the complementary effects of the two agents: ulinastatin attenuates pulmonary capillary endothelial injury, while Xuebijing reduces pro-inflammatory cytokine levels. Additionally, Xuebijing may promote pulmonary vasodilation and improve perfusion, which, together with the vascular permeability-lowering effect of ulinastatin, improves gas exchange [35]. However, this mechanism requires further clinical validation.

The ELWI quantifies the extent of pulmonary edema and vascular permeability. A decrease in ELWI generally indicates reduced pulmonary capillary leakage and improved clearance of edema fluid [36]. In the three trials reporting this index [13, 15, 22], the reduction was consistently greater in the combination group, suggesting a distinct advantage in managing sepsis-related pulmonary edema.

The APACHE II score is a comprehensive measure of physiological derangement and organ dysfunction in critically ill patients and is associated with hospital mortality, ICU length of stay and the risk of multi-organ failure. Across seven studies reporting this outcome [10-13, 15, 18, 22], the decline in APACHE II scores was greater in the combination therapy group than in the control group. Notably, Li et al. [11], who studied patients with particularly severe disease, observed a 10.7-point greater improvement with combination therapy, suggesting that even in high-risk patients, this regimen may help correct acute physiological disturbances and mitigate organ injury.

The overall response rate, a commonly used indicator of clinical benefit, was significantly higher with combination therapy than with control (RD 0.179, 95% CI 0.101-0.257; NNT = 5.6), representing a 17.9% absolute increase. This suggests that the combination regimen enables more patients to achieve symptomatic relief.

The 28-day survival rate is a standard endpoint for assessing long-term prognosis in sepsis-induced lung injury and directly reflects the impact of treatment on patient survival. Combination therapy was associated with an average 11.8% absolute improvement in 28-day survival, with an NNT of 8.5, indicating that for every 8.5 patients treated with the combination, one additional death is prevented. This finding suggests that the combination regimen is particularly beneficial for improving long-term survival in patients with moderate to severe sepsis complicated by lung injury.

Combination therapy also significantly shortened the duration of mechanical ventilation. Improved gas exchange and controlled inflammation likely accelerate recovery, reduce healthcare resource utilization and contribute to better long-term clinical outcomes.

Several outcomes in this meta-analysis showed substantial heterogeneity, reflecting variability in treatment effects among the included studies. This heterogeneity is likely due to differences in baseline patient characteristics, such

as inflammatory status and the extent of organ dysfunction at enrollment. Variability in intervention protocols and control group designs may also have contributed, as some studies used conventional treatment alone as the comparator while others employed ulinastatin.

Sensitivity analyses, in which each study was systematically removed and pooled estimates were recalculated, yielded consistent results across all iterations, with effect sizes continuing to favor combination therapy over control. These findings indicate that, despite some between-study variability, the overall conclusion that combination therapy confers superior efficacy remains robust.

Several limitations inherent to this meta-analysis warrant careful consideration when interpreting the findings. First, the methodological rigor of the included RCTs was generally modest. Only four of the twelve RCTs were assessed as having a low risk of bias using RoB 2.0 tool and most lacked blinding or adequate allocation concealment, which may have introduced performance and detection biases, potentially leading to an overestimation of treatment effects, particularly for subjective outcomes such as the overall response rate. Second, despite conducting subgroup analyses, substantial heterogeneity remained for certain outcomes, notably TNF-α and oxygenation index, with I^2 exceeding 90%. This residual heterogeneity suggests that the pooled estimates for these outcomes may not represent a single consistent effect across diverse patient populations and treatment protocols and should therefore be interpreted with caution. Third, none of the included studies reported long-term outcomes beyond 28 days, such as quality of life, cognitive function, or hospital readmission rates. Consequently, our conclusions are confined to short-term physiological and survival benefits and the durability of the treatment effect and its impact on long-term functional recovery are unknown. Fourth, all studies were conducted in China and, based on the study settings, likely enrolled predominantly Han Chinese patients, which restricts the external validity of the findings to other ethnic populations or healthcare systems where standards of care, microbial epidemiology and genetic backgrounds may differ. Fifth, considerable variation existed in the dosing regimens of both Xuebijing and ulinastatin across studies; as a result, our pooled estimates reflect a general effect across heterogeneous protocols and do not permit identification of an optimal dose. Finally, Egger's test for the overall response rate, based on only four studies, indicated potential small-study effects ($P = 0.009$), suggesting the presence of publication bias. This raises the possibility that unpublished negative trials exist and our results may therefore overestimate the true effect size, particularly for outcomes where the observed benefit was modest.

Further large-scale, multicenter RCTs with enhanced methodological rigor, including allocation concealment and, where feasible, blinding, are needed to address these limitations and validate the present findings. Future trials should standardize dosing protocols, incorporate dose-finding components, extend follow-up to include six-month assessments of quality of life and cognitive function and enroll diverse ethnic populations to confirm generalizability. Transparent reporting of withdrawals and adverse events, together with prospective trial registration, will also enhance methodological quality and reduce publication bias.

Conclusion

In summary, these findings indicate that Xuebijing combined with ulinastatin offers clinically meaningful benefits for patients with sepsis-associated ALI. Combination therapy was associated with notable reductions in key inflammatory mediators (TNF-α, IL-6, HMGB-1, PCT and CRP), improved oxygenation, reduced pulmonary edema, lower APACHE II scores, shorter durations of mechanical ventilation and higher overall response and 28-day survival rates, all while maintaining a favorable safety profile. Although heterogeneity was observed for some outcomes, the overall evidence is robust and supports a synergistic effect of these two agents, a finding with substantial clinical value for critically ill patients. Large-scale, multicenter RCTs are warranted to determine optimal dosing strategies and to evaluate long-term outcomes beyond 28 days.

Disclosure of conflict of interest

None.

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References

[1] Liu H, Dong J, Xu C, Ni Y, Ye Z, Sun Z, Fan H and Chen Y. Acute lung injury: pathogenesis and treatment. J Transl Med 2025; 23: 926.

[2] GBD 2021 Global Sepsis Collaborators. Global, regional and national sepsis incidence and mortality, 1990-2021: a systematic analysis. Lancet Glob Health 2025; 13: e2013-e2026.

[3] Wang Z and Wang Z. The role of macrophages polarization in sepsis-induced acute lung injury. Front Immunol 2023; 14: 1209438.

[4] Lv K and Liang Q. Macrophages in sepsis-induced acute lung injury: exosomal modulation and therapeutic potential. Front Immunol 2025; 15: 1518008.

[5] Cao S and Han P. The effect of ulinastatin on sepsis outcomes: an umbrella review of meta-analysis. Clin Ther 2025; 47: 377-383.

[6] Cao JP, Piao XH, Zhu LX and Feng PF. Xuebijing and somatostatin against acute pancreatitis: a systematic review and network pharmacology. Medicine (Baltimore) 2024; 103: e40964.

[7] Yu B, Chen L and Huang D. Immunomodulatory therapy and mortality in patients with sepsis: a meta-analysis. Int Arch Allergy Immunol 2025; [Epub ahead of print].

[8] Zhong G, Han Y, Zhu Q, Xu M, Chang X, Chen M, Men L, Zhang Q and Wang L. The effects of Xuebijing injection combined with ulinastatin as adjunctive therapy on sepsis: an overview of systematic review and meta-analysis. Medicine (Baltimore) 2022; 101: e31196.

[9] Papet E, Moutel G, Pinson J, Roussel E, Bridoux V and Tuech JJ. A scoping review focused on cooperative group involvement in surgical randomized controlled trials. J Surg Res 2026; 318: 120-125.

[10] Yang XT, Li D, Zhao LX, Zhang N, Su HY and Wang Y. Effects of Xuebijing injection combined with ulinastatin on severe pneumonia complicated with sepsis. Northwest Pharm J 2025; 40: 171-176.

[11] Li D, Yang XT, Zhao LX, Zhang N, Su HY, Wang Y and Zhao LJ. Effect analysis of ulinastatin injection combined with Xuebijing injection in the treatment of severe pneumonia with sepsis. Clin Misdiagn Misther 2025; 38: 35-39.

[12] Gong GY, Ou H, Zhang WJ, Zhou J, Yang M, Li TQ and Xu ZH. Clinical study on Xuebijing combined with ulinastatin in the treatment of septic acute lung injury. China Pharm 2022; 31: 105-108.

[13] Li LH, Yang YZ, Lin R and Hong LM. Clinical observation of different doses of Xuebijing injection combined with ulinastatin injection in the treatment of sepsis complicated with acute lung injury. China Pharm 2020; 31: 1617-1621.

[14] Zheng WW and Zhang ZB. Effect of Xuebijing injection combined with ulinastatin injection on sepsis complicated with acute lung injury and its influence on HMGB1/TLR4/NF-κB signaling pathway. J Transl Med 2024; 13: 259-263.

[15] Liu Y, Mei JQ, Shi BZ, Li YT, Xu M, Yang MH and Wang C. Clinical efficacy of Xuebijing injection combined with ulinastatin on pulmonary vascular permeability in patients with sepsis complicated with ARDS. Chin J Integr Tradit West Med Intens Crit Care 2021; 28: 385-389.

[16] Zhang YW, Zhao ML, Zhang S, Zhou KL, Gao H, Wang JH, Zhao X and Li C. Effect of Xuebijing combined with ulinastatin on sepsis-induced acute respiratory distress syndrome. Clin Focus 2018; 33: 575-578.

[17] Wang JM. Clinical effect of different doses of Xuebijing combined with ulinastatin in the treatment of sepsis complicated with acute lung injury. J Med Theory Pract 2023; 36: 194-196.

[18] He MQ and Li X. Effects of ulinastatin combined with Xuebijing on APACHE II score and hemodynamics in patients with severe pneumonia complicated with sepsis. North Pharm J 2024; 21: 106-108.

[19] Chen B, Wan XF and Wang JH. Application observation of Xuebijing injection combined with ulinastatin in patients with severe pneumonia and sepsis. J Emerg Tradit Chin Med 2017; 26: 2008-2010.

[20] Zhou CE and Fang ZC. Effect of Xuebijing combined with ulinastatin on immune function in patients with sepsis. Mod J Integr Tradit Chin West Med 2013; 22: 131-132.

[21] Zhou CE and Fang ZC. Clinical study on Xuebijing combined with ulinastatin in the treatment of sepsis. J Clin Pulm Med 2013; 18: 647-648.

[22] Zhen GD, Shan YJ, Qiao HY, Wang WW, Gai LX and Li ZF. Efficacy of Xuebijing injection in the adjunctive therapy of acute respiratory distress syndrome caused by sepsis. Am J Transl Res 2019; 11: 7117-7124.

[23] Dai L, Chen M, Chen Q, Zhuang Y, Jiang H and Xu Y. Efficacy of Xuebijing injection for the treatment of acute lung injury: a meta-analysis of randomized controlled trials. Heliyon 2024; 10: e33313.

[24] Meng WT, Qing L, Zhou Q and Xu WG. Xuebijing attenuates decompression-induced lung injuries. Diving Hyperb Med 2020; 50: 343-349.

[25] Zheng J, Xiang X, Xiao B, Li H, Gong X, Yao S and Yuan T. Xuebijing combined with ulinastatin benefits patients with sepsis: a meta-analysis. Am J Emerg Med 2018; 36: 480-487.

[26] Xiao SH, Luo L, Liu XH, Zhou YM, Liu HM and Huang ZF. Curative efficacy and safety of traditional Chinese medicine xuebijing injections combined with ulinastatin for treating sepsis in the Chinese population: a meta-analysis. Medicine (Baltimore) 2018; 97: e10971.
[27] Chen G, Gao Y, Jiang Y, Yang F, Li S, Tan D and Ma Q. Efficacy and safety of Xuebijing injection combined with ulinastatin as adjunctive therapy on sepsis: a systematic review and meta-analysis. Front Pharmacol 2018; 9: 743.
[28] Liu G, Qu X, Jiang R, Wu Y, Qin Z, Zhang H, Ma R, Xue J, Wang J, Xu X, Yan C, Wei X and Guo L. Effects of different dosages/frequency of Xuebijing injection (a Chinese patent) for sepsis: a network meta-analysis of randomized controlled trials. Front Med (Lausanne) 2025; 12: 1577414.
[29] Unger EF and Clissold DB. Xuebijing injection for the treatment of sepsis: what would a path to FDA approval look like? JAMA Intern Med 2023; 183: 655-657.
[30] Meng ZY, He JY, Ma JH, Gan TY, He HB, Zhang Y, Liu J, Zhang JH, Li HR, Qin HL and Jia LL. Anti-arthritis effects of total triterpenoids from fruits of Chaenomeles speciosa based on TLR4/NF-κB/NLRP3 signaling pathway. Zhongguo Zhong Yao Za Zhi 2025; 50: 6654-6665.
[31] Li J, Shao R, Xie Q, Qin K, Ming S, Xie Y and Du X. Ulinastatin promotes macrophage efferocytosis and ameliorates lung inflammation via the ERK5/Mer signaling pathway. FEBS Open Bio 2022; 12: 1498-1508.
[32] Cui J, Deng Y, Li X, Gao L, Li J, Li Z, Qu H, Chu Y, Gu Y, Meng M and Li R. Herbal-based Xuebijing injection ameliorated vascular endothelial dysfunction via inhibiting ACLY/MYB/RIG-I axis in sepsis-associated lung injury. Phytomedicine 2025; 140: 156573.
[33] Ren T, Chen Q, Xu J, Jiang H, Guo T, Wu Y, Xu Y and Dai L. Xuebijing alleviates sepsis-induced acute lung injury by inhibiting alveolar epithelial cell apoptosis via cAMP/PKA signaling pathway. J Ethnopharmacol 2025; 353: 120370.
[34] Xie X, Liu Y, Zhi S, Huang W and Li N. Effect of octreotide combined with ulinastatin on the creatinine-to-albumin ratio and systemic immune-inflammation index in patients with severe acute pancreatitis. Am J Transl Res 2025; 17: 9327-9340.
[35] Zou F, Zou J, Du Q, Liu L, Li D, Zhao L, Tang M, Zuo L and Sun Z. XueBiJing injection improves the symptoms of sepsis-induced acute lung injury by mitigating oxidative stress and ferroptosis. J Ethnopharmacol 2025; 337: 118732.
[36] Zeng S, Cui S, Li Y, Yao Z, Li Y, Cao Y, Wen L, Li M, Zheng J and Wang H. New insights on continuous renal replacement therapy for acute respiratory distress syndrome: a systematic review and meta-analysis. Clin Respir J 2025; 19: e70045.

Appendix S1. Complete Search Strategies for Each Database

1. PubMed search strategy (conducted on January 15, 2026)
("Xuebijing"[Mesh] OR "Xuebijing"[Title/Abstract] OR "Xuebijing injection"[Title/Abstract] OR "Chinese herbal drugs"[Mesh] OR "Drugs, Chinese Herbal"[Mesh] OR "Plant Extracts, Chinese"[Mesh])
AND
("Ulinastatin"[Supplementary Concept] OR "ulinastatin"[Title/Abstract] OR "urinary trypsin inhibitor"[Title/Abstract] OR "UTI68"[Title/Abstract] OR "Miraclid"[Title/Abstract])
AND
("Sepsis"[Mesh] OR "Severe Sepsis"[Mesh] OR "Septicemia"[Title/Abstract] OR "Bloodstream infection"[Title/Abstract] OR "Pyemia"[Title/Abstract] OR "Systemic inflammatory response syndrome"[Title/Abstract])
AND
("Acute Lung Injury"[Mesh] OR "ALI"[Title/Abstract] OR "ARDS"[Title/Abstract] OR "Acute Respiratory Distress Syndrome"[Title/Abstract] OR "Acute lung injury"[Title/Abstract])

2. Embase search strategy (analogous to PubMed with Emtree terms):
('xuebijing'/exp OR 'xuebijing':ti,ab OR 'xuebijing injection':ti,ab)
AND
('ulinastatin'/exp OR 'ulinastatin':ti,ab OR 'urinary trypsin inhibitor':ti,ab)
AND
('sepsis'/exp OR 'septic shock'/exp OR 'sepsis':ti,ab OR 'septicemia':ti,ab)
AND
('acute lung injury'/exp OR 'acute respiratory distress syndrome'/exp OR 'ali':ti,ab OR 'ards':ti,ab)

3. Cochrane Library search strategy:
#1 MeSH descriptor: [Xuebijing] explode all trees (if available) OR (Xuebijing):ti,ab,kw
#2 MeSH descriptor: [Ulinastatin] explode all trees OR (ulinastatin):ti,ab,kw
#3 MeSH descriptor: [Sepsis] explode all trees OR (sepsis):ti,ab,kw
#4 MeSH descriptor: [Acute Lung Injury] explode all trees OR (ALI):ti,ab,kw
#5 #1 AND #2 AND #3 AND #4

4. Web of Science search strategy:
TS=((“Xuebijing” OR “Xuebijing injection”) AND (“Ulinastatin” OR “urinary trypsin inhibitor”) AND (“Sepsis” OR “Septicemia”) AND (“Acute lung injury” OR “ALI” OR “ARDS”))

5. Chinese databases (CNKI, Wanfang, VIP) search strategy (consistent across databases):
(SU='Xuebijing' OR SU='Xuebijing injection') AND (SU='Ulinastatin' OR SU='Ulinastatin injection') AND (SU='Sepsis' OR SU='Septicemia' OR SU='Systemic inflammatory response syndrome') AND (SU='Acute lung injury' OR SU='ALI' OR SU='ARDS' OR SU='Acute respiratory distress syndrome')

Supplementary Table 1. Comparison of estimates from random-effects and fixed-effect models for key outcomes

Outcome	Random-effects estimate (95% CI)	Fixed-effect estimate (95% CI)	Conclusion unchanged
APACHE II score	SMD 1.07 (0.84, 1.30)	SMD 1.22 (1.05, 1.39)	Yes
TNF-α	SMD -4.85 (-6.76, -2.95)	SMD -1.35 (-1.58, -1.12)	Yes
PCT	SMD -1.26 (-1.88, -0.64)	SMD -1.13 (-1.38, -0.88)	Yes
Oxygenation index	SMD 2.15 (1.32, 2.98)	SMD 1.19 (0.95, 1.42)	Yes
Total effective rate	-	RD 0.179 (0.101-0.257)	-

Note: "-" indicates that the estimate was not reported or was not applicable. Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; PCT, procalcitonin; RD, risk difference; SMD, standardized mean difference; TNF-α, tumor necrosis factor-α.