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Clinical efficacy of ulinastatin in patients with pulmonary edema

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective: To methodically assess the clinical impact of ulinastatin on patients suffering from pulmonary edema.

Methods: PubMed, Web of Science, Cochrane Library, Embase, Chinese National Knowledge Infrastructure (CNKI), Wanfang data, Chinese Scientific Journal Database (VIP), and Chinese Biomedical Literature Database (CBM) databases were searched using such keywords as ulinastatin, pulmonary edema, and randomized controlled trial (RCT). The search time was from the establishment of the database to August 2023. Two researchers were responsible for literature screening and data collection respectively. After the risk of bias in the included studies was evaluated, meta-analysis was performed using statistical software RevMan 5.4 and GRADE profiler software was used to evaluate evidence quality.

Results: Nine RCTs were included in the meta-analysis. Meta-analysis results showed that compared with conventional treatment group, the incidence of pulmonary edema of the patients in the ulinastatin group decreased, with odds ratios (OR) of 0.36 (95% CI: 0.20, 0.657), extravascular pulmonary water index (EVLWI) decreased, with mean difference (MD) of −0.75 (95% CI: −1.32, −0.17), ventilator use time decreased, with MD of −2.86 (95% CI: −0.26, 0.23), the intensive care unit (ICU) length of stay decreased, with MD of −1.56 (95% CI: −1.75, −1.38). The pulmonary vascular permeability index (PVPI) decreased in ulinastatin group, with MD of −0.10 (95% CI: −0.24, 0.03), but the difference was not statistically significant.

Conclusion: Compared with conventional treatment, ulinastatin may reduce the incidence of pulmonary edema, decrease EVLWI, ventilator use time and the ICU length of stay in patients with pulmonary edema, but it could not reduce PVPI.

Abbreviations: 95% CI = 95% confidence intervals, CBM = Chinese Biomedical Literature Database, CNKI = Chinese National Knowledge Infrastructure, EVLWI = extravascular pulmonary water index, ICU = intensive care unit, IL-6 = interleukin-6, JNK = c-Jun N-terminal kinase, MD = mean difference, OR = odds ratios, PICCO = pulse indicator continuous cardiac output, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PROSPERO = Prospective Register of Systematic Reviews, PVPI = pulmonary vascular permeability index, RCT = randomized controlled trial, TNF-α = tumor necrosis factor-α, VIP = Chinese Scientific Journal Database.

Keywords: conventional treatment, intensive care unit, meta-analysis, pulmonary edema, systematic review, ulinastatin

1. Introduction

Pulmonary edema is 1 of the common critical illnesses in clinical practice. Pulmonary edema is a state of fluid accumulation in the pulmonary interstitium and alveolar space caused by various etiologies and is a syndrome resulting from a variety of diseases.[1] It may be formed by intrinsic lung lesions or systemic dysfunction.[2] It has been shown that the incidence of pulmonary edema accounts for 7.6% of all hospitalized patients, while the in-hospital mortality among them reaches 11.9%.[3] Therefore, in clinical treatment, we should not only pay attention

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to controlling the development of the primary disease, but also actively prevent and treat the occurrence of complications such as pulmonary edema.

Ulinastatin is an endogenous urinary trypsin inhibitor derived from the isolation and purification of male urine. It is essentially a protease inhibitor and a class of glycoproteins. It consists of 143 amino acid residues in tandem with 2 Kunitz-type protease inhibitor domains.[4] Ulinastatin can inhibit the activity of a variety of hydrolytic enzymes, stabilize lysosomal membranes, inhibit the secretion of lysosomal enzymes, while scavenging oxygen free radicals. It can also exert anti-inflammatory effects, inhibit neutrophil infiltration and the release of inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), effectively reduce systemic inflammatory response, improve human microcirculation and tissue perfusion to achieve the purpose of reducing pulmonary edema.[5,6] Clinical practice has shown that ulinastatin has a good anti-inflammatory effect and also has a positive effect on improving lung function in humans.[7] In this study, we compared the clinical effects of ulinastatin and conventional treatment in patients with pulmonary edema through meta-analysis in order to provide evidence-based medicine basis for the treatment of patients with pulmonary edema.

2. Methods

2.1. Protocol and registration

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[8] and was pre-registered on the Prospective Register of Systematic Reviews (PROSPERO) platform (registration number #CRD42023461983).[9]

2.2. Search strategy

The main terms used to construct the search strategy were ulinastatin, pulmonary edema, RCT. PubMed, Web of Science, Cochrane Library, Embase, Chinese National Knowledge Infrastructure (CNKI), Wanfang data, Chinese Scientific Journal Database (VIP), and Chinese Biomedical Literature Database (CBM) were searched from the date of database inception to August 2023. In addition, the references of the included studies were traced to supplement relevant studies.

2.3. Literature screening

Literature screening, data extraction, and cross-checking were conducted by 2 independent researchers. In case of any disagreements, a third researcher was consulted for resolution. Reasons for excluding literature were clearly recorded, and an exclusion criteria list was created. Efforts were made to contact the original authors via email or phone for any missing data. During the screening and evaluation of literature, the titles and abstracts were initially reviewed to remove duplicates and articles that did not meet the requirements. Subsequently, the full texts were further examined to determine the included studies.

2.4. Eligibility criteria

2.4.1. Inclusion criteria. Type of study: randomized controlled trials (RCT), language is limited to Chinese and English; Participants: all conditions that may cause pulmonary edema, age > 18 years old, gender, nationality, race, source of infection, pathogen and course of disease were not limited; Intervention measures and comparison: Ulinastatin was injected intravenously in the observation group, and other conventional treatments were consistent with the measures in the control group; and Outcome measures: The incidence of pulmonary edema was used as the primary outcome measure, while extravascular pulmonary water index (EVLWI), pulmonary vascular permeability index (PVPI), ventilator use time and the intensive care unit (ICU) length of stay were used as secondary outcome measures.

2.4.2. Exclusion criteria. Studies that included underage patients; duplicate publications; studies without outcome measure data; studies with incomplete data or unavailable data; non-Chinese/English studies; and animal experiments.

2.5. Bias risk assessment for included studies

The risk of bias was assessed using the RCT bias risk assessment tool built into Cochrane Review Manager (5.4.1). Two investigators independently evaluated the bias risk of the included studies, and cross-checked the evaluation results. Disagreements were discussed or adjudicated by a third investigator. The evaluation domains included: whether the random allocation method was correct; whether the allocation hiding method was used; whether the blinding method was used; whether the outcome data were complete; whether there was selective reporting of study results; and other sources of bias. Each evaluation domain was judged as high, uncertain, or low risk of bias.

2.6. Data extraction

The following data were extracted: general information, including publication country, publication year, publication journal, first author and title; basic characteristics of study subjects, including sample size, gender composition, age distribution and disease severity; study characteristics, including study objective, study type, administration method, dose, duration and results of ulinastatin; key elements of bias risk evaluation; and outcome indicators, including the incidence of pulmonary edema, EVLWI, PVPI, ventilator use time and the ICU length of stay.

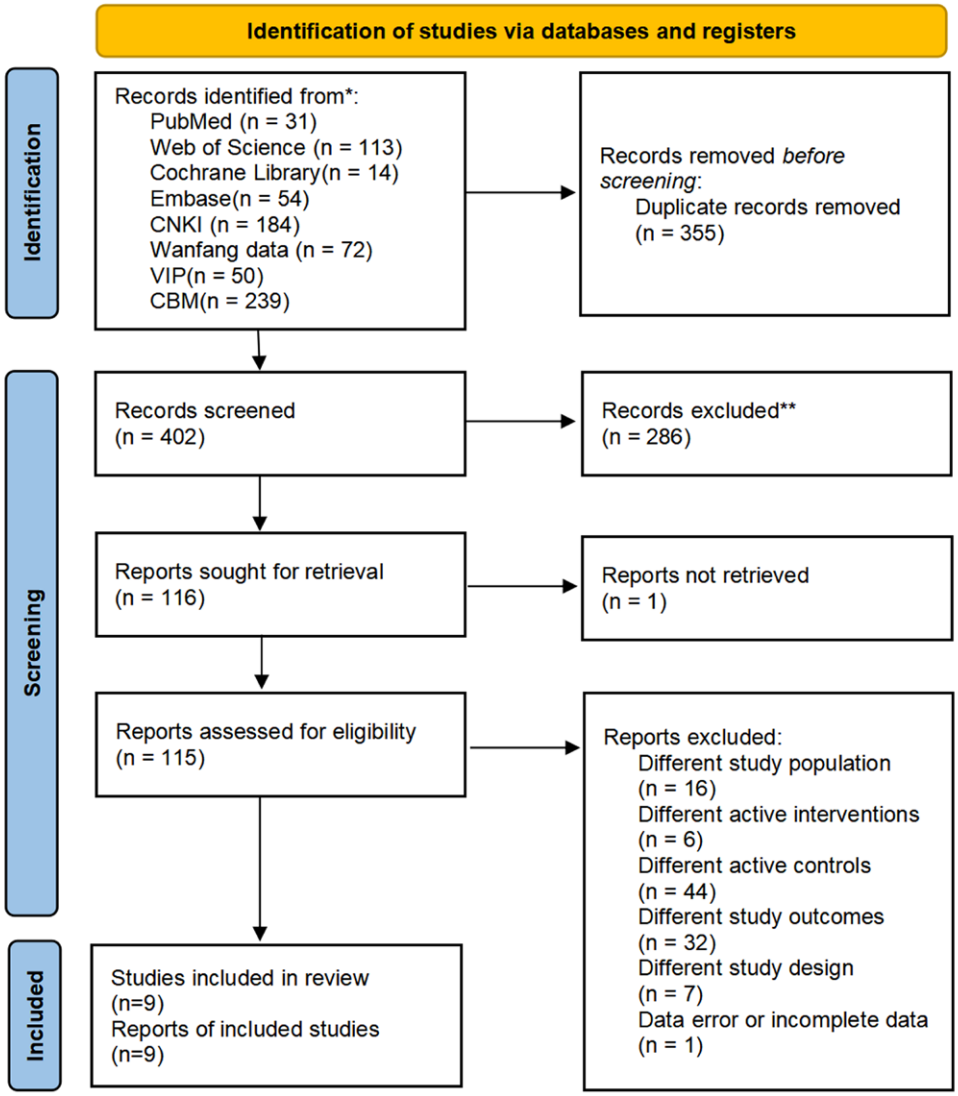
2.7. Statistical analysis

The statistical analysis in this study was performed using statistical software RevMan 5.4. Mean difference (MD) was used for continuous data, odds ratio (OR) was used for binary data, and 95% confidence intervals (95% CI) were obtained for each effect size (ES). The I^2 test was used to assess the heterogeneity among studies. $P \leq .05$ was considered statistically significant. For outcome measures, the GRADE (https://gdt.gradepro.Org) system was used to assess the level of evidence quality.

3. Results

3.1. Search results

A total of 757 studies were retrieved, including 31 from PubMed, 113 from Web of Science, 14 from Cochrane Library, 54 from Embase, 184 from CNKI, 72 from Wanfang data, 50 from VIP, and 239 from CBM. The search strategies and results are listed in Table S1, Supplemental Digital Content, http://links.lww.com/MD/O247. After filtering for duplicates and excluding studies that did not match PICOS based on titles and abstracts, a total of 10 full-text articles were retrieved. After carefully reading the entire texts, 9 studies[10–18] (involving 577 patients) were included in the meta-analysis. The PRISMA flowchart is shown in Figure 1.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 1. PRISMA 2020 flow diagram.

3.2. Study characteristics

Nine RCTs were included with a total of 577 patients, including 292 patients in the ulinastatin group and 285 patients in the conventional treatment group. Basic characteristics of the included studies are detailed in Table 1.

3.3. Quality evaluation

The 9 included RCT studies were all single center studies. Four of the articles clearly stated in the methodology section that the randomization scheme was generated by a random number table, 1 article used allocation concealment, and no blinding method was used in any of the articles. The outcome data of all included studies were relatively complete, with no bias due to incomplete outcome reporting, and the reported methods and results were consistent. Other sources of bias were unclear. The risk of bias assessment results for the included studies are illustrated in Figure 2.

3.4. Efficacy for outcome measures

3.4.1. The incidence of pulmonary edema. A total of 4 studies reported the incidence of pulmonary edema. Heterogeneity analysis showed consistency across studies ($I^2 = 0$), so the fixed effects model was used for analysis. The incidence was 18.85% in the ulinastatin group compared to 38.26% in the conventional treatment group. The results showed that ulinastatin was effective in reducing the incidence of pulmonary edema in patients compared with conventional treatment, and the difference was statistically significant (OR [95% CI] = 0.36 [0.20, 0.657], $Z = 3.28$, $P = .001$) (Fig. S1, Supplemental Digital Content, http://links.lww.com/MD/O247).

Table 1

Characteristics of included studies.

Author	Study design	Region	Sample size	Age (mean, SD)	Gender	Outcome indicator	Underlying disease and severity
J. Ju 2021	RCT	China	100	72.53, 14.62	51,49	④⑤	Acute pulmonary edema
Y. Li 2020	RCT	China	16	35, 7.80	7,9	②③	Burn burn surface area (% TBSA) 65.5, 7.98 velocity-area methods (% TBSA) 29, 5.34
H. W. Ni 2021	RCT	China	86	40.71, 15.87	22,64	②③④	Neurogenic pulmonary edema GCS score 4.99, 1.62
S. Qing 2010	RCT	China	67	34.6, 9.75	NA	①	Severe craniocerebral injury GCS score 4.25, 0.41
J. H. Qu 2010	RCT	China	64	33.85, 4.52	10,54	①	Severe craniocerebral injury
G. Yang 2018	RCT	China	64	39.3, 4.62	27,37	⑤	Severe traumatic wet lung PO_2/FiO_2 192.8, 27.93
X. H. Yang 2017	RCT	China	74	64.3, 3.28	25,49	④⑤	Acute cerebrovascular disease with neurogenic pulmonary edema
Y. H. Zhang 2008	RCT	China	82	32.1, 11.23	20,62	①	Extremely severe craniocerebral injury
M. L. Hu 2004	RCT	China	24	NA	NA	①	Pneumothorax

Note: ① The incidence of pulmonary edema, ② EVLWI, ③ PVPI, ④ Ventilator use time, ⑤ ICU length of stay.

Abbreviations: EVLWI = extravascular pulmonary water index, ICU = intensive care unit, PVPI = pulmonary vascular permeability index, RCT = randomized controlled trial.

3.4.2. EVLWI. Two studies including 102 patients were included. Heterogeneity analysis showed consistency across studies ($I^2 = 0$), so the fixed effects model was used for analysis. The results showed that ulinastatin could effectively reduce EVLWI in patients compared with conventional treatment, and the difference was statistically significant (MD [95% CI] = −0.75 [−1.32, −0.17], $Z = 2.54$, $P = .01$) (Fig. S2, Supplemental Digital Content, http://links.lww.com/MD/O247).

3.4.3. PVPI. Two studies including 102 patients were included. Heterogeneity analysis showed consistency across studies ($I^2 = 0$), so the fixed effects model was used for analysis. The results showed that ulinastatin could effectively reduce PVPI in patients compared with conventional treatment, and the difference was statistically significant (MD [95% CI] = −0.10 [−0.24, 0.03], $Z = 1.47$, $P = .14$) (Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/O247).

3.4.4. Ventilator use time. A total of 3 studies including 260 patients were included. Heterogeneity analysis showed heterogeneity among studies ($I^2 = 94\%$), so a random-effects model was used for analysis. The results showed that ulinastatin could shorten the duration of ventilator use in patients compared with conventional treatment, and the difference was statistically significant (MD [95% CI] = −2.86 [−4.28, −1.45], $Z = 3.96$, $P < .0001$) (Fig. S4, Supplemental Digital Content, http://links.lww.com/MD/O247).

3.4.5. ICU length of stay. A total of 3 studies including 238 patients were included. Heterogeneity analysis showed consistency across studies ($I^2 = 0$), so the fixed effects model was used for analysis. The results showed that ulinastatin could shorten ICU length of stay in patients compared with conventional treatment, and the difference was statistically significant (MD [95% CI] = −1.56 [−1.75, −1.38], $Z = 16.90$, $P < .00001$) (Fig. S5, Supplemental Digital Content, http://links.lww.com/MD/O247).

3.5. GRADE grading of evidence quality

GRADE quality of evidence grading for outcome measures is detailed in Table 2.

4. Discussion

Pulmonary edema is 1 of the common complications in hospitalized patients.[19] Its pathogenesis is the imbalance of systemic blood circulation status and capillary permeability. According to etiology, pulmonary edema can be divided into cardiogenic and non-cardiogenic pulmonary edema.[2] The most common clinical symptoms of pulmonary edema are dyspnea and orthopnea, and some patients experience cough, sputum, irritability, and even coma and cyanosis in severe cases. Therefore, it is particularly important to take effective and active measures to deal with and prevent pulmonary edema in clinical treatment.

Clinically, the treatment of pulmonary edema is often based on etiological treatment, while maintaining airway patency, correcting oxygen insufficiency, reducing pulmonary vascular hydrostatic pressure, increasing plasma colloid osmotic pressure, improving pulmonary capillary permeability, and preventing and controlling infection. Specific therapeutic measures include oxygen inhalation, cardiotonic, diuretic, vasodilator, anti-inflammatory, and fluid load restriction. Ulinastatin, a glycoprotein hydrolase inhibitor extracted from urine, is able to exert potential protective effects on human organs. Several existing clinical studies have confirmed that ulinastatin can exert anti-inflammatory and anti-oxidative stress effects through multiple pathways.[4]

When ulinastatin exerts its anti-inflammatory effects, its mechanism mainly involves the following aspects: hemodynamic changes, vascular permeability changes, chemotaxis of neutrophils, and tissue damage.[4] It has other unique mechanisms of action, and it has been demonstrated[20–22] that ulinastatin helps to reduce the content of malondialdehyde, increase the content of superoxide dismutase, limit Thr183 phosphorylation of c-Jun N-terminal kinase (JNK), and reduce the production of reactive oxygen species, thereby interfering with NF-κB signaling and exerting antioxidant effects, further reducing vascular endothelial injury in oxidative stress, and exerting organ protection. Yan Qingfeng et al[21] found that ulinastatin could reduce the production of kinins and inhibit the abnormal dilatation of vascular smooth muscle, and also improve microcirculatory disturbances and tissue reperfusion. Therefore, ulinastatin is effective in relieving symptoms of pulmonary edema by reducing inflammatory responses, inhibiting hydrolase activity, improving microcirculation and tissue perfusion, as well as reducing pulmonary capillary endothelial and/or alveolar epithelial permeability.[10]

The results of this meta-analysis showed that the incidence of pulmonary edema (GRADE evidence grade: moderate) was significantly reduced in patients in the ulinastatin group. Compared with the conventional treatment group, ulinastatin reduced EVLWI (GRADE evidence grade: moderate),

ventilator time (GRADE evidence grade: very low), and ICU length of stay (GRADE evidence grade: moderate), but there was no significant difference in PVPI (GRADE evidence grade: moderate) levels in patients. This result was analyzed in this study as follows.

EVLWI and PVPI are important indicators to measure the severity of pulmonary edema, and they have a positive impact on the evaluation of the condition and prognosis as well as the adjustment of treatment strategies.[23] EVLW is an independent factor for evaluating mortality in critically ill patients.[24] At the same time, some studies[25–27] have found that PVPI can reflect the pathological changes of the pulmonary capillary endothelium and has a very high accuracy for identifying hyperpermeability pulmonary edema. The results of this analysis showed that there was a significant difference in EVLWI between the 2 groups, but there was no significant difference between PVPI. The results of a retrospective cohort study conducted by Dong et al[28] showed that the use of ulinastatin was effective in reducing extravascular lung water index and PVPI and reducing the inflammatory response of patients, thereby improving the vascular permeability of patients and relieving the condition of pulmonary edema. Because there were only 2 studies included in EVLWI and PVPI indicators, and there was significant heterogeneity, this may also be the reason why the difference was not statistically significant.

In this study, ulinastatin was found to shorten ventilator time and ICU length of stay compared with conventional treatment. Karnad et al[29] found that ulinastatin increased ventilator-free days and shortened ICU length of stay in patients through a multicenter RCT involving 7 centers. In addition, ulinastatin can shorten the duration of mechanical ventilation, ICU stay and total hospital stay on the basis of conventional treatment such as respiratory support,[30] and the results of this study are consistent with this. It is worth noting that the outcome measure of shortened ventilator time was very heterogeneous, but only 3 articles were included, so subgroup analysis was not suitable. However, during the study, we tried sensitivity analysis and eliminated it one by one to find the source of heterogeneity, unfortunately no positive results were obtained.

All 9 articles included in this study were RCTs, but there are still the following limitations: The included studies were all Chinese studies and all were single center studies, and most of the studies had a small sample size, which may have some biases and affect the generalization of the conclusions; Publication bias may exist by searching only computer databases and not including other types of gray literature; Extravascular lung water index and PVPI were not measured in the same way, both studies used Pulse Indicator Continuous Cardiac Output (PICCO) monitoring, but 1 study[11] used transpulmonary thermodilution, while the other study[12] used pulse contour cardiac output monitoring technique; and The dose and duration of ulinastatin used in the included studies were not the same, but subgroup analysis could not be performed due to the limited number of studies.

5. Conclusion

By summarizing the available evidence, we found that ulinastatin combined with conventional therapy was effective in reducing the incidence of pulmonary edema, reducing EVLWI, shortening ventilator time and ICU length of stay, and significantly improving pulmonary edema symptoms in patients

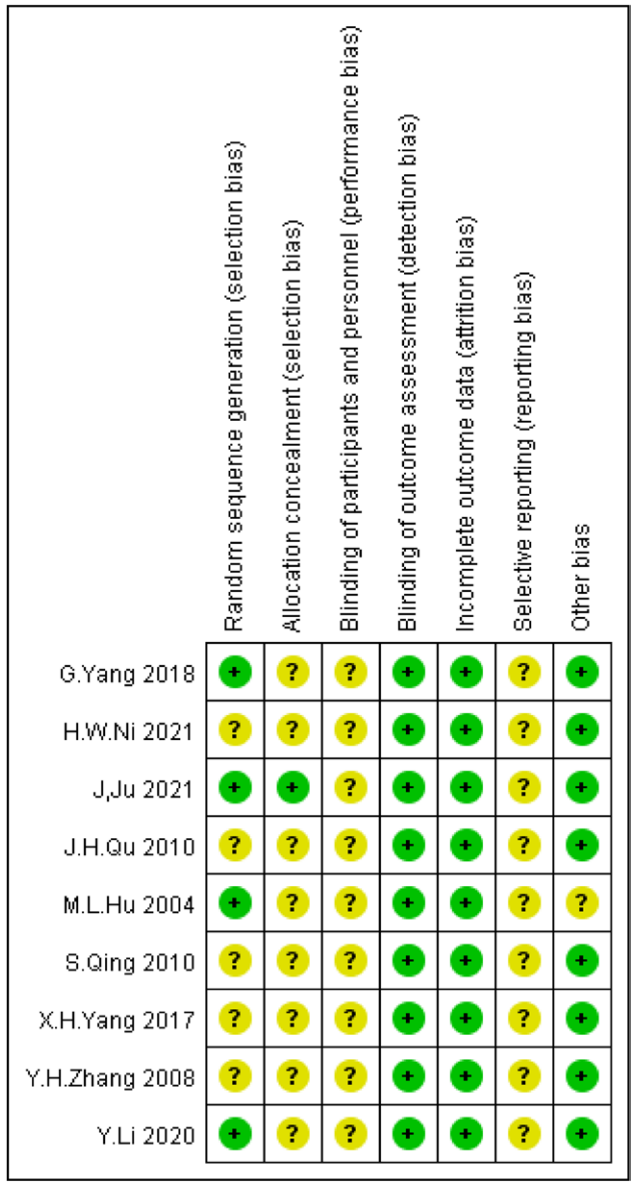


Figure 2. Risk of bias assessment of the included studies. Red color: high risk, Yellow color: unclear risk, Green color: low risk.

Table 2

GRADE grading of evidence quality.

Outcome indicator	The number of RCTs	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
The incidence of pulmonary edema	4	237	Not serious	Not serious	Not serious	Serious	Not estimable	⊕⊕⊕○
EVLWI	2	102	Not serious	Not serious	Not serious	Serious	Not estimable	⊕⊕⊕○
PVPI	2	102	Not serious	Not serious	Not serious	Serious	Not estimable	⊕⊕⊕○
Ventilator use time	3	260	Not serious	Very serious	Not serious	Very serious	Not estimable	⊕○○○
ICU length of stay	2	238	Not serious	Not serious	Not serious	Serious	Not estimable	⊕⊕⊕○

Note: ⊕⊕⊕○: moderate, ⊕○○○: very low.

Abbreviations: EVLWI = extravascular pulmonary water index, ICU = intensive care unit, PVPI = pulmonary vascular permeability index, RCT = randomized controlled trial.

associated with pulmonary edema, however, there was no significant difference in PVPI levels in patients. Considering that the overall level of studies included in this meta-analysis is not high and the sample size is insufficient, the conclusions drawn have certain limitations on the value of guiding clinical practice, and physicians are required to be cautious in the process of interpretation and application. In addition, multicenter, prospective RCTs are also necessary to clarify its rational use regimen and its efficacy and safety in different stages of different diseases or conditions according to the application effect of different doses of ulinastatin.[31] Therefore, the efficacy of ulinastatin in the treatment of pulmonary edema remains controversial and needs to be verified by more high-quality high-level large-scale multicenter clinical RCT studies.

Author contributions

Conceptualization: Ruimin Tan, Huihui Yang.
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