Annals of Medicine and Medical Research

Research Article
Published: 27 Nov, 2023

Effects of Various Pharmacotherapy on Clinical Outcomes in Patients with Acute ARDS/ALI: A Systematic Review and Network Meta-Analysis

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Abstract

Objective: On account of the high fatality rate of ARDS/ALI, we performed a network meta-analysis to investigate the efficacy of various drugs (Low molecular weight heparin, Tanreqing, Glucocorticoid, Ulinastatin, Sivelestat sodium, Xuebijing) based on conventional treatment.

Data sources: The literature search was mainly conducted in China National Knowledge Infrastructure (CNKI), WanFang Data, PubMed, Embase, Scopus, Cochrane Library, Google Academic, and Web of Science (SCI) from studies published up to November 2022 in which the partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FIO_2) ratio or mortality was assessed in patients with ARDS/ALI, who received different drugs on the base of conventional treatment.

Study selection: Studies were screened according to inclusion and exclusion criteria. Ultimately, a total of 51 Randomized Controlled Trials (RCTs) were enrolled. 19 studies were included with mortality outcomes and 32 studies with oxygenation index outcomes.

Data extraction: We assessed the studies for eligibility, extracted the data, pooled the data. The extracted data included basic study information such as author, year of publication, experimental design, patient (age and gender of the included patients), sample size, detailed treatment strategy, and clinical outcomes.

Data synthesis: The clinical data of the oxygenation index and mortality were analyzed using Stata17.0, Stata13.0, and Review management 5.3 software. We used a Bayesian Random-effects model to combine direct comparisons with indirect evidence in Stata software.

Conclusion: Low molecular weight heparin is a first rank in primary outcomes (oxygenation index), and Glucocorticoid obtains a first rank in secondary outcomes (mortality). In conclusion, based on conventional treatment, the combination of low molecular weight heparin and glucocorticoid may be a perforable treatment in ARDS/ALI. Low molecular weight heparin increased oxygenation index and reduced mortality in the first place compared with conventional treatment and Xuebijing.

Keywords: Mortality; Oxygenation index; Pharmacotherapy; ARDS/ALI; Network meta-analysis

Abbreviations

CT: Conventional Treatment; LMWH: Low Molecular Weight Heparin; TRQ: Tanreqing; GH: Glucocorticoid Hormone; USTA: Ulinastain; SS: Sivelestat Sodium; XBJ: Xuebijing

Take-Home Message

First, the combination of low molecular weight heparin and glucocorticoid may be a perforable treatment in ARDS/ALI. Low molecular weight heparin increased oxygenation index and reduced mortality in the first place compared with conventional treatment and Xuebijing. Second, low molecular weight heparin increased oxygenation index and reduced mortality in the first place compared with conventional treatment and Xuebijing. Third, the combination of drug therapy was clinically better than the conventional treatment alone.

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Received Date: *07 Nov 2023*
Accepted Date: *22 Nov 2023*
Published Date: *27 Nov 2023*

Citation:
Kairui M, Yulin Y, Lijuan C, Yicheng L. Effects of Various Pharmacotherapy on Clinical Outcomes in Patients with Acute ARDS/ALI: A Systematic Review and Network Meta-Analysis. Ann Med Medical Res. 2023; 6: 1068.

Introduction

Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI) can be caused by a variety of infectious or non-infectious pathogenic factors, showing different pathophysiological features and clinical manifestations [1]. The case fatality rate of diffuse inflammatory lung injury was high. Despite many advances in the treatment and management of ARDS in recent years. But due to the nature of the disease, the number of clinical studies and the sample size of inclusion on ARDS/ALI are not very large at present. So, there are still no proven effective drugs for ARDS caused by various etiologies, and the optimal drugs for patients with ALI or ARDS are uncertain [2]. There are some meta-analysis papers on ARDS/ALI disease [3-6]. However, traditional pairwise meta-analysis can only be used to compare specific factors between a drug and cannot be used to compare the entire set of parameters relevant to different drugs. Therefore, Therefore, oxygenation index and mortality of different drugs after treating ARD/ALI cannot be compared by traditional pairwise meta-analysis. Accordingly, the results obtained from traditional pairwise meta-analyses have significant limitations. Fortunately, a Network Meta-Analysis (NMA) is an extension of pairwise meta-analysis to compare three or more treatments for a given medical condition, based on combining information from multiple existing comparisons among subsets of the treatments [7,8]. Given these advantages, we used a network meta-analysis to search the literature for data examining drugs in patients with ALI or ARDS. Based on these data, we had a collection of six different types of drugs and considered each drug as a unique treatment strategy. Subsequently, the effectiveness of various drugs was compared to identify the optimal drugs for patients with ALI or ARDS.

Materials and Methods

We conducted our systematic review by the methods recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8].

Literature search

We systematically looked for the following databases: We searched the China National Knowledge Infrastructure (CNKI), WanFang Data, PubMed, Embase, Scopus, Cochrane Library, Google Academic, and Web of Science (SCI) using a combination of MeSH terms and text words. Additional records were searched for grey literature (unpublished studies) using the Chinese Clinical Trial Register and the Clinical Trials. And some further trials were also hand-searched through industry submissions and relevant systematic reviews. We reviewed the reference lists of published meta-analyses. We did not restrict our search based on language, the dosage of treatment, or the year of publication. The most recent search date was November 2022. The search strategy was (Tanreqing OR glucocorticoid OR Low molecular weight heparin OR Ulinastatin OR Sivelestat sodium OR Neutrophil elastase inhibitors OR Xuebijing OR Bone marrow mesenchymal stem cells OR statins OR Xuanbai Chengqi Decoction) AND (acute respiratory distress syndrome OR Acute lung injury OR ARDS OR ALI). There were fifty-one RCT studies included in this study [9-58]. There are a total of 21 pieces of literature reporting case mortality rates. There are a total of 30 kinds of literature reporting oxygenation index. we mainly conducted a network meta-analysis on the oxygenation index of four treatments (Low molecular weight heparin, Tanreqing, ulinastatin, sivelestat sodium and Xuebijing) in the treatment of ARDS/ALI. We conducted a network meta-analysis of the mortality rates of three treatment regimens (low molecular weight heparin, glucocorticoid, and Xuebijing) (Supplementary appendix).

Inclusion and exclusion criteria

Inclusion criteria: (1) randomized controlled trials comparing different drugs treatments for acute respiratory distress syndrome/ acute lung injury; (2) the control group receiving either conventional treatment or conventional treatment combined with placebo; (3) outcome including one of the two outcome levels of oxygenation index or mortality; (4) adult patients only;

Exclusion criteria: (1) studies without primary data, such as commentaries, conference abstracts; (2) nonrandomized trials, such as reviews, retrospective studies, observational studies, case reports, animal studies, studies conducted on children, unrelated studies; (3) duplicated publications or repeated experiments; (4) no sufficient data (literature that was emailed twice to the corresponding authors of studies and did not receive a response was dropped); (5) trials with other medications or other treatment regimens, such as combined blood purification, rhubarb, or prone ventilation. (6) Oxygenation index within 3 days and mortality within 7 days.

Outcome measures and data extraction

Two authors independently extracted data using a predefined standard data extraction form. Any discrepancy was resolved by discussion with a third reviewer. The extracted data included basic study information such as author, year of publication, experimental design, patient (age and gender of the included patients), sample size, detailed treatment strategy, experimental period, and clinical outcomes. The primary outcome of this study was the PaO_2/FiO_2 ratio (defined as an important index that allows organ tissues to get enough oxygen for oxygen cooperation to obtain energy). The secondary outcomes of this study were mortality (defined as a percentage of people or animals who die from a disease in a given period in the total number of sick people or animals). We contacted the corresponding authors to seek assistance in the case of missing data and sent a table containing the extracted data to those authors for supplementary data or verification. We emailed at least twice. (Supplementary appendix). We recorded the oxygenation index as close to 7 days as possible for all analyses. If the information at 7 days was not available, we used data ranging between 7 and 14 days (we gave preference to the timepoint closest to 7 days). We recorded mortality as close to 28 days as possible for all analyses. If the information at 28 days was not available, we used data ranging between 28 and 60 days (we gave preference to the timepoint closest to 28 days). In some literature, both the control group and the experimental group received other treatment programs. We did not exclude this literature. because they did not affect our experimental results.

Risk of bias evaluation

We assessed the study's risk of bias following the Cochrane Handbook for Systematic Reviews of Interventions. The risk of bias graph and risk of bias summary was conducted using Cochrane Collaboration's Review Manager (RevMan) 5.3 software. Because our outcome level was measured by blood gas analysis indicators and therefore had some objectivity, so blinding of outcome assessment and blinding of participants were considered low risk. (Supplementary appendix).

Quality assessment

Additionally, we assessed the certainty of evidence contributing to network estimates of the main outcomes with the Grading of

Figure 1: Network evidence map of oxygenation index and mortality.

Recommendations Assessment, Development, and Evaluation (GRADE) framework, and drew proportional bar charts and pie charts. (Supplementary appendix).

Subgroup analysis and meta-regression analysis

We evaluated whether treatment effects for the two outcomes were robust with a subgroup analysis of dosage, country, and ventilation strategy summarizes the definition of covariates. Meta-regression analysis was performed for these subgroups.

Statistical analysis

For studies published more than once (i.e., duplicates), we included only the report with the most informative and complete data. The outcomes were analyzed using Stata17.0, Stata13.0, and Review management 5.3 software to draw network diagrams and compare multiple interventions directly or indirectly. Statistical significance was defined as $P<0.05$. For continuous outcome data, the analysis was performed using the treatment-specific data (sample means and standard difference) that were explicitly reported in the published studies. In some studies that did not report the standard difference, the standard difference was derived using the reported mean and confidence interval for the difference between treatments in the geometric mean change from baseline, mean range, or standard error or by inverting the result of the test statistic. For categorical variables, the Odds Ratio (OR) was acquired by comparing the ratio of drugs in the experimental group to the ratio of drugs in the control group. The continuous outcome was evaluated by Weighted Mean Difference (WMD, indicators changed from baseline), along with a 95% Confidence Interval (CI). The discontinuous outcome was assessed by Odds Risk (OR) and its 95% Confidence Interval (CI). The treatment effect of drugs was ranked by the Surface Under Cumulative Ranking Curve Probabilities (SUCRA), and the SUCRA is expressed as a percentage, the larger the value, the better the efficacy. The consistency of results was tested by performing the node-splitting generalized linear mixed model to analyze the heterogeneity between studies. The model of consistency was fitted when the node split model was P value >0.05; otherwise, the inconsistency model was used. Heterogeneity for all pairwise comparisons was assessed by predictive interval plot. The transitivity assumption underlying network meta-analysis was evaluated by comparing the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons. (Supplementary appendix). We used comparison-adjusted funnel plots to investigate whether results in imprecise trials differ from those in more precise trials. (Supplementary appendix).

Results

Network evidence map

Network of the comparisons of the partial pressure of arterial oxygen/fraction of inspired oxygen ratio (F/I) in the network meta-analysis. The size of a given node is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of each line is proportional to the number of trials (specified next to the line) comparing the connected treatments. There were thirty-nine studies included in this study. There are a total of 30 pieces of literature reporting oxygenation index [28-57]. Six clinical studies on Tanreqing in the treatment of ARDS/ALI [28-32]. Four clinical studies on Tanreqing in the treatment of ARDS/ALI [28-32], Seven clinical studies on ulinastatin in the treatment of ARDS/ALI [32-38]. Three clinical studies on sivelestat sodium in the treatment of ARDS/AL [39-41]. Eleven clinical studies on Xuebijing in the treatment of ARDS/ALI [48-57]. Five clinical studies on low molecular weight heparin in the treatment of ARDS/ALI [43-47]. There is a total of 21 kinds of literature reporting mortality [9-30]. Five clinical studies on the treatment of ARDS/ALI with low molecular weight heparin [9-13]. Eleven studies on the treatment of ARDS and ALI with glucocorticoid [14-25]. And five clinical studies on the treatment of ARDS and ALI with Xuebijing [23-27]. The network maps of the included studies reported the primary outcomes (oxygenation index) and secondary outcomes (mortality) are shown in Figure 1.

Results of traditional meta-analysis

We conducted a meta-analysis on the two outcomes of drug therapy for ARDS/ALI, and the difference in oxygenation index in drug therapy of ARDS/ALI was statistically significant. [low molecular weight heparin: $P<0.01$, SMD=2.61, 95% CI (2.30, 2.92); Tanreqing: $P<0.01$, SMD=1.23, 95% CI (1.03, 1.43); Ulinastatin: $P<0.01$, SMD=0.95, 95% CI (0.76, 1.14); Sivelestat sodium: $P<0.01$, SMD=0.97, 95% CI (0.63, 1.31); Xuebijing: $P<0.01$, SMD=0.89, 95% CI (0.73, 1.05)]. And the difference in mortality of ARDS/ALI treated with drugs was statistically significant. [Xuebijing: $P<0.05$, OR=0.70, 95% CI (0.51, 0.97); glucocorticoid: $p<0.05$, OR=0.65 95% CI (0.47, 0.88); Low molecular weight heparin: $p<0.05$, OR=0.68, 95% CI (0.48, 0.98)]. The results of statistical analysis showed that the deadly events of ARDS/ALI treated by these three drugs were less than those treated by conventional treatment. It also showed that the oxygenation index of ARDS/ALI treated by these five drugs were more than those treated by conventional treatment. (Supplementary appendix). When meta-analysis was conducted for each drug in the included studies, we found that Ulinastatin was heterogeneous in the included studies, so

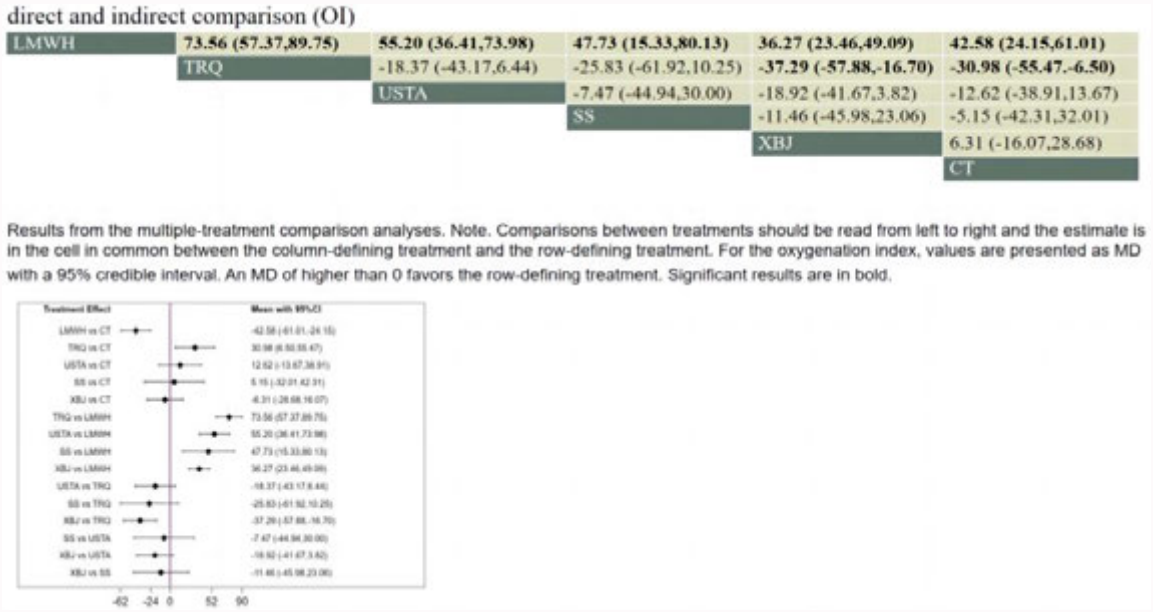

Figure 2: Results from the multiple-treatment comparison analyses. Note. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For the oxygenation index, values are presented as MD with a 95% credible interval. An MD of higher than 0 favors the row-defining treatment. Significant results are in bold.

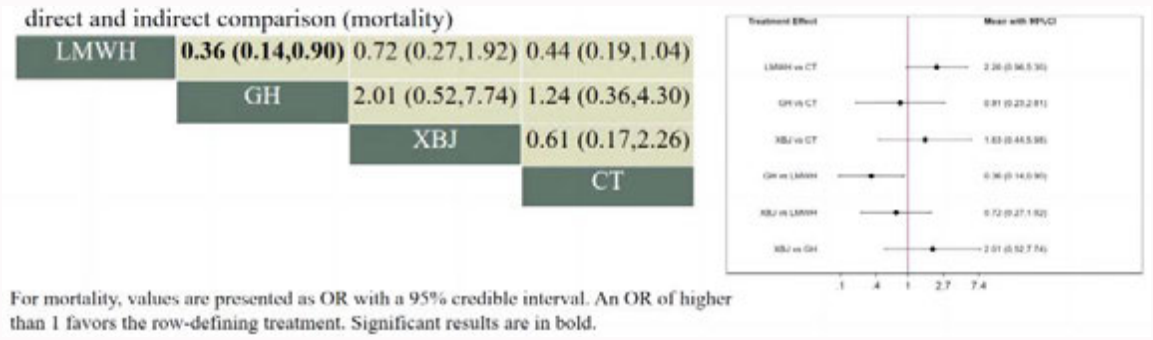

Figure 3: For mortality, values are presented as OR with a 95% credible interval. An OR of higher than 1 favors the row-defining treatment. Significant results are in bold.

we conducted subgroup analysis and meta-regression analysis for this drug.

Results of subgroup analysis and meta-regression analysis

We divided the ulinastatin literature into three subgroups: normal treatment conventional ventilation therapy, unconventional mechanical ventilation therapy, and invasive mechanical ventilation therapy. There was no statistically significant difference in heterogeneity among the three subgroups. The meta-regression analysis indicates that the difference in treatment effect among the three subgroups was no statistically significant (P>0.05). These results indicate that the therapeutic effect of various mechanical ventilation among the three subgroups is no statistically significant difference. (Supplementary appendix).

Oxygenation index

For direct and indirect comparison in terms of oxygenation index, statistically, significant differences were observed in comparison A (LMWH *vs.* TRQ), comparison B (USTA *vs.* LMWH), comparison C (SS *vs.* LMWH), comparison D (XBJ *vs.* LMWH), comparison E (CT *vs.* LMWH), comparison F (XBJ *vs.* TRQ), and comparison G (CT *vs.* TRQ). Compared to Tanreqing, Ulinastatin, Sivelestat sodium, Xuebijing, and Conventional treatment, Low molecular weight heparin was associated with an improvement in oxygenation index; the respective MDs (95% Confidence Intervals) were 73.56 (57.37, 89.75), 55.20 (36.41, 73.98), 47.73 (15.33, 80.13), 36.27 (23.46, 49.09), and 42.58 (24.15, 61.01). And compared to Tanreqing, Conventional treatment was associated with an improvement in oxygenation index. The MDs (95% Confidence Intervals) is 30.98 (6.50, 55.47). And compared to Tanreqing, Xuebijing was associated with an improvement in oxygenation index. The MDs (95% Confidence Intervals) is -37.29 (-57.88, -16.70) (Figure 2).

Mortality

For direct and indirect comparison in terms of mortality, statistically, significant differences were observed between glucocorticoid and Low molecular weight heparin. The OR (95 % Confidence Intervals) was 0.36 (0.14, 0.90). Compared to low molecular weight heparin, glucocorticoid was associated with a reduction in mortality (Figure 3).

Data table of SCURA (OI)

Treatment	SUCRA	PrBest	MeanRank
Tanreqing	45.7	0.4	3.7
Conventionaltreatment	0	0	6
Low molecular weight heparin	96.9	86	1.2
Ulinastain	69.7	6.4	2.5
Sivelestat Sodium	55.7	7.2	3.2
Xuebijing	31.9	0	4.4

Cumulative probability line graph and SUCRA rank in terms of oxygenation index. Each drug has a probability of being the best treatment or the worst treatment.

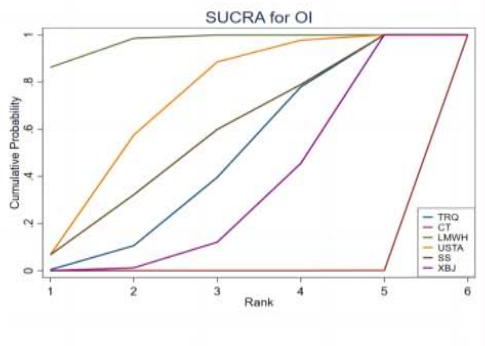

Figure 4: Cumulative probability line graph and SUCRA rank in terms of oxygenation index. Each drug has a probability of being the best treatment or the worst treatment.

Data table of SCURA (mortality)

Treatment	SUCRA	PrBest	MeanRank
Low molecular weight heparin	69.9	32.9	1.9
Conventionaltreatment	10.1	0	3.7
Glucocorticoid	82.1	58.1	1.5
Xuebijing	37.9	9	2.9

Cumulative probability line graph and SUCRA rank in terms of mortality. Each drug has a probability of being the best treatment or the worst treatment.

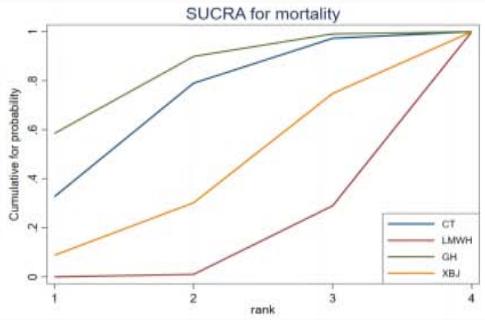

Figure 5: Cumulative probability line graph and SUCRA rank in terms of mortality. Each drug has a probability of being the best treatment or the worst treatment.

Rank

As shown in Figure 6, in the SCURA, the surface area for low molecular weight heparin reaches almost 96.9%, confirming that it is the best intervention. The SUCRA command is used for a more precise estimation of cumulative ranking probabilities. Based on the SUCRA results, Low molecular weight heparin is followed by Ulinastatin (69.7%), Sivelestat Sodium (55.7%), and Tanreqing (45.7%), Xuebijing (31.9%), and Conventional treatment (0%). A clinical interpretation of the results is that the administration of Glucocorticoid hormone is recommended to ensure oxygenation index improvement in the treatment of ARDS/ALI (Figure 4). And we summarized the rankings of the compared drugs in terms of mortality. Glucocorticoid had the greatest potential to decrease mortality. The probability of it holding the top ranking was 82.1%, followed by low molecular weight heparin (69.9%) and Xuebijing (37.9%). Conventional treatment (10.1%) was estimated to be the worst drug in terms of mortality. A clinical interpretation of the results is that the administration of Glucocorticoid is recommended to ensure mortality reduction in the treatment of ARDS/ALI (Figure 5). (Supplementary appendix).

Cluste rank

We had two outcome levels of the drug produced by a bubble chart. As can be seen from the bubble chart, low molecular weight heparin increased oxygenation index and reduced mortality in the first place compared with conventional treatment and Xuebijing (Figure 6).

Discussion

In this study, low molecular weight heparin ranked first among the five drugs that improve oxygen index of ARDS/ALI. This result is consistent with the results of some current studies. A meta-analysis showed that antiplatelet therapy is associated with improvement of oxygen index, reduced mortality and lower incidence of ARDS/ALI in critically ill patients, particularly those with predisposing conditions such as high-risk surgery, trauma, pneumonia, and sepsis [58]. A review suggested that further delineating the role of platelets in ARDS and particularly the efficacy of antiplatelet therapy is of profound importance and a crucial avenue for ongoing research [59]. A meta-analysis suggests that adjunctive treatment with LMWH appears to have additional benefits in terms of reducing 7th-day and 28th-day mortality and increasing oxygen index among ALI/ARDS patients [60]. This study once again confirmed that low molecular weight heparin can improve oxygenation index of ARDS/ALI. And the results of this study also suggest that the relatively best drug to reduce mortality is Glucocorticoid. This is also consistent with the results of some studies on the treatment of ARDS/ALI with glucocorticoids. Some clinical trials show that glucocorticoid treatment shows favorable effects on clinical outcomes, including oxygenation index, ventilator-free days, ICU-free days, and mortality [61-63]. A study showed that higher PaO_2/FiO_2 was a significant protective factor against mortality in ARDS patients and one level increase of PaO_2/FiO_2 level decreased 0.9% risk of mortality [64]. Even though some studies have shown that glucocorticoids have a positive effect on the clinical outcome of ARDS/ALI, we cannot have clear and definitive evidence of the clinical significance of glucocorticoids in ARDS/ALI from them. Because these findings were based on different treatment regimens, such as prolonged treatment, different doses [65-68], false positives, required invasive mechanical ventilation, or poor quality and restrictive literature. In addition, different types of glucocorticoid drugs produce different clinical effects. A study showed that an important advantage of dexamethasone is its extended half-life in

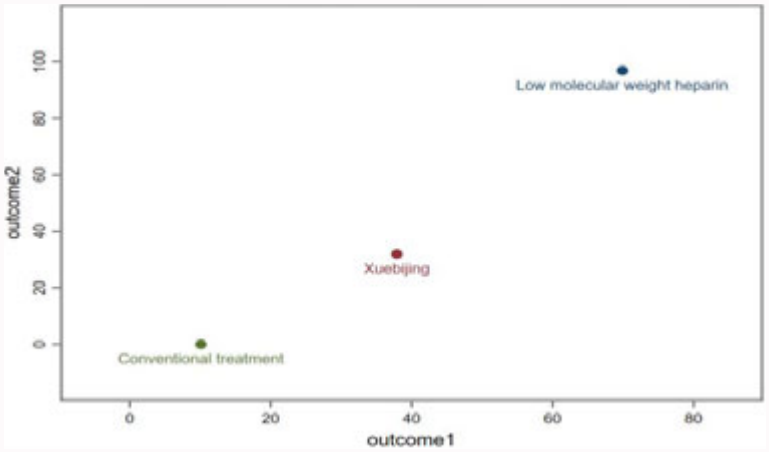

Figure 6: Outcome1 stands for SUCRA of oxygenation index; outcome2 represents the mortality SUCRA.

the organism, which may decrease the time required for therapy compared to alternative GCs [69]. The preliminary results of a large randomized, controlled, open-label trial conducted in the United Kingdom are in favor of dexamethasone use. Some studies also showed that glucocorticoid treatment was associated without a significant survival benefit, or with significantly higher mortality in adult patients with ARDS/ALI [70,71]. The worst-ranked treatment in both case fatality rate and oxygenation index was the conventional treatment, indicating that the combination of drug therapy was clinically better than the conventional treatment alone. Although the results of our analysis in this paper show that low molecular weight heparin and glucocorticoids are the first in the treatment of ARDS. But the side effects of both drugs cannot be ignored. For low molecular weight heparin, the prescription of an anticoagulation treatment should be weighed against the risk of bleeding. This is particularly important because a study observed several cases of major bleeding and 3 subsequent deaths were directly attributed to the consequences of anticoagulant therapy references. So it is crucial to identify clinical or laboratory parameters able to determine what the maximum dose of anticoagulant therapy a patient can receive to minimize the risk of bleeding. For glucocorticoids, a study had shown no statistically significant difference in the oxygenation index of ARDS/ALI treated with glucocorticoids [72]. As previously discussed, endogenous GCs are central for metabolic homeostasis and systemic inflammatory events during tissue repair and pathogens elimination [73]. Due to this fact, long-term exogenous intake of synthetic GCs can provide adverse effects, such as extreme shut down of inflammatory responses, leading to a higher susceptibility to secondary infections establishment [74]. Besides, GCs in glucose metabolism give rise to Insulin Resistance (IR) conditions, which can evolve into Type-2 Diabetes (T2D) and other metabolic disorders [75,76]. For this reason, synthetic GCs medication needs to be handled carefully, to avoid complications rather than therapeutic effects. Therefore, it is difficult to determine the effect of glucocorticoids on the clinical outcome of ARDS/ALI. We know from the results that enhancing oxygenation index and reducing mortality are not the same drug, but from the results of rank, we also know that glucocorticoids rank first and low molecular weight heparin second in the mortality rank. And the gap between the two drugs is not very big.

In response to the results of this study, we recommend that low molecular weight heparin and glucocorticoids should be used as drugs of first choice. A study showed that the association of anti-coagulant heparin and the corticosteroid dexamethasone could be a very effective and promising therapeutic tool in avoiding COVID-19 complications when used for severely ill patients. And the study also suggests that the multitarget impact of heparin as an anti-viral, antithrombotic and anti-inflammatory drug in the early stage of COVID-19 could significantly reduce the need for dexamethasone treatment in the initial phase of this disease [77]. We graded each comparison and rank of primary outcomes. The studies we included were all randomized controlled trials, so we treated the initial level of evidence as a high-quality level, Then the quality of the literature is downgraded according to five factors: Study limitation (risk of bias), indirectness, Inconsistency, Imprecision and Publication bias. And we made percentage bar charts (for each comparison) and pie charts (for ranking) based on bias risk charts and network contribution charts. It also assigns different weights to low/unclear/high (0/-1/-2). Finally, we determined that the documentary evidence level of this study was modern. This level of evidence can be interpreted to mean that we have moderate confidence in the predicted value, which may be close to the true value, or it may be very different. (Supplementary appendix). Researchers around the world are trying to find a new treatment to improve the survival rate of ARDS/ALI or reduce the side effects of drugs. A study showed that targeted nanoparticles can be used for therapy in ALI and could help to overcome the clinical limitations of current treatments [78,79]. A study showed that Mesenchymal Stem Cells (MSCs) play an important role in the prevention and treatment of ALI. However, the low survival rate of transplanted MSCs reduces their effectiveness [80,81]. A study shows that targeting NOX4 may therefore prove to be an innovative therapeutic option that is markedly effective in treating ALI/ARDS [82]. A study showed that UFH treatment alleviated lung injury in vivo by reducing IL-6 in bronchoalveolar lavage fluid and protecting TJs in LMVECs for sepsis-induced ARDS or ALI [83-85]. There are some limitations regarding this article. First, At the beginning, we included literature on many different kinds of drugs, but when we conducted traditional meta-analysis on these drugs, the results showed that the outcome indexes of many drugs were not statistically significant. So, we ended up excluding drugs that were not statistically positive. Finally, three drugs were included in the analysis of ARDS fatality rate and five drugs were included in the analysis of ARDS oxygenation index. Second, the fact that researchers, funding agencies, the types of drugs approved for marketing in different countries, the dose of drugs and the period of administration, could affect the RCT research issues and

outcomes should be factored in. Third, the presence of bias because of low number of articles for each pharmacological intervention should be considered. Four, some of the drugs included in our study are traditional Chinese medicines, such as Xuebijing and Tanreqing. Most of the literature on these drugs comes from China, so the risk of regional bias cannot be excluded. Five, this network meta-analysis could only produce relatively simple results rather than comprehensive and diverse results. Six, the results are largely confirmatory in nature and the advancement of science and knowledge beyond current state is limited.

In conclusion, based on conventional treatment, the combination of low molecular weight heparin and glucocorticoid may be a perforable treatment in ARDS/ALI. In addition, low molecular weight heparin increased oxygenation index and reduced mortality in the first place compared with conventional treatment and Xuebijing. And the combination of drug therapy was clinically better than the conventional treatment alone. In terms of the insufficient of this study, more high-quality RCTs are needed to implement to support our conclusions.

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