Effect of different doses and time-courses of corticosteroid treatment in patients with acute respiratory distress syndrome: A meta-analysis

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Abstract. While previous trials have indicated that the use of corticosteroids for patients with acute respiratory distress syndrome (ARDS) is effective, the dosage and time-course for the use of corticosteroids remain a subject of controversy. The present study aimed to address and resolve these problems. PubMed, Embase and the Cochrane Library databases were searched from inception to March 2017 for randomized controlled trials (RCTs), which included patients with ARDS using corticosteroids. Related data were extracted independently by two investigators. The Mantel-Haenszel method was used with random-effects modeling to calculate the pooled odds ratio (OR) and 95% confidence interval (CI) for the mortality of patients with ARDS, and the risk of new infection arising from the use of glucocorticoids. The inverse variance method was used to calculate the mean difference (MD) and 95% CI for the duration of mechanical-free ventilation and the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FIO_2 ratio). The use of low-dose corticosteroids significantly reduced the mortality rate of patients with ARDS (OR: 0.43; 95% CI: 0.24-0.79; P=0.006) while the use of high-dose corticosteroids provided no significant benefit to reducing the mortality rate (OR: 1.33; 95% CI: 0.86-2.04; P=0.20). The present study identified that glucocorticoids reduced the mortality rate of patients during the early stages of ARDS (OR: 0.61; 95% CI: 0.43-0.86; P=0.005). Glucocorticoids significantly reduced the duration of mechanical ventilation (MD: 3.08; 95% CI: 1.49-4.68; P<0.05) and significantly improved the PaO_2/FiO_2 ratio (MD: 66.39; 95% CI: 57.79-74.98; P<0.05). The use of corticosteroids did not significantly increase the rate of infectious complications (OR: 0.60; 95% CI: 0.32-1.12; P>0.05). The use of low-dose corticosteroids may significantly reduce the mortality rate, particularly in the early stages of ARD, shorten the duration of mechanical ventilation and improve the PaO_2/FiO_2 ratio without increasing the risk of a new infection.

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Abbreviations: ARDS, acute respiratory distress syndrome; RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval; MD, mean difference; M-H, Mantel-Haenszel

Key words: corticosteroid, ARDS, dose, time-course, meta-analysis

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening disease with high mortality rates of 40-50% (1), and can lead to hypoxemic respiratory failure requiring mechanical ventilation (2,3). There are many causes for this syndrome, including shock, aspiration pneumonia, infection, sepsis and a combination of other reasons (1). This condition can give rise to excessive and persistent inflammation by increasing vascular permeability, extravasation of plasma and leucocyte infiltration (2), resulting in a series of complications, such as sepsis, acute pancreatitis, pulmonary fibrosis and disseminated intravascular coagulation. These diseases can lead to secondary systemic inflammatory reactions that result in multiple organ failure, such as respiratory, circulatory and renal failure (4). If there were no effective and timely treatments, this disease would exacerbate quickly and even become life-threatening within just a short period of time.

Glucocorticoids have been reported as important substances in maintaining endothelial integrity and vascular permeability (5-8). Glucocorticoids also modulate many pro-inflammatory and anti-inflammatory cytokines, and play a key role in immune homeostasis (9). Consequently, corticosteroids are considered to represent an effective therapy for patients with ARDS. Previous randomized trials and some meta-analyses (10-13) have demonstrated the efficacy of corticosteroids in reducing the mortality of ARDS.

However, several important issues remain unresolved and are under dispute. First and foremost, it is not clear as to what

dose and time-course of corticosteroids can reduce mortality in patients with ARDS. Previously published meta-analyses were limited because they illustrated the problem from just one or a few perspectives (12-14), such as the dose of glucocorticoid. Secondly, glucocorticoids have many side effects, including an increase in infectious and neuromyopathic complications. Additional potential risks include hyperglycemia, poor wound healing, psychosis, pancreatitis and prolonged muscle weakness with impaired functional status (15,16).

Furthermore, it is difficult to control the side effects of glucocorticoid while achieving an effective therapeutic effect. Previous meta-analyses have not fully addressed the issues relating to complications (17,18). Previous trials showed that methylprednisolone could improve the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FIO_2 ratio) and reduce periods of mechanical ventilation in ARDS (10,12). Furthermore, the impact of dose or treatment duration on the efficacy of corticosteroids remains unclear. The present study conducted a systematic review and quantitative synthesis to address these issues.

Materials and methods

Search strategy. A systematic search into the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (EMBASE.com) and Cochrane Library databases (www.update-software.com/clibng/cliblogon.htm) was conducted, from inception to May 2017, restricting the publication language to English. The following key words were used as search terms: 'ARDS'; 'adult respiratory distress syndrome'; 'acute respiratory distress syndrome'; 'respiratory insufficiency'; 'shock lung'; 'respiratory failure'; 'lung injury' AND 'steroids'; 'corticosteroids'; 'glucocorticoids'; 'hydrocortisone'; 'prednisolone' AND 'randomized controlled clinical trials'; 'controlled trials'; and 'randomized trials' and 'random control test'.

Inclusion and exclusion criteria. The present study included all randomized controlled trial (RCT) designs that reported mortality outcomes, users of different doses of corticosteroid along with non-users for comparison, and the users of corticosteroid in different phases of ARDS.

The diagnosis criterion of ARDS was in accordance with the current Berlin Definition of Acute Respiratory Distress Syndrome (19). In order to increase the reliability of data and experiments, all patients with ARDS were included, depending upon the standard of the relative trial period.

In order to assess the efficiency of corticosteroids on ARDS, data relating to the length of mechanical ventilation, the length of intensive care unit stay and the PaO_2/FIO_2 ratio were included. All patients were required to have a diagnosis of ARDS/acute lung injury and be 18 years of age, or older.

Previous studies were excluded if they were duplicated studies, did not use a control group, involved animal experiments, *in vitro* studies or multiple subjects, or if the identified study was a meeting abstract.

Quality assessment and data extraction. Data were extracted independently by two reviewers and any differences were resolved through discussion. Quality assessment

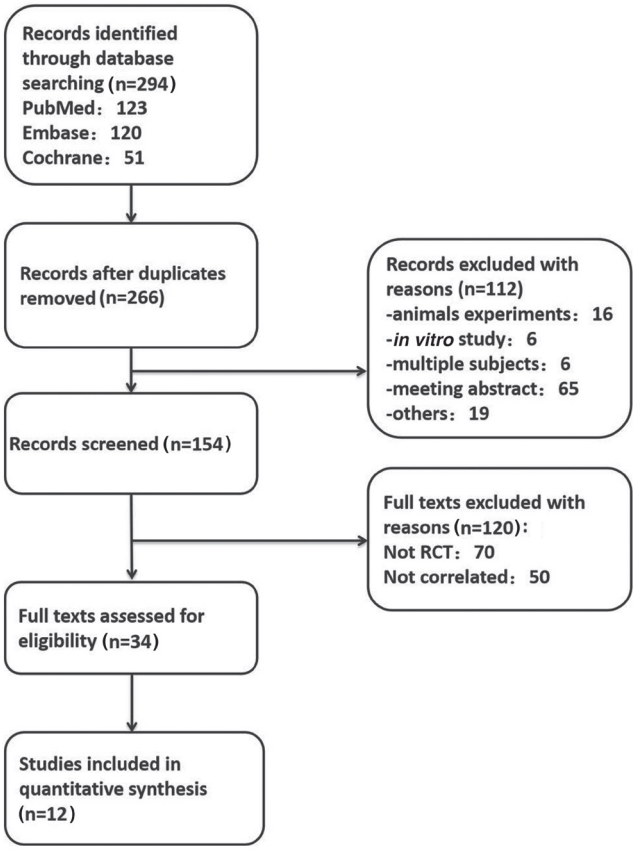

Figure 1. Literature screening procedure. RCT, randomized controlled trial.

of the previous studies was performed using The Cochrane Collaboration's Risk of Bias tool (20), reporting of randomization method, allocation concealment, blinding of outcome assessment, completeness of follow-up and bias of selective reporting. Review Manager 5.2 software (version 5.2; The Nordic Cochrane Centre, The Cochrane Collaboration; ims.cochrane.org/revman) was also used to create funnel plots with which to evaluate publication bias.

Statistical analysis. All data were assimilated using Review Manager 5.2 software provided by The Cochrane Collaboration Group. For dichotomous data, the Mantel-Haenszel (M-H) method was used to estimate the odds ratio (OR) with a 95% confidence interval (CI) (21). The mortality rate by the usage of low-dose and high-dose of corticosteroids, and mortality outcomes in patients with ARDS who were administered with steroids at different course using the M-H method were compared. The mean difference (MD) was calculated between treatment and control groups for continuous outcomes, such as the duration of mechanical ventilation, the length of intensive care unit stay and PaO_2/FIO_2 ratios. The number of patients required for treatment was calculated as the inverse of the absolute risk reduction, based upon the pooled risk ratio and the baseline risk (20). $P<0.05$ was considered to indicate a statistically significant difference. The I^2 test was used to evaluate the pooled variation between all eligible trials and Cochran's Q statistic to assess heterogeneity. In addition, bias risk was also assessed, based upon standards reported in the Cochrane Handbook (22).

Table I. Detailed features of the included studies.

Author, year	Participants, n		Clinical trials	Phases of clinical trials	Treatment phase	Regimen	(Refs.)
	Treatment	Control					
Annane *et al*, 2006	85	92	Yes	IV	Early phase	Hydrocortisone, 200 mg/day for 7 days, low dose	(10)
Confalonieri *et al*, 2005	23	23	Yes	IV	Early phase	Hydrocortisone, 240 mg/day for 7 days, low dose	(11)
Lee *et al*, 2005	12	8	No		Early phase	Methylprednisolone 2 mg/kg/day for 25 days, low dose	(24)
Liu *et al*, 2012	12	14	No		Early phase	Hydrocortisone, 300 mg/day for 7 days, low dose	(25)
Meduri *et al*, 2007	63	28	No		Early and late phase	Methylprednisolone, 1 mg/kg/day for 28 days, low dose	(12)
Seam *et al*, 2012	55	24	No		Early phase	Methylprednisolone, low dose not available	(26)
Steinberg *et al*, 2006	89	91	Yes	IV	Early and late phase	Methylprednisolone, 2 mg/kg/day for 25 days, low dose	(27)
Wan *et al*, 2011	38	43	Yes	IV	Early phase	Dexamethasone, 1 mg/kg/day for 3 days, low dose	(28)
Foster, 2010	39	42	No		Not reported	Methylprednisolone, 3 mg/kg/day for 3 days, high dose	(13)
Meduri and Eltorky 2015	67	49	No		Not reported	Glucocorticoid, 3 mg/kg/day for 3 days, high dose	(3)
Weigelt *et al*, 1985	39	42	No		Early phase	Methylprednisolone, 120 mg/kg/day for 2 days, high dose	(17)
Bernard *et al*, 1987	50	49	No		Early phase	Methylprednisolone, 120 mg/kg/day for 1 day, high dose	(29)

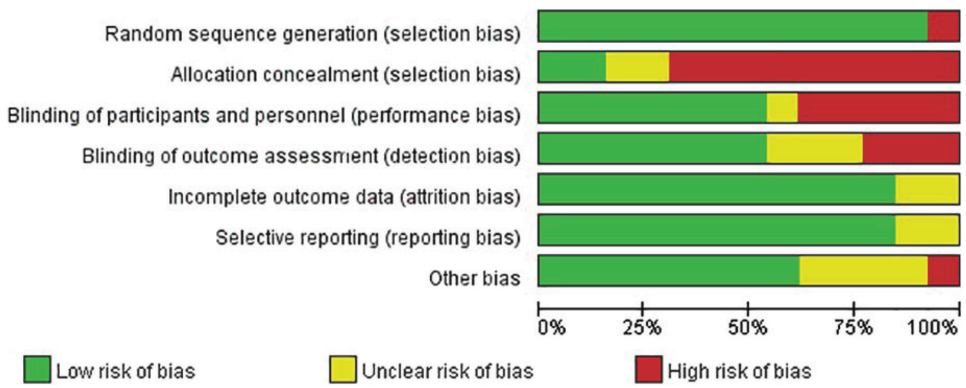

Figure 2. Quality assessment of studies.

Results

Literature search results and population characteristics. Using the aforementioned methods, 294 published articles were identified, which were relevant to the topic of ARDS and glucocorticoids. A total of 28 duplicates and 112 other articles (animal experiments, *in vitro* studies, multiple subjects and wrong abstracts) were excluded, leaving 154 articles. Next, 120 more citations were excluded after careful review of the titles and abstracts. According to the specific inclusion and exclusion criteria of the present study, a total of 12 articles were eligible for the final meta-analysis. A flowchart of the present meta-analysis is presented in Fig. 1.

A total of 1,505 patients with ARDS were included, with 780 cases in the treatment group and 725 cases in the control group. The treatment group was divided into two groups depending on the dose and time-course.

In total, 8 trials used low-dose therapy and 4 trials used high-dose therapy (Table I). To keep consistency, the same cutoff value was used, and a dose of corticosteroid (≤2.0 mg/kg/day or equivalent) of methylprednisolone or equivalent) was defined as low dose, while a dose of corticosteroids (>2.0 mg/kg/day methylprednisolone or equivalent) was defined as a high dose, according to the guidelines for clinical usage of glucocorticoids (23).

The treatment group was divided into 2 groups depending on the specific phase of ARDS (Table I); there were 8 trials involving glucocorticoid intervention during the early phase of ARDS onset (course of disease ≤7 days) and 2 trials involving the treatment of late ARDS with glucocorticoid (course of disease >7 days); other trials were excluded because of a lack of reporting. Standard care, mechanical ventilation and other supportive care were applied to patients in both groups.

Quality assessment. As presented in Fig. 2, the quality of the studies included in the present investigation was assessed using the Cochrane Risk of Bias Tool. Some studies failed to provide a clear method of blinding (including the blinding of participants, and personnel and outcome assessment), while a few studies revealed limitations in sample size. A funnel plot of publication bias is presented in Fig. 3; the plot is symmetrical and distributed at the top of the scale, thus indicating that there is either no publication bias or only minor publication bias.

Mortality outcomes in patients with ARDS who were treated with different doses of steroids. In total, 12 trials (10-13,17,24-30) were deemed to be suitable to assess whether glucocorticoid treatment was beneficial to patients with ARDS in terms of reducing mortality. Sub-group analyses of the mortality data, according to different doses and duration of glucocorticoid therapy, were also performed. As shown in Fig. 4, 8 trials (10-12,24-28) were identified comparing the impact of low-dose glucocorticoid treatment on the mortality rates of patients with ARDS with appropriate controls. A significantly lower mortality was identified in the low-dose group compared with the controls (combined OR: 0.43; 95% CI: 0.24-0.79; P<0.05). Another sub-group with only 4 trials identified (13,17,29,30) studied

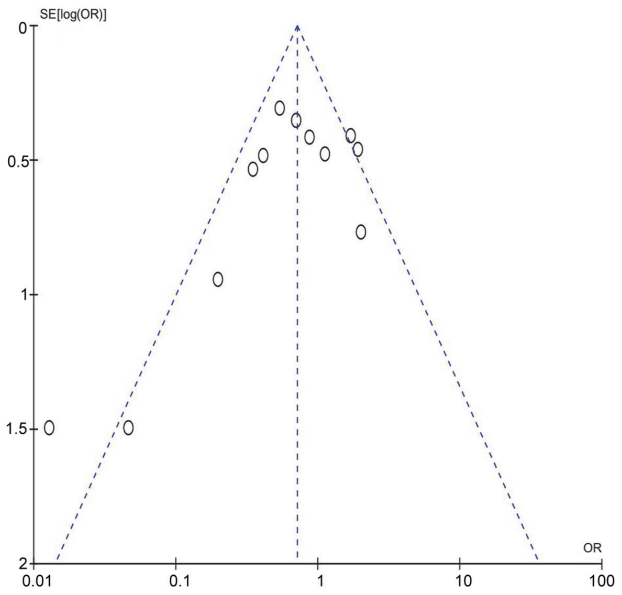

Figure 3. Funnel plots were created to evaluate publication bias using Review Manager 5.2 software (The Cochrane Collaboration). The plot appears symmetrical and distributed at the top of the scale, thus indicating that there is either no publication bias or only minor publication bias. OR, odds ratio.

the effect of high-dose glucocorticoid treatment on the mortality rates of ARDS. As shown in Fig. 4, the group of patients with ARDS receiving high-dose glucocorticoid treatment failed to show any benefit (combined OR: 1.33; 95% CI: 0.86-2.04; P>0.05).

Mortality outcomes in patients with ARDS who were administered steroids at different times. As shown in Fig. 5, 8 trials (10,11,17,24-26,28,29) were identified which compared the impact of early glucocorticoid administration on the mortality rates of patients with ARDS with the controls. Patients who were given corticosteroids early, compared with no corticosteroids, showed lower levels of mortality (OR: 0.61; 95% CI: 0.43-0.86; P=0.005). This analysis failed to show any benefit of late administration of corticosteroids compared with controls (no corticosteroids), in terms of mortality in patients with late ARDS (P>0.05).

Effect of steroid treatment on the duration of mechanical ventilation. A total of 4 trials (10,12,27,28) were identified which investigated whether steroids could reduce the number of days on which patients with ARDS were mechanically ventilated. As shown in Fig. 6, the number of mechanical ventilation-free days was significantly higher in the treatment group compared with the control group (MD: 3.08; 95% CI: 1.49-4.68; P<0.05).

Effect of steroid treatment on the PaO_2/FiO_2 ratio. A total of 3 trials (11,12,28) were identified as having investigated whether corticosteroids could augment the PaO_2/FiO_2 ratio in patients with ARDS. As shown in Fig. 7, the PaO_2/FiO_2 ratio was significantly increased in the treatment group when compared with the controls (MD: 66.39; 95% CI: 57.79-74.98; P<0.05).

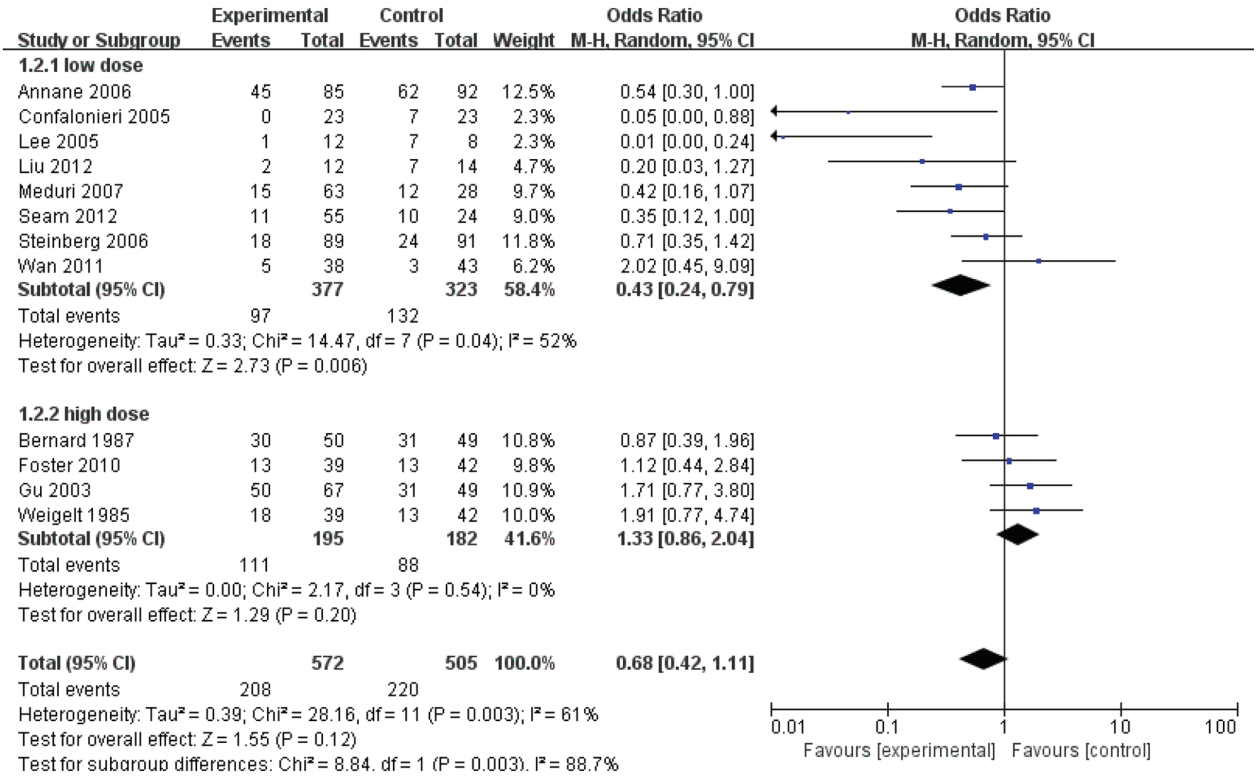

Figure 4. Meta-analysis of the mortality in patients with acute respiratory distress syndrome treated with low-dose and high-dose of corticosteroids. M-H, Mantel-Haenszel; CI, confidence interval.

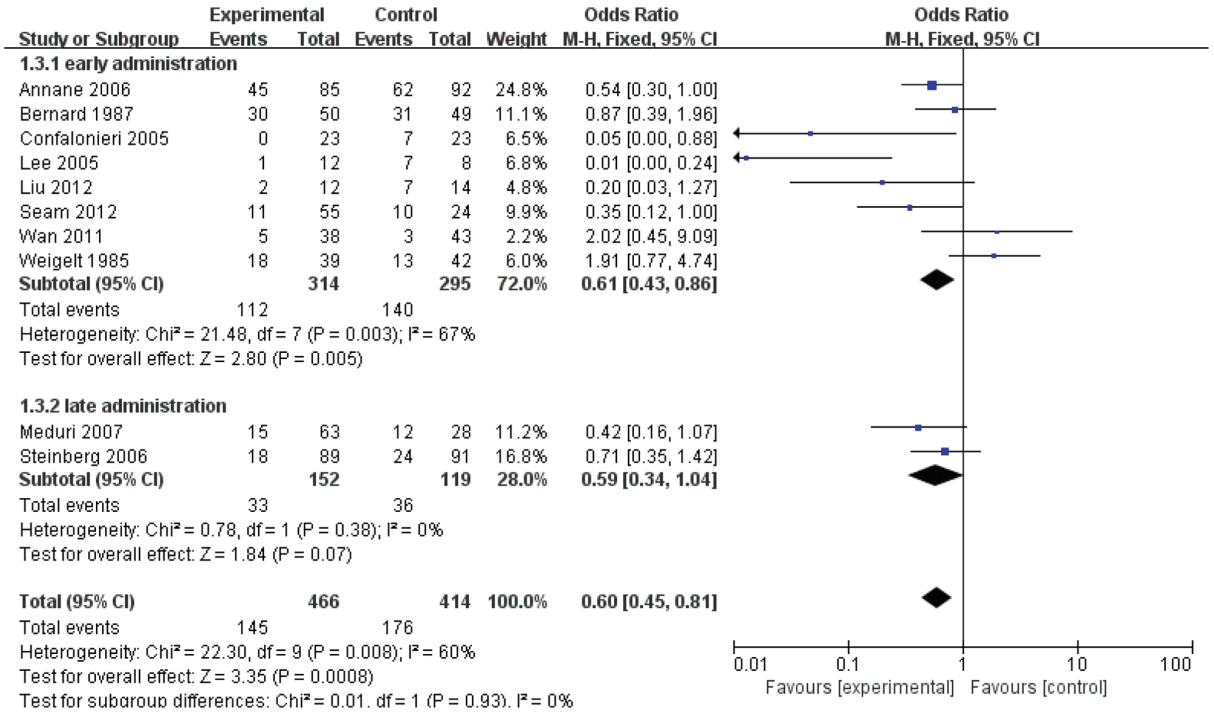

Figure 5. Mortality in patients with acute respiratory distress syndrome with different administration of steroids. M-H, Mantel-Haenszel; CI, confidence interval.

Meta-analysis of the risk of new infection in patients with ARDS treated with steroids. In total, 5 trials (10-12,25,27) were identified which investigated whether corticosteroids could increase the risk of a new infection (side effects). As shown in Fig. 8, the use of corticosteroids did not increase the risk of a new infection when compared with controls (OR: 0.60; 95% CI: 0.32-1.12; P>0.05).

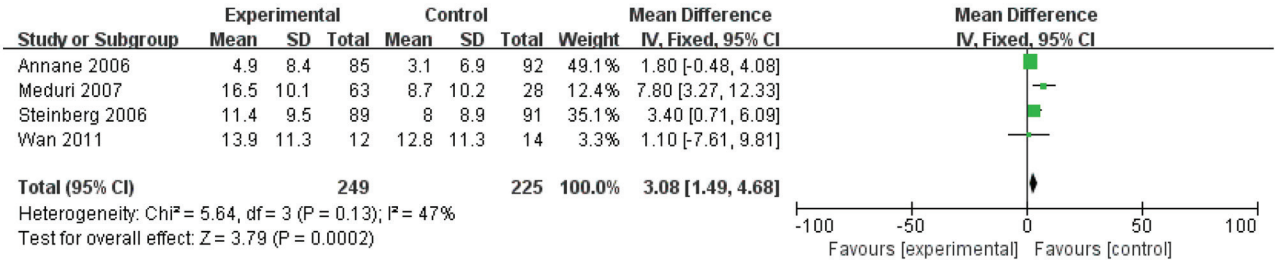

Figure 6. Meta-analysis of the effects of steroids on the duration of mechanical ventilation days. M-H, Mantel-Haenszel; CI, confidence interval.

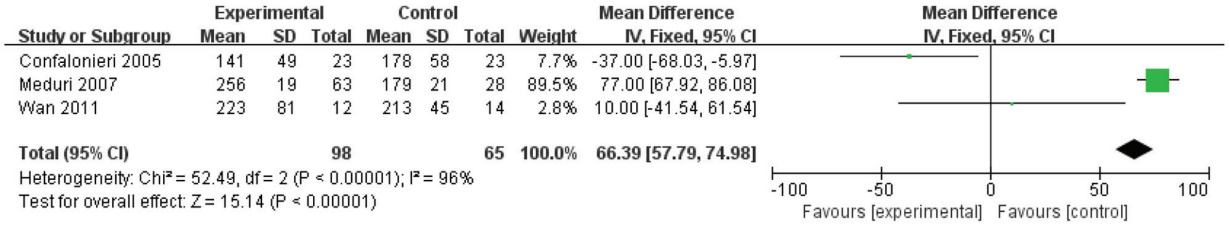

Figure 7. Meta-analysis of the effects of steroids on improving the ratio of arterial oxygen partial pressure to fractional inspired oxygen. CI, confidence interval.

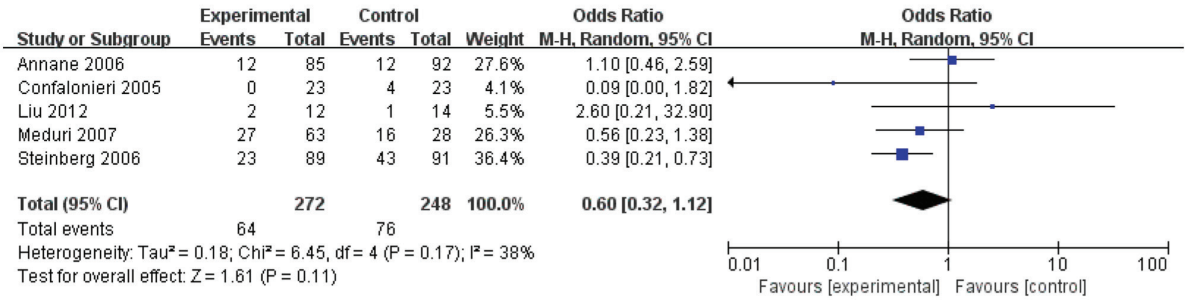

Figure 8. Meta-analysis of the risk of new infection of steroid treatment for patients with acute respiratory distress syndrome. M-H, Mantel-Haenszel; CI, confidence interval.

Discussion

ARDS is an inflammatory disease process of the lungs which occurs in response to a variety of reasons. ARDS is characterized clinically by severe hypoxemia, reduced lung compliance and bilateral radiographic infiltrates (1). Although the prevalence of ARDS is expected to increase worldwide, there is no effective treatment for this fatal disease. Corticosteroids have been the most widely studied drugs for ARDS and are the only agents that have shown promise as a potential treatment. In the present study, the increased sample size allowed the detection of a significant treatment effect in terms of mortality reduction. As a result, a lower mortality rate was identified in the low-dose group compared with the control group, with a combined OR of 0.43 and a 95% CI of 0.24-0.79. Furthermore, there was a significantly lower mortality in patients who were administered with steroids early compared with the controls (OR: 0.46; 95% CI: 0.21-1.01), but not when comparing patients with late administrations of corticosteroids with the controls. The beneficial effects of corticosteroid therapy observed in the present analysis concurred with previous trials, which showed improved PaO_2/FiO_2 ratios and reduced periods of mechanical ventilation in ARDS in response to treatment with low doses of methylprednisolone (10-12). Furthermore, the pooled estimates, provided by the random effects model, considered the heterogeneity evident across existing studies.

Over recent decades, the dosage and timing of corticosteroid therapy for patients with ARDS has changed. Prior to 1990, previous studies usually used a high daily dose (30 mg/kg) over a short period of time (≤2 days) in order to prevent or treat ARDS. Some investigators suggested different treatment doses for early ARDS and persistent ARDS in which a duration of ARDS ≤3 days was considered as early ARDS and ≥5 days as persistent or non-resolving ARDS (31,32). In addition, sub-group analysis of the ARDS net steroid study recommended against starting corticosteroid therapy >14 days after the onset of ARDS (25). These findings suggested that a particular sub-group of patients with ARDS might benefit the most from corticosteroid therapy: Those with persistent ARDS and an onset of ARDS <14 days.

The results in a number of previous studies (10-12,24,25) have demonstrated that treatments with low doses of corticosteroids have been associated with a lower mortality rate for

patients with ARDS. In 2006, a previous study conducted by Annane *et al* (10) demonstrated that a 7 day treatment, involving low doses of corticosteroids, was associated with better outcomes in septic shock-associated early ARDS non-responders, but not in responders. In this previous study, patients underwent a short corticotropin test with 250 mg tetracosactrin (Synacthène Ciba), which was administered intravenously before randomization. Patients were then graded as responders when cortisol increased by <9 g/dl (250 nmol/l) (10). The effect on mortality was consistent in both randomized and non-randomized studies (cohort studies), and highlighted the need for multiple-center, placebo-controlled, randomized and double-blind trials to confirm efficacy. In 2014, a previous study conducted by Ruan *et al* (33) showed that the effects of corticosteroids on the mortality of patients with ARDS differed by way of the duration of outcome measures and by etiologies. Corticosteroids did not improve longer-term outcomes and may have caused harm in certain sub-groups. However, the number of RCTs and sample size were relatively small. There were only two studies in some sub-group analyses and the statistical power was insufficient in some cases. In the present study, different sub-groups were analyzed and only RCT studies were selected, resulting in a more scientifically rigorous conclusion.

Due to the limitations of the present data, it was only possible to conduct a pooled analysis of mortality in relation to incident infection, and the number of days alive and off mechanical ventilation. Therefore, the effects of glucocorticoids on ARDS was not investigated thoroughly. Compared with other meta-analyses, the effect of prolonged glucocorticoid treatment was not assessed, as outcome data from pooled studies were used. The present study was also limited by the inclusion of small to moderately sized RCTs with a relatively small number of events and the satisfied and RCT designs were included to solve the problem of corticoids in patients with ARDS, resulting in the inclusion of two old studies. Furthermore, it was not possible to completely rule out publication bias.

The present meta-analysis suggested that corticosteroid treatment can reduce the mortality rate of patients with ARDS, particularly in the early stages. Glucocorticoid treatment can alleviate systemic inflammation and accelerate the resolution of ARDS. However, high-dose glucocorticoid treatment and the late administration of glucocorticoids did not significantly improve the outcome of patients with ARDS. This result suggested that the duration of glucocorticoid therapy is just as important, in terms of treatment effects, as the dose itself. The present results also suggested that the number of days the patients remained alive, and the number of days for on/off mechanical ventilation, as well as the PaO_2/FiO_2 ratio, improved following the administration of glucocorticoid. The use of steroids was not associated with the risk of new infection in patients with ARDS undergoing steroid treatment. Therefore, the present analyses demonstrated that corticosteroid therapy is associated with a trend towards reduced mortality rates.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

BW and DDL conceptualized and designed this study. SSS provided the study materials. DDL, HZ and XWZ collected and assembled the data. SSS and XWZ analyzed and interpreted the data. All authors wrote the manuscript and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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