

Effect of glucocorticoids on mortality in patients with acute respiratory distress syndrome: A meta-analysis

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Abstract. To date, the efficacy of glucocorticoid therapy to reduce mortality in patients with acute respiratory distress syndrome (ARDS) has remained controversial among the studies available. The present meta-analysis study aimed to further clarify the impact of glucocorticoid therapy on mortality in patients with ARDS by performing a pooled analysis of the previous data. The PubMed, Chinese Knowledge Infrastructure, Wanfang and Cochrane trials databases were searched for relevant studies published between 1966 and 2016. Randomized controlled trials (RCTs) that included the use of glucocorticoids in patients with ARDS and had reported on mortality were included. Odds ratios (OR) and 95% confidence intervals (CI) for mortality were calculated. A total of 10 RCTs were included in the meta-analysis. Of these, 4 studies used high-dose glucocorticoid therapy, while 6 used low-dose glucocorticoid therapy. In the pooled analysis, glucocorticoids were indicated to significantly reduce ARDS-associated mortality (OR=0.64, 95% CI: 0.48-0.85, P=0.002). Further subgroup analysis indicated the following: i) Long-term low-dose glucocorticoid therapy reduced ARDS-associated mortality compared with that in the control group (OR=0.60, 95% CI: 0.44-0.82, P=0.001), whereas high-dose short-term glucocorticoid therapy did not reduce mortality (OR=0.82, 95% CI: 0.43-1.57, P=0.55). ii) Early initiation of glucocorticoid therapy was associated with reduced mortality compared with that in the control group (OR=0.60, 95% CI: 0.44-0.83, P=0.002); however, late initiation did not reduce mortality (OR=0.36, 95% CI: 0.03-3.76, P=0.39). iii) Therapeutic rather than preventive use of glucocorticoids reduced mortality (OR=0.65, 95% CI: 0.49-0.86, P=0.003). Overall, the present

meta-analysis suggests that early initiation of long-term low-dose glucocorticoid therapy reduces mortality of patients with ARDS.

Introduction

Acute respiratory distress syndrome (ARDS) refers to acute inflammatory injury to the lung. The condition is characterized by increased vascular permeability, extravasation of plasma, pulmonary edema and acute hypoxemic respiratory failure (1). ARDS is associated with a high mortality rate. Several treatment strategies have been applied for patients affected; however, only few of these, with the exception of lung-protective mechanical ventilation, have had an impact on ARDS outcomes (2,3). Since inflammation is a key pathogenetic mechanism of ARDS (1), it is reasonable to explore therapies that modulate acute lung inflammation.

Glucocorticoids are the most commonly used anti-inflammatory and immunomodulatory drugs. Studies that investigated the role of glucocorticoids in ARDS have yielded inconsistent results. Several studies indicated that glucocorticoids did not reduce the risk of ARDS-associated mortality (4-6). However, in one study, glucocorticoids were reported to reduce the intensive care unit (ICU) mortality in patients with ARDS (7). The present meta-analysis was performed to assess the effect of glucocorticoid therapy on mortality in patients with ARDS.

Materials and methods

Selection of studies. The PubMed (reference period: January 1, 1966 to December 31, 2016), Chinese Knowledge Infrastructure and Wanfang databases (reference period: January 1, 1982 to December 31, 2016), and the Cochrane trials database (reference period: January 1, 1966 to December 31, 2016) were searched for all relevant publications pertaining to acute lung injury and ARDS.

The following search terms were used: 'acute lung injury', 'acute respiratory distress syndrome' AND 'glucocorticoids', 'corticosteroid', 'steroid', 'methylprednisolone', 'dexamethasone', 'hydrocortisone', 'prednisolone' AND 'randomized', 'random', 'randomly' AND 'patient'. If a study was included in a review and was indexed in the PubMed database, associated studies were further explored using the

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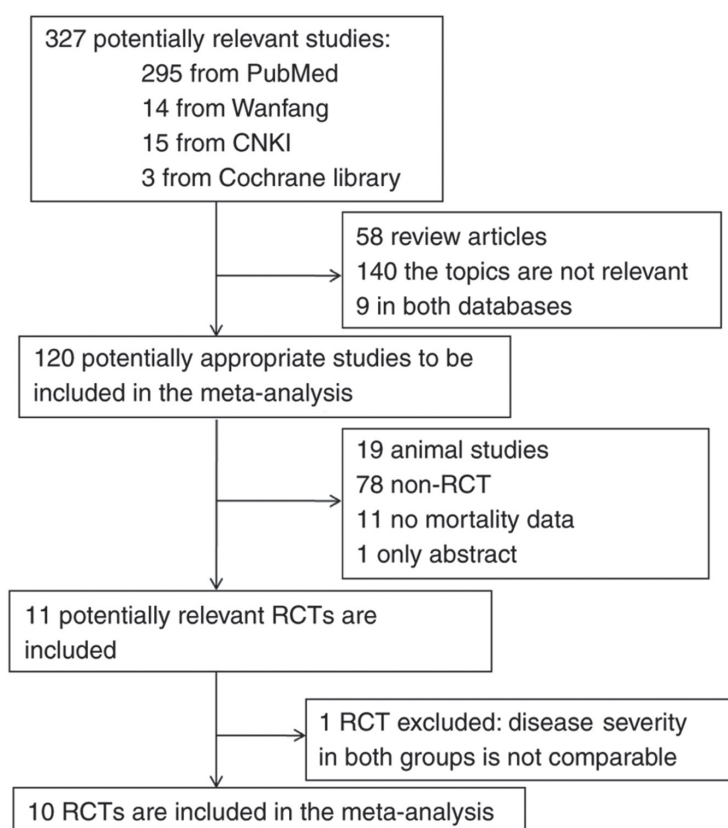


Figure 1. Schematic illustration of literature search and study-selection criteria. RCT, randomized controlled trial; CNKI, Chinese Knowledge Infrastructure.

‘Related Articles’ option. The reference lists of relevant papers were manually screened to identify additional studies.

Randomized controlled trials (RCTs) that fulfilled the following criteria were included: i) Patients with ARDS; ii) patients aged ≥ 18 years; and iii) use of glucocorticoids. The trials were excluded if they i) were non-RCTs; ii) were published as an abstract only; or iii) did not report the mortality data.

Quality assessment. Three reviewers independently assessed the methodological quality using a 10-point scoring system based on a previous meta-analysis (8). This 10-point scoring system includes ‘Randomization’, ‘Allocation concealment’, ‘Blinding’, ‘Inclusion and exclusion criteria defined’, ‘Similar baseline at study entry’, ‘Treatment protocol clearly described’, ‘Cointervention that may affect outcome’, ‘Outcome definition’, ‘Extent of follow-up clearly described’ and ‘Intention-to-treat analysis’. In contrast, Cochrane system includes ‘Sequence generation’, ‘Allocation concealment’, ‘Blinding of participants, personnel and outcome assessors’, ‘Incomplete outcome data’, ‘Selective outcome reporting’ and ‘Other sources of bias’ (Cochrane Handbook for Systematic Reviews of Interventions). Since the 10-point scoring system includes more parameters compared with Cochrane, the former scoring system was chosen.

Data extraction and clinical outcomes. The identification of trials and data extraction were independently performed by two reviewers (QL and CYZ), and any disagreements were resolved via consultation with a third reviewer (RH). The outcome measure was mortality.

Statistical analysis. Meta-analysis was performed using the Mantel-Haentzel method to calculate the odds ratios (OR) for mortality along with 95% confidence interval (CI) (8). Heterogeneity among the studies was assessed using the Cochran's Q statistic. In case of lack of significant heterogeneity ($P > 0.05$), the fixed-effects model was used for the meta-analysis, while a random-effects model was used in case of significant heterogeneity ($P \leq 0.05$). The degree of heterogeneity was tested with I^2 statistics using the Review Manager software; values $< 25\%$ were considered indicative of low heterogeneity, while values of 25-50% and $> 50\%$ were considered indicative of moderate and high heterogeneity, respectively (9). The meta-analysis was performed using Review Manager 5.0.24 (Cochrane Library Software).

Results

Selection and characteristics of trials. A flow chart depicting the study selection is provided in Fig. 1. A total of 327 articles (298 in English language and 29 in Chinese), were retrieved in the database search. Any studies published in languages other than English and Chinese were excluded. Of these, 316 studies that were not relevant were excluded. One study was excluded due to the serum creatinine levels in the methylprednisolone group were significantly higher compared with those in the control group (10), implying that disease severity in the two groups was not comparable. Except for serum creatinine levels, other baseline parameters, including age, sex, etiology and blood pressure in both groups were

Table I. Characteristics of the randomized controlled trials included in the meta-analysis.

First author (year)	Group	Age (years) ^a	PaO ₂ /FiO ₂	ARDS definition	Etiologic factors	(Refs.)
Weigelt (1985)	GC (n=25) Control (n=14)	19-75 19-72	165-350 95-345	PaO ₂ <100 mmHg on 40% oxygen or PaO ₂ <350 mmHg on 100% oxygen.	Sepsis, shock, massive transfusion, contusion, alveolar hypoventilation, aspiration.	(4)
Bernard (1987)	GC (n=50) Control (n=49)	55±2 56±2	NA NA	(1) PaO ₂ ≤70 mmHg on 40% oxygen; (2) Bilateral diffuse infiltrates on chest radiography and (3) PAWP ≤18 mmHg.	Sepsis, aspiration, infectious pneumonia, pancreatitis, shock, fat emboli, and other causes or multiple causes.	(11)
Luce (1988)	GC (n=38) Control (n=37)	50±2.5 53±2.5	NA NA	(1) The new onset of diffuse infiltrates involving all 4 quadrants of the chest roentgenogram; (2) PaO ₂ /PAO ₂ <0.30 and (3) PAWP ≤18 mmHg.	Pneumonia, peritonitis and others.	(5)
Meduri (1998)	GC (n=16) Control (n=8)	47±3.9 51±6.6	110±11 123±11	AECC criteria	NA	(12)
Confalonieri (2005)	GC (n=23) Control (n=23)	60.4±17.3 66.6±14.7	141±49 178±58	AECC criteria	CAP	(13)
Steinberg (2006)	GC (n=89) Control (n=91)	49.0±19.0 49.2±16.5	126±42 126±40	AECC criteria	Trauma, sepsis, multiple transfusions, aspiration, pneumonia and other.	(6)
Annane (2006)	GC (n=85) Control (n=92)	61±16 59±18	NA NA	AECC criteria	Lung and other infections with septic shock.	(14)
Meduri (2007)	GC (n=63) Control (n=28)	50.1±15.3 53.2±15.3	118.4±51.2 125.9±38.6	AECC criteria	Pneumonia, aspiration of gastric content, sepsis and other.	(7)
Seam (2012)	GC (n=55) Control (n=24)	49.7±2.1 53.9±3.4	119.5±6.9 126.2±8.2	AECC criteria	CAP, HAP, intra-abdominal and urinary tract infection, endocarditis, necrotizing fasciitis, bacteremia of unknown source, ehrlichiosis, aspiration, postoperation, pancreatitis and other.	(15)
Tongyoo (2016)	GC (n=98) Control (n=99)	64.5±17.3 64.3±16.0	175.4±6.9 172.4±6.7	AECC criteria	Severe sepsis or septic shock.	(16)

GC, glucocorticoid; PaO₂, partial pressure of oxygen in artery; FiO₂, fraction of inspired oxygen; PAWP, pulmonary artery wedge pressure; AECC, American-European Consensus Conference; NA, not available; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; ARDS, acute respiratory distress syndrome. ^aValues are expressed as range (Ref. 4) or mean ± standard deviation (other studies).

comparable (10). A total of 10 RCTs fulfilled the inclusion criteria and were selected for the final analysis (4-7,11-16). The characteristics of the studies included are summarized in Table I. The major categories of ARDS risk factors included pneumonia, sepsis, trauma, shock and aspiration. The definition of ARDS in the studies included was largely consistent with the Berlin definition (17).

The treatment regimens and mortality data are provided in Table II. The treatment regimens varied considerably between studies (Table II). In 8 studies, glucocorticoid treatment was initiated in the early phase of ARDS (within 1 week of diagnosis) (4,5,7,11,13,14-16); in 2 studies, glucocorticoid therapy was initiated in the later phase of ARDS (>1 week after diagnosis) (6,12). The dosage of glucocorticoids ranged from 40 to

Table II. Treatment regimens and mortality data of the trials included in the meta-analysis.

First author (year)	Treatment timing	Drug	Dosing and course of treatment	Intention (prevention or treatment)	Mortality end-point	Mortality status (dead/alive)	(Refs.)
Weigelt (1985)	Early	MTPS	120 mg/kg/d for 2 d	Treatment	Hospital	GC: 11/14 Control: 6/8	(4)
Bernard (1987)	Early	MTPS	120 mg/kg/d for 1 d	Treatment	45 d	GC: 30/20 Control: 31/18	(11)
Luce (1988)	Early	MTPS	8 mg/kg/d for 1 d	Prevention	Hospital	GC: 9/4 Control: 12/2	(5)
Meduri (1998)	Later	MTPS	2 mg/kg/d for 4 d and tapering; 32 d	Treatment	Hospital	GC: 2/14 Control: 5/3	(12)
Confalonieri (2005)	Early	Hyd	Single 200 mg followed by 240 mg/d; 7 d	Treatment	Hospital and 60 d	GC: 0/23 Control: 7/16	(13)
Steinberg (2006)	Later	MTPS	Single 2 mg/kg followed by 2 mg/kg/d for 14 d and tapering; 25 d	Treatment	60 d	GC: 28/61 Control: 29/62	(6)
Annan (2006)	Early	Hyd	200 mg/d; 7 d	Treatment	28 d	GC: 54/31 Control: 67/25	(14)
Meduri (2007)	Early	MTPS	Single 1 mg/kg followed by 1 mg/kg/d for 14 d and tapering; 28 d	Treatment	Hospital	GC: 15/48 Control: 12/16	(7)
Seam (2012)	Early	MTPS	1 mg/kg/d for 14 d and tapering; 28 d	Treatment	ICU stay	GC: 11/44 Control: 10/14	(15)
Tongyoo (2016)	Early	Hyd	50 mg 4/d; 7 d	Treatment	60 d	GC: 34/64 Control: 40/59	(16)

MTPS, methylprednisolone; Hyd, hydrocortisone; GC, glucocorticoid; ICU, intensive care unit; d, days.

60 or 1 to 2 mg/kg/day of methylprednisolone or equivalent. Glucocorticoid doses were tapered in 4 studies (6,7,12,15). The treatment duration was also different among studies (range, 1-32 d). Due to limitations in the understanding of the mechanisms and characteristics of ARDS, in that ARDS was at first thought to be a short-term acute inflammation in the lung in the past, glucocorticoids were used only for 1 or 2 days in 3 early studies (4,5,11). Glucocorticoids were used to treat but not prevent ARDS in most studies except for one study (5).

A summary of the methodological quality and the score for each of the trials included is provided in Table III. The studies included in the meta-analysis scored 7 points on average in the 10-point scoring system, which was indicative of high quality.

Mortality outcomes. The pooled analysis revealed that glucocorticoid therapy for ARDS was associated with reduced mortality compared with the controls. The OR for mortality after glucocorticoid therapy was 0.64 (95% CI: 0.48-0.85, $P=0.002$; fixed-effects model) compared with the control group (Fig. 2A).

Next, subgroup analysis according to the dose, duration of glucocorticoid therapy and the timing of intervention were

performed. The results indicated that long-term (≥ 7 d) low-dose glucocorticoid therapy (40-60 or 1-2 mg/kg/d methylprednisolone or equivalent) (6,7,12,13,14-16) reduced ARDS-associated mortality compared with that in the control group (OR=0.60, 95% CI: 0.44-0.82, $P=0.001$; fixed-effects model; Fig. 2B). A total of 3 studies evaluated short-term (< 7 days) high-dose glucocorticoid therapy (4,5,11) and the result showed that short-term (< 7 days) high-dose glucocorticoid therapy did not affect ARDS-associated mortality (OR=0.82, 95% CI: 0.43-1.57, $P=0.55$; fixed-effects model; Fig. 2C).

Initiation of glucocorticoid therapy in the early phase of ARDS (within 1 week of diagnosis) significantly reduced ARDS-associated mortality compared with that in the control group (OR=0.60, 95% CI: 0.44-0.83, $P=0.002$; fixed-effects model; Fig. 2D); however, initiation of glucocorticoid therapy in the later phase of ARDS (> 1 week after diagnosis) had no effect on mortality (OR=0.36, 95% CI: 0.03-3.76, $P=0.39$; random-effects model; Fig. 2E).

Preventive use of glucocorticoids in critically ill patients did not reduce ARDS-associated mortality compared with that in the control group (5); however, therapeutic use of

Table III. Methodological quality assessment for each of the studies included.

First author (year)	Randomization	Allocation concealment	Blinding	Inclusion and exclusion criteria defined	Similar baseline at study entry	Treatment protocol clearly described	Cointervention that may affect outcome	Outcome definition	Extent of follow-up clearly described	Intention-to-treat analysis	Final score (Refs.)
Weigelt (1985)	0	0	1	1	0	1	1	1	1	0	6 (4)
Bernard (1987)	1	0	1	1	1	1	0	1	1	0	7 (11)
Luce (1988)	1	0	1	1	0	1	0	1	1	0	6 (5)
Meduri (1998)	1	1	1	1	1	1	0	1	1	1	9 (12)
Confalonieri (2005)	1	1	1	1	0	1	0	1	1	0	7 (13)
Steinberg (2006)	1	0	1	1	1	1	0	1	1	1	8 (6)
Annane (2006)	0	0	1	1	1	1	0	1	1	0	6 (14)
Meduri (2007)	1	0	1	1	0	1	1	0	0	1	6 (7)
Seam (2012)	1	0	1	0	1	1	0	1	1	1	7 (15)
Tongyoo (2016)	1	1	1	1	1	1	1	1	1	1	10 (16)

glucocorticoids significantly reduced ARDS-associated mortality (OR=0.65, 95% CI: 0.49-0.86, P=0.003; fixed-effects model; Fig. 2F).

The effect of combined early initiation, long-term low dose glucocorticoids on ARDS-associated mortality were next compared to all other combinations. The pooled analysis results showed that the combination of early initiation, long-term low dose glucocorticoids (7,13,14-16) significantly reduced ARDS-associated mortality (OR=0.54, 95% CI: 0.37-0.79, P=0.001; fixed-effects model; Fig. 2G), whilst all other combinations (4-6,11,12) exerts no effects on ARDS-associated mortality (OR=0.80, 95% CI: 0.52-1.23, P=0.30; fixed-effects model; Fig. 2H).

Discussion

ARDS is a common type of organ failure in critically ill patients and is associated with high morbidity and mortality (18). Development of effective therapies for ARDS is an active area of research. Although lung-protective mechanical ventilation improves outcomes for patients with ARDS (2), there are currently pharmacological therapies for ARDS with proven effectiveness. Considering the pivotal role of acute inflammation in the pathogenesis of ARDS, several studies have investigated the use of glucocorticoids in these patients (4,7,13); however, the results were largely inconsistent. The present meta-analysis suggested that glucocorticoids reduce ARDS-associated mortality. In particular, long-term low-dose glucocorticoid therapy, when initiated at an early stage, was associated with reduced mortality. These results indicate that glucocorticoids have a promising role in ARDS.

There was much variability between the studies included with regard to the dosage and duration of glucocorticoid therapy. In early times, short-term (<7 days) high-dose glucocorticoids (up to 120 mg/kg/d of methylprednisolone or equivalent) were typically used to treat or prevent ARDS (4,5,11). For the early studies did not show the benefit from short-term high-dose glucocorticoids treatment, and then most studies used low-dose glucocorticoids (40-60 or 1-2 mg/kg/day omethylprednisolone or equivalent) with tapering over a relatively long period for therapeutic rather than prophylactic purposes (6,7,12,13,14-16). Based on the results of the present pooled analysis, long-term treatment with low-dose glucocorticoid provided a survival benefit, while short-term treatment at a high dose did not, which is similar to the results obtained by Meduri *et al* (19). The reason may be that in ARDS, inflammation tends to persist for a long time (20); therefore, the long-term use of glucocorticoids may have a persistent effect on ARDS. On the contrary, short-term use of high-dose glucocorticoids had no significant beneficial effect to reduce mortality and was associated with a high incidence of side effects (4,5,11). Relevant Guidelines of the Society of Critical Care Medicine and European Society of Intensive Care Medicine 2017 conditionally recommend the use of methylprednisolone in early ARDS (up to day 7 of onset) at a dose of 1 mg/kg/d; for late persistent ARDS (after day 6 of onset), the guidelines recommend a dose of 2 mg/kg/d followed by gradual tapering (21).

The timing of initiation of glucocorticoid therapy for ARDS is another issue of interest. The present results suggest

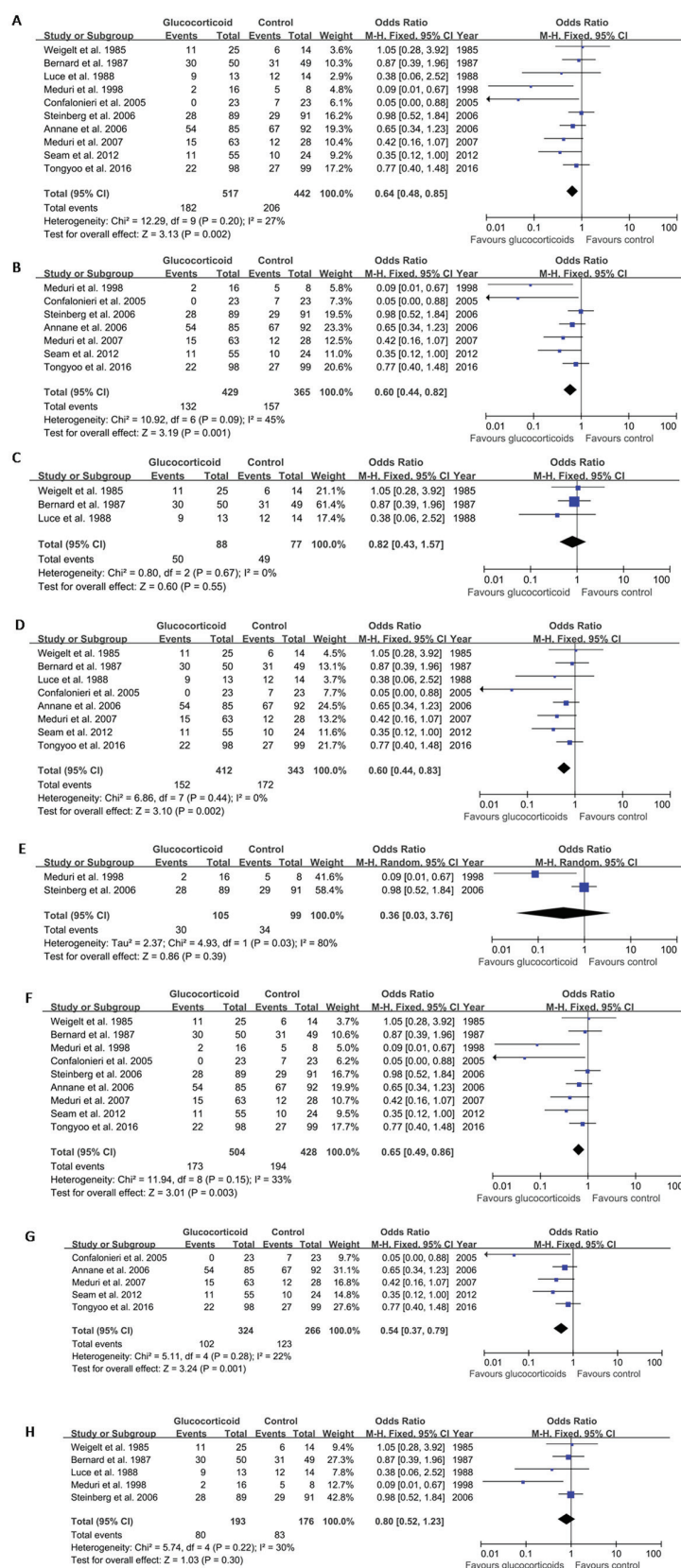


Figure 2. Combined analysis for mortality in ARDS patients comparing glucocorticoid-treated patients with the control. (A) Pooled analysis for the studies included indicated that glucocorticoids reduce ARDS-associated mortality compared with that in the control group. (B) Subgroup analysis indicated that long-term low-dose glucocorticoid therapy reduced ARDS-associated mortality; however, (C) short-term high-dose glucocorticoid therapy had no effect on ARDS-associated mortality compared with that in the control group. (D) Initiation of glucocorticoid therapy within 1 week of ARDS markedly reduced ARDS-associated mortality. (E) Initiation of glucocorticoid therapy in the later phase of ARDS did not affect mortality. (F) Therapeutic rather than preventive use of glucocorticoids reduced ARDS-associated mortality. (G) The combination of early initiation, long-term low dose glucocorticoids significantly reduced ARDS-associated mortality. (H) All other combinations had no effect on ARDS-associated mortality. ARDS, acute respiratory distress syndrome; M-H, Mantel-Haentzel; df, degrees of freedom.

that glucocorticoid treatment initiation within 1 week of ARDS onset provided a significant survival benefit, while treatment initiation at >1 week after ARDS diagnosis did not. This indicates that the use of glucocorticoids after the stage of irreversible lung injury may not offer much of a benefit.

Certain studies have explored the preventive application of glucocorticoids in critically ill patients; the results suggested that preventive use of glucocorticoids did not improve ARDS-associated mortality (5,10,13), while therapeutic use of glucocorticoids, based on the pooled analysis results, reduced ARDS-associated mortality. It is obvious that an adequate inflammatory response in critically ill patients, particularly in infection patients, helps to eliminate invading pathogens; therefore, use of glucocorticoids in this phase may lead to adverse effects (22). However, when acute lung inflammation has progressed to ARDS, the use of glucocorticoids appears to provide a benefit by reducing excessive inflammation and the associated tissue injury.

The present meta-analysis has various limitations that should be considered. First, the studies included in the meta-analysis spanned >20 years. With advances in intensive care medicine, various novel techniques and therapeutic strategies have been developed, including lung-protective ventilation strategy and extracorporeal membrane oxygenation; these are likely to have had an impact on the mortality rate of patients with ARDS. Furthermore, although the studies included reported on in-hospital mortality data, the mortality end-points were not identical among the different studies since they either ICU or hospital mortality were also assessed; this may have introduced an element of bias. In addition, there are several etiological factors of ARDS, including infection, trauma, major operations and sepsis, and ARDS induced by different etiologic factors may be classified into different subphenotypes (23), which may influence the therapeutic response. However, based on the present results, it is impossible to identify any sub-groups of patients that are likely to benefit from glucocorticoid therapy. Finally, the effect of glucocorticoids on the long-term prognosis of patients with ARDS (>6 months) is uncertain due to the relatively short duration of follow-up in most studies.

Overall, the present study suggested that early initiation of low-dose glucocorticoids with long-term administration reduces ARDS-associated mortality. Further well-designed prospective trials are required to provide recommendations for glucocorticoid use in ARDS subpopulations.

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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

QZ, JXS and JSL conceived and designed the present study. RH, QL and CYZ performed data extraction. JXS and JSL ensured the quality of the data. QZ and QL analyzed the data. QZ, JXS and RH drafted the manuscript. All authors read and approved the final 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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