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*Review Article*

# Effectiveness of Glucocorticoids in Acute Respiratory Distress Syndrome: An Umbrella Review

**Semagn Mekonnen Abate**,[1] **Hailemariam Mulugeta Kassim**,[1] **Bivash Basu**,[2] **and Solomon Nega**[3]

[1]*Department of Anesthesiology, College of Health Sciences and Medicine, Dilla University, Dilla, Ethiopia*
[2]*University of Calcutta, Medical College, Department of Anesthesiology, Kolkata, India*
[3]*Department of Internal Medicine, College of Health Sciences and Medicine, Dilla University, Dilla, Ethiopia*

Correspondence should be addressed to Semagn Mekonnen Abate; semmek17@gmail.com

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*Objectives*. Acute respiratory distress syndrome is a very challenging condition that is associated with high morbidity and mortality. This review was intended to evaluate evidence on the effectiveness of glucocorticoid treatment for acute respiratory distress syndrome. *Method*. A comprehensive search strategy was conducted on PubMed/Medline, Cochrane Library, Science Direct, and LILACS. Data extraction was carried out by two independent reviewers using a customized checklist. The quality of each systematic review was assessed by two independent reviewers using an AMSTAR tool, and the overall quality of evidence was generated with online GRADEpro GDT software for primary and secondary outcomes. *Results*. The umbrella review included nine systematic reviews and meta-analysis and one narrative review with 8491 participants. The methodological quality of the included studies was moderate-to-high quality. The overall quality of evidence and recommendations varied form high to very low. *Conclusion*. There is high-to-moderate quality evidence that early low-dose prolonged glucocorticoid therapy reduces mortality in ARDS. However, randomized controlled trials with large sample sizes to address ventilator-free days, the incidence of infection, and other glucocorticoid-associated adverse events are required as the quality of evidence for these secondary outcomes which were low to very low. *Registration*. This umbrella review was registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42019130539).

## 1. Background

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung process associated with increased pulmonary vascular permeability, increased lung weight, and hypoxaemic respiratory failure which results in significant morbidity and mortality worldwide [1–6]. The first clinical description of ARDS was traced back to Rezoagli et al. who, in 1967 reported 12 patients having refractory cyanosis due to hypoxaemic respiratory failure requiring mechanical ventilation [6]. In 1994, the American European Consensus Conference (AECC) established a uniform definition and diagnostic criteria which comprised acute onset, bilateral chest infiltration, and hypoxaemia with no evidence of left atrial hypertension and capillary wedge pressure greater than 18 cm $H_2O$ [7]. This definition, however, had a number of limitations and was modified by the American Thoracic Society and the Society of Critical Care Medicine in Berlin to establish the Berlin definition in 2012 [4].

The onset of respiratory symptoms within one week of a known insult, severity of hypoxaemia as mild (200 mmHg > $PaO_2 \leq 300$ mmHg), moderate (100 mmHg > $PaO_2 \leq$ 200 mmHg), and severe ($PaO_2 \leq 100$ mmHg), requirement of positive end-expiratory pressure (PEEP) of ≥5 $cmH_2O$, and the exclusion of a cardiogenic cause for pulmonary edema with echocardiography were the major components of the Berlin definition [4].

The Kigali modification of the Berlin definition, which can be utilized in resource-limited settings where arterial blood gas analysis may not be available, defined ARDS without the

requirement for PEEP, as the presence of bilateral opacities on the chest radiograph or lung ultrasound and hypoxaemia defined as $SpO_2/FIO_2$ less than or equal to 31 [8–11].

ARDS is a clinical syndrome associated with respiratory failure secondary to pulmonary and nonpulmonary insults [3, 6, 12]. Pulmonary risk factors include pneumonia, which accounted for more than 50 percent followed by aspiration of gastric content and pulmonary contusion, whereas as sepsis, noncardiogenic shock and massive blood transfusion are the most common nonpulmonary causes of ARDS [5, 12].

The incidence of ARDS remains high. A large observational study (LUNG SAFE) with 50 high- and middle-income countries including 459 intensive care unit (ICU) centers revealed that the incidence of ARDS was 10.4% with patient mortality of around fifty percent in severe cases [1]. However, the incidence and mortality of ARDS in resource-limited low- and middle-income countries are even higher [2, 13].

Management of ARDS is very challenging and associated with high morbidity and mortality. Recent studies revealed that low tidal volume ventilation (6 ml/kg ideal body weight), prone positioning (16–20 hrs), airway recruiting maneuvers, extracorporeal membrane oxygenation (ECMO), and lung stem cell provision decrease patient mortality, decrease ventilator-free days, and improve time to ICU discharge. However, glucocorticoid administration for prevention and/or treatment of ARDS did not show conclusive evidence of benefit [14].

Three systematic reviews and meta-analysis of randomized controlled trails (RCTs) revealed that early and prolonged administration of methylprednisolone reduced mortality and duration of mechanical ventilation [15–17]. On the other hand, five meta-analyses of randomized controlled trials failed to show conclusive evidence on mortality benefit of glucocorticoids in a patient with ARDS [18–22]. A systemic review by Curtis failed to show a significant benefit of glucocorticoids for the late stages of ARDS [23]. Therefore, this umbrella review is aimed to evaluate the evidence regarding the efficacy of glucocorticoids in the treatment and prevention of ARDS.

## 2. Objectives and Research Question

*2.1. Objectives.* The objective of this umbrella review was to evaluate the evidence of effectiveness of glucocorticoid treatment for ARDS.

*2.2. Research Question*

(1) Do we have high-quality evidence on the effectiveness of glucocorticoids for ARDS?

(2) When should glucocorticoids be initiated for ARDS?

(3) Is a low-dose regimen of glucocorticoids more effective than high-dose regimen glucocorticoids in ARDS?

## 3. Methods

*3.1. Types of Studies.* All systematic reviews of randomized controlled trials and cohort studies comparing the effectiveness of glucocorticoids in ARDS without language or date restrictions were included. This umbrella review was registered in PROSPERO, the International Prospective Register of Systemic Reviews (CRD42019130539).

*3.2. Types of Participants.* All systematic reviews incorporating adult ICU patients with ARDS receiving glucocorticoid and placebo were considered.

*3.3. Intervention.* The intervention was any type of glucocorticoids administered to patients with acute respiratory distress syndrome.

*3.4. Comparator.* The control was patients who took a placebo or other forms of treatment with the purpose of comparing it with glucocorticoids.

*3.5. Types of Outcomes.* The primary outcomes were hospital mortality and the number of mechanical ventilator-free days. The secondary outcomes were duration of ICU stay and glucocorticoid-related adverse effects including the incidence of infection, hyperglycemia, and neuromuscular dysfunction.

*3.6. Eligibility Criteria*

*3.6.1. Inclusion Criteria.* Systematic reviews and meta-analyses evaluating the effectiveness of glucocorticoids for the treatment and/or prevention of ARDS were included in this umbrella review.

*3.6.2. Exclusion Criteria.* Systematic reviews assessing the effectiveness of glucocorticoid in pediatrics ARDS, cross-sectional studies, and clinical reviews were excluded.

*3.6.3. Search Strategy.* The search strategy was intended to explore all available published and unpublished systematic reviews on the effectiveness of glucocorticoids for treatment or prevention of acute respiratory distress syndrome. A three-phase search strategy was employed in this umbrella review from August 2019 to April 2020 without language restriction. An initial search on PubMed/Medline, Cochrane Library, Science Direct, LILACS, and African Online Journal was carried out followed by an analysis of the text words contained in title/abstract and indexed terms. A second search was undertaken by combining free text words and indexed terms with Boolean operators. The third search was conducted with the reference lists of all identified reports and articles for additional studies. Finally, an additional and grey literature search was conducted on Google Scholar up to ten pages. The results of the search strategy were presented with the PRISMA flowchart (Figure 1). The search strategy conducted in PubMed was as follows.

*3.7. Methodological Quality Assessment.* The methodological quality of each included systematic review was evaluated

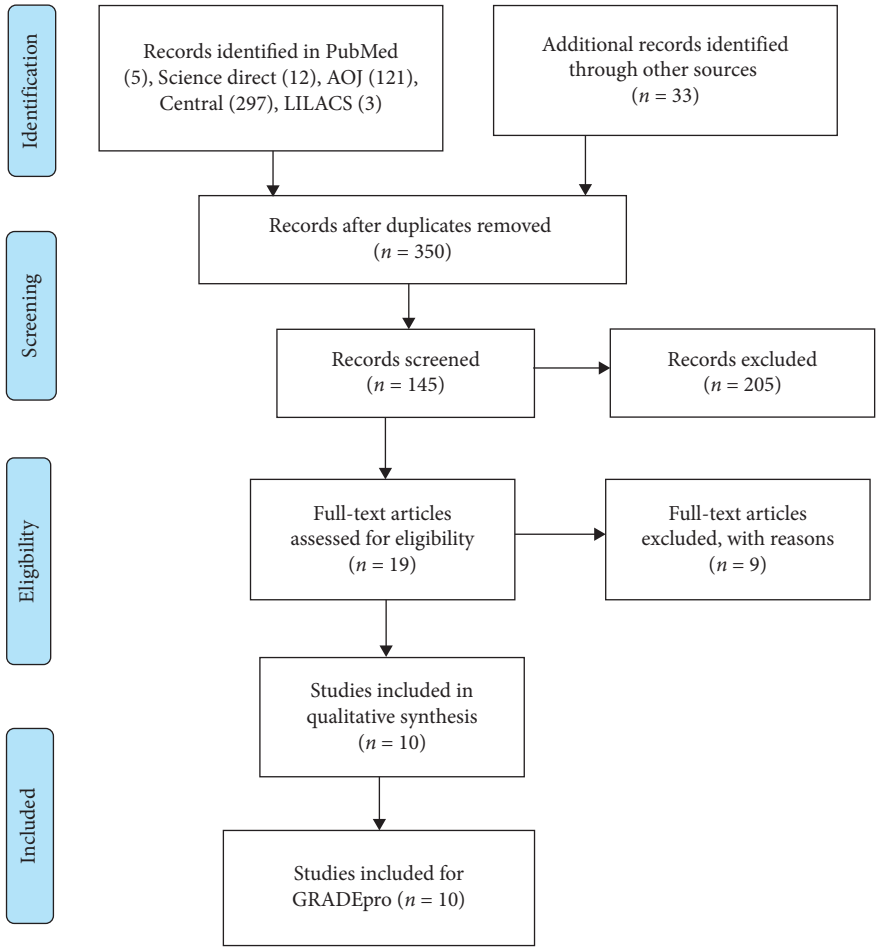


Figure 1: PRSIMA flow diagram.

with the AMSTAR tool (assessing the methodological quality of systematic reviews) by two independent authors [24]. Each positive finding was allocated 1 point, and the sums of the points were used to allocate a final score to each systematic review. Disagreements between the first 2 reviewers were adjudicated and resolved by a third reviewer. The included systematic reviews were classified as follows according to the AMSTAR scores: high quality 8–11, moderate quality 4–7, and low-quality 0–3 score values (Table 1). The AMSTAR tool (assessing the methodological quality of systemic reviews) used the following criteria:

Q1: "was an "a priori" design provided?"

Q2: "were there duplicate study selection and data extraction?"

Q3: "was a comprehensive literature search performed?"

Q4: "was the status of publication (i.e., the grey literature) used as an inclusion criterion?"

Q5: "was a list of studies (included and excluded) provided?"

Q6: "were the characteristics of the included studies provided?"

Q7: "was the scientific quality of the included studies assessed and documented?"

Q8:"was the scientific quality of the included studies used appropriately in formulating conclusions?"

Q9: "were the methods used to combine the findings of studies appropriate?"

Q10: "was the likelihood of publication bias assessed?"

Q11: "was the conflict of interest included?"

*3.7.1. Data Extraction.* The data from each systematic review and meta-analysis were extracted by two independent reviewers for description of included studies and grading the overall quality of evidence of each systemic reviews and meta-analysis. The data extracted included author, year of publication, number of RCTs included, number of participants, methodological quality, outcome of interest, total events in treatment and control, and effect sizes (odds ratio, relative risk, mean difference, and 95% confidence interval). The overall quality of evidence was graded with online GRADEpro GDT software. The umbrella review was presented as per the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) [25].

Table 1: Assessment of methodological quality.

| Author | Year | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Meduri et al. [15] | 2018 | ✓ | × | ✓ | × | ✓ | ✓ | × | ✓ | ✓ | × | ✓ | 7 |
| Yang et al. [22] | 2017 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | × | ✓ | × | 8 |
| Meduri et al. [17] | 2016 | ✓ | × | × | × | × | ✓ | × | × | ✓ | ✓ | ✓ | 5 |
| Horita et al. [18] | 2015 | ✓ | ✓ | ✓ | × | ✓ | ✓ | ✓ | × | ✓ | ✓ | ✓ | 9 |
| Ruan et al. [21] | 2014 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | × | × | ✓ | 9 |
| Khilnani and Hadda [19] | 2011 | ✓ | ✓ | ✓ | ✓ | × | × | × | ✓ | × | × | × | 5 |
| Sessler and Gay [23] | 2010 | ✓ | × | × | × | × | × | ✓ | ✓ | × | × | × | 3 |
| Tang et al. [16] | 2009 | ✓ | ✓ | ✓ | ✓ | × | ✓ | × | × | ✓ | × | × | 6 |
| Peter et al. [20] | 2008 | ✓ | ✓ | ✓ | ✓ | × | × | ✓ | ✓ | ✓ | × | ✓ | 8 |
| Marik et al. [29] | 2011 | × | ✓ | × | × | × | ✓ | × | ✓ | × | × | × | 3 |

*3.7.2. Grading the Quality of Evidence.* The overall quality of evidence for the studied outcome was evaluated using the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation) [26, 27]. The system incorporates study quality (risk of bias), inconsistency (comparison of effect estimates across studies), indirectness (applicability of the population, intervention, comparator, and outcomes to the clinical decision), imprecision (certainty of confidence interval), and high probability of publication bias. The overall quality of evidence was categorized as follows by evaluating and combing the above five parameters for mortality, mechanical ventilator-free days, and incidence of infection**:**

(1) Effective interventions indicated that the review found high-quality evidence of effectiveness for an intervention

(2) Possibly effective interventions indicated that the review found moderate-quality evidence of effectiveness for an intervention, but more evidence is needed

(3) Ineffective interventions indicated that the review found high-quality evidence of lack of effectiveness (or harm) for an intervention

(4) Probably ineffective interventions indicated that the review found moderate-quality evidence suggesting a lack of effectiveness (or harm) for an intervention, but more evidence is needed

(5) No conclusions possible indicated that the review found low or very low-quality evidence, or insufficient evidence to comment on the effectiveness or safety of an intervention

## 4. Results

*4.1. Description of Included Studies.* The search strategy identified 350 systematic reviews and meta-analysis from different databases as described in the methodology section. Nineteen systematic reviews and meta-analysis were selected for further evaluation after the successive screening. Finally, ten systematic reviews and meta-analysis with 8491 participants were included for the umbrella review (Table 2) and the rest were excluded with reasons (Table 3). The systematic reviews and meta-analysis included in the umbrella review were published from 2008 to 2018 with participant size varied from 567 to 1474. The methodological quality of included systematic reviews was ranged from low-to-high quality. Four systematic reviews were rated as high quality while another four were moderate quality. There was only one systematic review scored low with the methodological assessment.

Nine of the included systematic reviews were systematic review and meta-analysis [15–18, 20–23, 28, 29] whereas only one systematic review was narrative review [19]. The methodological quality assessment was reported only in 3 systematic reviews [17, 20, 22]. One study reported the GRADE prosummary table [17]. Publication bias was reported in two studies [18, 22]. Three systematic reviews included both cohort and randomized controlled trials [16, 21, 23] while the other 7 systematic reviews included only randomized controlled trials [15, 17–20, 22, 29].

The majority of systematic reviews compared the efficacy of early low-dose glucocorticoid while two studies compared the effectiveness of glucocorticoid for late and unresolving ARDS [16, 23]. Five systemic reviews assessed the benefit of glucocorticoid treatment for ARDS for a longer duration (>7 days) [15–17, 19, 22] whereas one study compared short-term(<7 days) therapeutic benefit of glucocorticoids for ARDS. All of the included studies assessed the therapeutic effectiveness of glucocorticoid in ARDS whereas 4 systematic reviews compared the preventive effectiveness of glucocorticoids in moderate and high-risk patients for ARDS as well [17, 18, 20, 21].

Hospital or ICU mortality was the primary outcome in 9 systematic reviews [15, 16, 18–23, 29] while one systematic review reported the number of mechanical ventilator-free days as a primary outcome [17]. Incidence of infection was mentioned in four systematic reviews [16, 20–22], and number of mechanical ventilator-free days was reported in three systemic reviews [15, 20, 23].

One systematic review reported neuromyopathy, lung injury score, multiorgan dysfunction syndrome score, and all major adverse events as a secondary outcome [23].

*4.2. Data Synthesis.* The primary objective of this umbrella review was to assess the existing evidence of the effectiveness of glucocorticoids for treatment of ARDS. The methodological quality of each systematic review was assessed with the AMSTAR tool. The overall quality evidence for the outcomes such as mortality, the number of mechanical

Table 2: Description of included studies.

| Author | Year | Design/participant ($N$) | Quality score | Primary outcome | Main findings |
|---|---|---|---|---|---|
| Meduri et al. [15] | 2018 | 9 RCTs ($N = 766$) | 7 | Mortality | Glucocorticoid revealed mortality reduction for ARDS (RR = 0.68, 95% CI 0.57 to 0.82) |
| Yang et al. [22] | 2017 | 14 RCTs ($N = 772$) | 8 | Mortality | Subgroup analysis of low- and high-dose glucocorticoid revealed mortality reduction (RR = 68, 95% CI 0.50 to 0.91) |
| Meduri et al. [17] | 2016 | 8 RCTs ($N = 569$) | 5 | Weaning | Glucocorticoids reduce MV free days |
| Horita et al. [18] | 2015 | 11 RCTs ($N = 949$) | 9 | Mortality | Glucocorticoid did not show significant difference on mortality reduction (RR = 0.77, 0.58 to 1.03) |
| Ruan et al. [21] | 2014 | 8 RCTS and 10 cohort ($N = 1474$) | 9 | Mortality | Subgroup analysis did not show significant difference in mortality (RR = 1.14, 95% CI 0.79 to 1.65) |
| Khilnani and Hadda [19] | 2011 | 9 RCTs ($N = 1025$) | 5 | Mortality | Glucocorticoid failed to show significant difference in mortality |
| Marik et al. [29] | 2011 | 8 RCTs ($N = 567$) | 3 | Mortality | Glucocorticoid revealed mortality reduction for ARDS (RR = 0.68, 95% CI 0.56 to 0.81) |
| Sessler and Gay [23] | 2010 | 4 RCTs and 5 cohort ($N = 648$) | 3 | Mortality | Subgroup analysis showed glucocorticoid mortality reduction (RR = 0.62, 95% CI 0.43 to 0.91) |
| Tang et al. [16] | 2009 | 4 RCTs and 5 cohort ($N = 648$) | 6 | Mortality | Subgroup analysis showed glucocorticoid mortality reduction (RR = 0.62, 95% CI 0.43 to 0.91) |
| Peter et al. [20] | 2008 | 9 RCTs (1073) | 8 | Mortality | Preventive steroid did not show significant benefit (OR = 1.55, 95% CI 0.58 to 4.05) |

RCTs: randomized controlled trials; CI: confidence interval; RR: relative risk; OR: odds ratio.

Table 3: Description of excluded studies.

| Author | Year | Reason for exclusion |
|---|---|---|
| Fernandez et al. [28] | 2005 | Clinical review of glucocorticoid for ARDS |
| Meduri et al. [30] | 2003 | Clinical review on biological efficacy of glucocorticoid |
| Japiassú et al. [31] | 2009 | Glucocorticoid for septic shock |
| Meduri et al. [32] | 2016 | Mini review on ICU acquired weakness due to prolonged steroid |
| Meduri et al. [33] | 2010 | Expert clinical review |
| Schwingshak and Meduri [34] | 2016 | Clinical review of prolonged glucocorticoid in pediatrics with ARDS |
| Haung et al. [35] | 2016 | Efficacy of glucocorticoid for severe community acquired pneumonia |
| Meduri et al. [17] | 2015 | Glucocorticoid for severe community acquired pneumonia |
| Delara et al. [36] | 2018 | Glucocorticoid for preterm infant in ARDS |

ventilator-free days, and incidence of infection was evaluated with online GRADEpro software. The quality of evidence for the primary outcome is provided in the GRADEpro summary table (Table 4), and the secondary outcomes are presented in Table 5. The efficacy of glucocorticoids for the treatment of ARDS is summarized in the following paragraphs.

*4.3. Early Glucocorticoid Therapy.* There are discrepancies among systemic reviews on early initiation of glucocorticoids (<7 days) for the mortality benefit of patients with ARDS. One systematic review with high quality of evidence showed 67% reduction in mortality (OR = 0.37, 95% confidence interval (CI) 0.16 to 0.86, 8 studies, and 501 participants) [22]. Another moderate quality of evidence systematic review revealed that early glucocorticoid therapy reduced mortality by 32% (RR = 0.68, 95% confidence interval (CI) 0.57 to 0.82, 9 studies, and 766 participants) [15]. One low-quality systematic review showed 38% mortality reduction (RR = 0.62, 95% confidence interval (CI) 0.43 to 0.91, 5 cohort and 4 RCTs, and 648 participants) [16]. However, one low-quality systematic reviews and one very low-quality systematic review did not show any significant difference in mortality between glucocorticoids and control [21, 23].

There was low-to-moderate quality evidence of a low incidence of infection and longer duration of mechanical ventilator-free days in patients managed with early low-dose glucocorticoids compared to controls [15, 18, 20, 22, 23, 29].

*4.4. Late Glucocorticoid.* The benefit of initiating glucocorticoids in late and unresolving phases of ARDS (after seven days) did not reveal a significant difference in mortality, mechanical ventilator-free days, and rates of infection. A moderate quality of evidence systemic review by Yang et al. did not show a significant difference in mortality (RR = 0.59, 95% confidence interval (CI) 0.34 to 1.03, two RCTs, and 271 participants) [22]. Another moderate quality of evidence review by Meduri et al. failed to show a significant benefit of late initiation of glucocorticoid for ARDS (RR = 0.67, 95% confidence interval (CI) 0.44 to 1.04, and 314 participants) [15].

Table 4: GRADE evidence summary table for effectiveness of glucocorticoids for mortality reduction.

| Author | Certainty assessment | | | | | | | No. of participants | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other consideration | Glucocorticoid | Control | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| Curtis et al. [23] | 3 | RCT | Serious | Serious | Not serious | Serious | None | 144 | 101 | — | MD 0.62 higher (0.43 higher to 0.9 higher) | ⊕◯◯◯ Very low | Critical |
| John et al. [20] | 3 | RCT | Not serious | Not serious | Not serious | Serious | None | 46/88 (52.3%) | 36/66 (54.5%) | OR 1.50 (0.30 to 5.94) | 97 more per 1,000 (from 281 fewer to 332 more) | ⊕⊕⊕◯ Moderate | Critical |
| Meduri et al. [15] | 9 | RCT | Serious | Not serious | Not serious | Not serious | None | 112/397 (28.2%) | 157/369 (42.5%) | RR 0.68 (0.57 to 0.82) | 136 fewer per 1,000 (from 183 fewer to 77 fewer) | ⊕⊕⊕◯ Moderate | Critical |
| Yang et al. [22] | 9 | RCT | Not serious | Not serious | Not serious | Not serious | None | 158/584 (27.1%) | 209/555 (37.7%) | RR 0.58 (0.44 to 0.75) | 158 fewer per 1,000 (from 211 fewer to 94 fewer) | ⊕⊕⊕⊕ High | Critical |
| Ruan et al. [21] | 8 | RCT | Serious | Not serious | Not serious | Serious | None | 173/391 (44.2%) | 167/334 (50.0%) | RR 0.91 (0.71 to 1.18) | 45 fewer per 1,000 (from 145 fewer to 90 more) | ⊕⊕◯◯ Low | Critical |

CI: confidence interval; RR: relative risk; OR: odds ratio; MD: mean difference.

Table 5: GRADE evidence summary table for effectiveness of glucocorticoids on the number of MV free days and infection rate.

| | | | Certainty assessment | | | | | No. of participants | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other consideration | Glucocorticoid | Control | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| Benjamin et al. [16] | 4 | RCT | Not serious | Serious | Not serious | Serious | None | 140 | 167 | — | MD 4.84 lower (9.28 lower to 0.39 lower) | ⊕⊕◯◯ Low | Important |
| Meduri et al. [17] | 4 | RCT | Not serious | Serious | Not serious | Serious | None | 186 | 136 | — | MD 5.76 higher (3.76 higher to 11.52 higher) | ⊕⊕◯◯ Low | Important |
| Yang et al. [22] | 4 | RCT | Not serious | Serious | Not serious | Not serious | None | 249 | 225 | — | MD 3.08 1.49 higher (4.68 higher to 0) | ⊕⊕⊕◯ Moderate | Important |
| *Incidence of infection* | | | | | | | | | | | | | |
| Benjamin et al. [16] | 9 | RCT | Serious | Not serious | Not serious | Not serious | None | 84/304 (27.6%) | 74/265 (27.9%) | RR 0.89 (0.65 to 1.23) | 31 fewer per 1,000 (from 98 fewer to 64 more) | ⊕⊕⊕◯ Moderate | Important |
| Meduri et al. [15] | 8 | RCT | Not serious | Not serious | Not serious | Serious | None | 22/299 (7.4%) | 27/270 (10.0%) | OR 0.77 (0.56 to 1.08) | 21 fewer per 1,000 (from 41 fewer to 7 more) | ⊕⊕⊕◯ Moderate | Important |
| Yang et al. [22] | 7 | RCT | Not serious | Serious[a] | Not serious | Not serious | None | 102/361 (28.3%) | 99/339 (29.2%) | OR 1.00 (0.44 to 2.25) | 0 fewer per 1,000 (from 138 fewer to 189 more) | ⊕⊕⊕◯ Moderate | Important |
| Ruan et al. [21] | 5 | RCT | Serious | Not serious | Not serious | Serious | None | 79/303 (26.1%) | 70/268 (26.1%) | RR 0.83 (0.65 to 1.06) | 44 fewer per 1,000 (from 91 fewer to 16 more) | ⊕⊕◯◯ Low | Important |

CI: confidence interval; RR: relative risk; OR: odds ratio; MD: mean difference; MV: mechanical ventilator.

*4.5. Prolonged Glucocorticoids.* Prolonged low-dose glucocorticoids initiated at least one week revealed certain mortality reduction in low-to-moderate quality evidence systematic reviews [15, 17]. Moderate-quality evidence from the systematic review of Ruan et al. showed a 56% reduction in mortality (OR = 0.44, 95% confidence interval (CI) 0.30 to 0.64, 6 RCTs, and 551 participants) [21]. Another two moderate-quality evidence systematic reviews by Meduri et al. in 2016 and 2018 revealed a significant mortality reduction by 44% and 32%, respectively [15, 17]. Another two low-quality evidence systematic reviews by Ruan et al. and Curtis et al. showed a significant reduction in mortality and mechanical ventilator-free days [21, 23].

*4.6. Short-Term Glucocorticoid.* The initiation of high-dose glucocorticoids for ARDS for less than a week did not show a significant difference in the reduction of mortality, mechanical ventilator-free days, and rates of infection [22]. Moderate-quality evidence from Yuan et al. failed to show a significant difference in mortality (OR = 0.77, 95% confidence interval (CI) 0.52 to 1.13, 6 RCT, and 588 participants) [21].

*4.7. Glucocorticoid for Prevention of ARDS.* The provision of glucocorticoids to high-risk patients to prevent acute respiratory distress syndrome did not show a significant difference in survival or incidences of infection. Low-quality evidence from Peter et al. showed an insignificant difference in mortality (OR = 1.52, 95% confidence interval (CI) 0.30 to 5.94, 3 RCTs, and 154 participants) [20]. Low-quality evidence from Ruan et al. also failed to show a significant difference in mortality (RR = 1.24, 95% confidence interval (CI) 0.57 to 2.72, 3RCTs, and 154 participants) [21].

## 5. Discussion

Acute respiratory distress syndrome is a challenging condition to manage in the intensive care unit and is associated with significant mortality and morbidity. Glucocorticoids have been employed for the management of ARDS in different dosages, for variable durations and time of initiation of therapy. Despite numerous randomized controlled trials and systematic reviews, there is no conclusive evidence on the effectiveness of glucocorticoids for ARDS. This umbrella review therefore aimed to assess the quality of evidence of available systematic reviews and meta-analysis on the effectiveness of glucocorticoids in ARDS.

Moderate-to-high quality of evidence was available to indicate that early low-dose glucocorticoid therapy reduces mortality and prolong mechanical ventilator-free days in patients with ARDS [22].

Moderate quality of evidence revealed that the incidence of infection with the use of glucocorticoids was not increased [15, 20]. Moderate quality of evidence revealed that incidence of infection with the use of glucocorticoids was not increased [16, 20, 22]. Moderate quality of evidence failed to show mortality benefit of glucocorticoids in late-phase ARDS, nor does that prolonged administration or high-dose short course glucocorticoid therapy have a significant impact on mortality [15, 17, 22, 23].

*5.1. Limitation of the Overview.* The umbrella review incorporated 10 systematic reviews with high to a very low quality of evidence. The majority of systematic reviews had moderate to a very low quality of evidence. Firm recommendations regarding the effectiveness of glucocorticoids in terms of time of initiation, duration of therapy, and dosage thereof remain challenging. Besides, some of the systematic reviews did not report the relevant information for the GRADE evidence profile.

## 6. Conclusion

This umbrella review summarizes the evidence from systematic review and meta-analysis of randomized controlled trials and cohort studies to address the effects of glucocorticoids for acute respiratory distress syndrome. The finding of this review is valuable for clinicians, researchers, and policy-makers for decision making and evidence translation. High quality of evidence favours initiation of early low-dose prolonged glucocorticoids to reduce mortality of ARDS. Further randomized controlled trials with larger sample sizes are however required to confirm or exclude efficacy of glucocorticoid therapy on ventilator-free days, as well as infection incidence and other glucocorticoid-associated adverse events.

## Abbreviations

AECC: American-European Consensus Conference
AMSTAR: Assessing the methodological quality of systemic reviews
ARDS: Acute respiratory distress syndrome
CI: Confidence interval
ECMO: Extracorporeal membrane oxygenation
GDT: Guideline development tool
ICU: Intensive care unit
MD: Mean difference
OR: Odds ratio
RCT: Randomized controlled trial
RR: Relative risk
PEEP: Positive end-expiratory pressure
PRISMA: Preferred Reporting Items for Systemic Review and Meta-analysis.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Ethical Approval

Ethical clearance and approval were obtained from the ethical review board of the College of Health Science and Medicine.

## Disclosure

This umbrella review was registered in PROSPERO, the International Prospective Register of Systemic Reviews (CRD42019130539).

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

## Authors' Contributions

SA and HK conceived the idea and design of the study. SA, HK, and VB involved in searching strategy, data extraction, quality assessment, analysis, and manuscript preparation. All the authors have read and approved the manuscript.

CI: confidence interval; RR: relative risk; OR: odds ratio; MD: mean difference; MV: mechanical ventilator.

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