ORIGINAL ARTICLE

Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials

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KEY WORDS

acute respiratory distress syndrome, corticosteroids, mortality, systematic review

EDITORIAL

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ABSTRACT

INTRODUCTION Acute respiratory distress syndrome (ARDS) is a rapidly progressing, inflammatory lung disease with a high mortality rate and no specific pharmacological treatment available.

OBJECTIVES We conducted a systematic review and meta-analysis on corticosteroid use in ARDS.

METHODS We searched 4 medical literature databases and retained randomized controlled trials on the use of corticosteroids in hospitalized adults with ARDS, which could be found there until February 2020. Two reviewers identified eligible studies, independently extracted data, and evaluated the risk of bias. The authors assessed the certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

RESULTS We included 7 randomized controlled trials involving 851 patients. They showed that corticosteroids reduced all-cause mortality (risk ratio [RR], 0.75; 95% CI, 0.59–0.95; $P = 0.02$; moderate certainty) and the duration of mechanical ventilation (mean difference [MD], –4.93 days; 95% CI; –7.81 to –2.06; $P < 0.001$; low certainty), and increased the number of ventilator-free days (MD, 4.28 days; 95% CI, 2.67–5.88; $P < 0.001$; moderate certainty), as compared with placebo. Corticosteroids also increased the risk of hyperglycemia (RR, 1.12%; 95% CI, 1.01–1.24; $P = 0.03$; moderate certainty), and the effect on neuromuscular weakness was unclear (RR, 1.3; 95% CI, 0.8–2.11; $P = 0.28$; low certainty).

CONCLUSIONS These results suggest that systemic corticosteroids may potentially improve mortality, shorten ventilation times, and increase the number of ventilator-free days in patients with ARDS. However, the studies included different corticosteroid classes and initiated drug administration at different times, as well as used various dosing regimens. Thus, caution in the actual clinical application of these results is recommended.

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INTRODUCTION Acute respiratory distress syndrome (ARDS) is a progressive, life-threatening inflammatory pulmonary condition characterized by alveolar injury leading to diffuse alveolar damage. Hospital mortality due to ARDS approaches 40% of patients, with 200 000 cases occurring annually in the United States. Timely diagnosis, treatment, and support may improve patient outcomes.[1-3] Corticosteroids have been proposed as a treatment for ARDS, with a particularly heightened interest in their potential role in reducing the pulmonary and systemic damage.[4] Corticosteroids reduce an inflammatory response and should act on the exudative, proliferative, and fibrotic phases of ARDS.[5,6] The efficacy of corticosteroid treatment in patients with ARDS remains unclear. For example, a recent Cochrane review of randomized controlled trials (RCTs) revealed no significant difference in all-cause mortality at 3 months or earlier or reduction in the duration of mechanical ventilation.[5] However, the results of a recent RCT suggested a potential beneficial effect of dexamethasone in ARDS, with reduced mortality, an increased number of ventilator-free days, and shorter mechanical ventilation times.[4]

WHAT'S NEW?

Acute respiratory distress syndrome (ARDS) is a life-threatening inflammatory pulmonary condition characterized by rapid progression and requiring respiratory support. No specific pharmacological therapy for ARDS is available. However, corticosteroids have been proposed as a treatment, prompting us to conduct a systematic review and meta-analysis on the use of these drugs in ARDS, along with a critical appraisal of eligible studies and assessment of their quality of evidence. Our review of 7 randomized controlled trials suggests that corticosteroid use may reduce mortality, shorten ventilation times, and increase the number of ventilator-free days. Corticosteroids in the treatment of ARDS have been gaining many advocates and doctors are potentially enticed to use them in patients with ARDS induced by coronavirus disease 2019 (COVID-19). However, the certainty of evidence is limited by the low number of studies, small sample sizes, clinical differences among patient populations studied, and the known adverse effects of corticosteroid use. Caution is urged in extrapolating these results to the bedside.

Nowadays, the treatment of ARDS is based on supportive care and management of the underlying disease. Currently, there are no approved pharmacological interventions for this condition.

Given the clinical equipoise and pressing need for optimal patient management, our systematic review aimed to consider the body of RCT evidence and determine the efficacy and safety of corticosteroid use in patients with ARDS.

METHODS

Data sources and search methods

The authors developed a protocol for this review, with predetermined eligibility criteria and methods. Given the global emergency situation and the present delay in the International Prospective Register of Systematic Reviews, the authors proceeded with this rapid review without formal registration.

Our initial perusal of the literature suggested that relevant systematic reviews on this clinical question can be found. We planned to examine the existing systematic reviews and include those judged methodologically strong. We found 2 systematic reviews that we considered relevant.

We used the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2) critical appraisal tool for systematic reviews, following the design and execution presented in a review by Lewis et al.[2] In a systematic review by Sun et al,[7] an adequate methodology was also used. However, we judged it to be of lower overall methodological quality than the Cochrane review by Lewis et al.[2] Apart from that, it included methodologically weaker retrospective studies, which was not our focus in this study. Therefore, we accepted and incorporated data from the review by Lewis et al[2] as part of our analysis.

Then, we updated the electronic database search, spanning between 2018 and February 14, 2020 and imposing an overlap search period to ensure that any publications in the publication pipeline were not missed by Lewis et al.[2] For some searches, we also set earlier search periods as a means of quality assurance.

We searched the following databases: 1) MEDLINE / PubMed (1996 to February 14, 2020), applying a search filter for RCTs with no limits; 2) EMBASE (2018 to February 14, 2020), limiting the search to humans; 3) Cochrane Central Register of Controlled Trials (to February 14, 2020), with no limits; and 4) CINAHL (2000 to February 14, 2020), limiting the search to humans (for the search strategy applied to the MEDLINE and EMBASE databases, see Supplementary material, *Appendix S1*).

Study selection Eligible studies were parallel-group RCTs that randomized patients with ARDS of any cause to corticosteroid therapy versus placebo or standard treatment or no glucocorticoid use. We sought studies reporting on at least 1 of the following outcomes: all-cause mortality, duration of mechanical ventilation, length of hospital stay, ventilator-free days (defined as the number of days alive free from mechanical ventilation), or adverse effects and complications of corticosteroid use. We abstracted data for each outcome at the longest follow-up. A team of 2 reviewers independently screened titles and abstracts in duplicate, obtained full texts of articles that either reviewer considered potentially eligible, and determined the final review eligibility of the full texts.

Data abstraction and quality assessment Two reviewers independently extracted relevant data (study design, study demographics such as author, year, location, and center status, patient demographics such as age, gender, sample size, intervention [corticosteroid class, the timing of corticosteroid initiation, and dosing regimens], comparator, and outcomes that included all-cause mortality, duration of mechanical ventilation, the number of ventilator-free days, and adverse events) and assessed the risk of bias using the Cochrane risk of bias tool for RCTs.[8] We also assessed 2 additional domains for the risk of bias, which we considered potential factors for a high risk of bias (stopping early for benefit and baseline imbalance). We also assessed the risk of bias of the RCTs included in the systematic review by Lewis et al,[2] independently of the previously published assessment. We sought this additional layer of quality assurance and independently appraised the risk of bias as opposed to a blind acceptance of the risk of bias determined in the included reviews. In instances when a study was not available as a full-length manuscript, we defaulted to the Cochrane risk of bias determination and details. To avoid the "unclear" responses reviewers often report when assessing the risk of bias, which hampers a more definitive interpretation, we used the following response options: "yes," "probably yes," "probably no," and "no."[9]

For the overall assessment of the risk of bias, we judged whether key domains (randomization, allocation concealment, blinding of patients and healthcare providers, data loss, and stopping early for benefit) were optimally described. If any

of the domains was not reported to be optimally handled, then we considered the study as having a high risk of bias.

Data synthesis and analysis We used random-effects modeling for all analyses conducted with the Mantel–Haenszel method, risk ratio (RR) for dichotomous outcomes, and mean difference (MD) for continuous variables.[10] We hypothesized that the following variables would be associated with a more substantial treatment effect: greater severity of ARDS, timing of corticosteroid therapy (<7 days vs ≥7 days), and a higher risk of bias. If data were reported as medians and interquartile ranges, we converted these to mean (SD) for meta-analytic pooling.[11] If continuous outcomes were reported with various measurement scales, we pooled them using the standardized mean difference instead of MD.

The subgroup analyses were conducted by ARDS severity as well as dose and early versus late administration of corticosteroids. We also performed sensitivity analyses based on the differential risk of bias. Studies stopped early for benefit were flagged as being at high risk of biased estimates.[12] Our sensitivity analysis was intended to separate studies at high risk of bias and examine their effect on the pooled estimate.

We conducted the meta-analyses using the Review Manager software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We assessed heterogeneity by visual inspection of forest plots, the Cochran's χ^2 test for heterogeneity, and the I^2 statistic (with results >50% considered as significant heterogeneity warranting exploration and explanation).[8,13]

We reported 95% CIs as measures of uncertainty with the presented estimates of effect. To estimate the absolute effects of the intervention, we sought large RCTs providing the best estimates of these outcomes.[14]

We used the control event rate to determine the baseline risk in computing the absolute effects. To compute the absolute effect, we multiplied the baseline risk value by the relative effect (and 95% CI) value.

GRADE methods We utilized the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of evidence for each outcome and for the entire body of evidence.[15] This outcome-centric approach for assessing the certainty of effect estimates evaluates the body of evidence for the risk of bias, imprecision, inconsistency (heterogeneity), indirectness, and publication bias.

RESULTS

We included 6 RCTs that were covered in the relevant meta-analyses obtained from the previous systematic review.[2] Our updated database searches identified 1524 unique citations (MEDLINE / PubMed, 253 citations; EMBASE, 371 citations; CINAHL, 463 citations; and Cochrane Central Register of Controlled Trials, 437citations). After reviewing references and screening titles and abstracts as well as full texts, 1 RCT was deemed firmly eligible for our systematic review (Supplementary material, *Figure S1*). We, therefore, included a total of 7 RCTs in this updated review (involving 851 patients) with relevant study characteristics shown in TABLE 1.

Study characteristics Primary studies were conducted in multiple countries (China, Egypt, Kuwait, Spain, Thailand, and the United States), with 43% of them being multicenter trials. Almost all the studies were funded by nonprofit organizations, except for the study by Zhao et al,[16] whose funding source was uncertain. Sample sizes ranged from 26 to 277 hospitalized patients, mostly men (51.5%–85.2%) and typically over 50 years of age. Patients received corticosteroid treatment with hydrocortisone,[17,18] methylprednisolone,[5,16,19] dexamethasone,[4] or inhaled budesonide. A placebo was used in 5 studies,[5,16-19] and 2 studies[4,20] compared the typical management of ARDS with and without corticosteroids. Follow-up ranged from 28 to 180 days from enrollment. Five studies[4,16-19] initiated study treatment within 7 days after the diagnosis of ARDS, 1 study[5] after at least 7 days following the diagnosis of ARDS, and 1 study[20] did not report the timing of study protocols concerning the diagnosis of ARDS.

Risk of bias assessment Three[5,18,19] of 7 trials (43%) enrolling 51.5% of the total sample had a low risk of bias (Supplementary material, *Table S1*). The loss to follow-up was rare: 6 trials (85.7%) had a near-complete follow-up with loss that was deemed not biasing, and only 1 study had the attrition rate greater than 5%. Worst-case and best-case plausible modeling assumptions about the outcomes of patients lost to follow-up were not needed. No study was stopped early for benefit. We did not develop funnel plots or statistical tests for publication bias due to the limited interpretability, which can be noted when the number of studies is lower than 10, as in our case. The comprehensiveness of the search strategy used in our study was considered exhaustive.

Outcomes **All-cause mortality** Seven trials[4,5,16-20] (including 851 patients) reported on all-cause mortality, whereby 119 of 443 patients (26.9%) in the corticosteroid groups died compared with 151 of 408 (37%) in the control groups (RR, 0.75; 95% CI, 0.59–0.95; P = 0.02; I^2 = 22%; moderate certainty) (FIGURE 1). The reported data were optimal for subgroup analyses based on ARDS severity. The absolute effect was 93 (95% CI, 19–152) fewer deaths per 1000 affected individuals (Supplementary material, *Table S2*).

We conducted a sensitivity analysis by excluding studies at high risk of bias.[16,17,20] The mortality benefit associated with the use of corticosteroids was robust and consistent (RR, 0.77; 95% CI, 0.61–0.98; P = 0.03). The subgroup test of

TABLE 1 Characteristics of the studies included in the review and meta-analysis (continued on the next 2 pages)

Study	Sample size[a]	Male sex, %	Inclusion criteria	Follow-up	Treatment intervention arm, dose vs treatment control arm, dose	Degree of hypoxemia or lung injury	Reported cause of ARDS	Notable comorbidities
Steinberg et al,[5] United States, multicenter	180; 89; 91	54.4	Patients intubated and receiving mechanical ventilation for 7 to 28 days after the onset of ARDS; continuous mechanical ventilation and the presence of persistent bilateral infiltrates were required from the onset of ARDS to study entry. On the study entry day, the PaO_2/FiO_2 ratio in the study patients had to be <200.	Patients followed until they died; discharged home when started to breathe without assistance or on day 180, whichever came first.	After at least 7 days after the diagnosis of ARDS Intravenous methylprednisolone sodium succinate (methylprednisolone) diluted in 50 ml of 5% dextrose in water. A single dose of 2 mg of methylprednisolone per 1 kg of predicted body weight was followed by a dose of 0.5 mg per 1 kg of predicted body weight every 6 hrs for 14 days, a dose of 0.5 mg per 1 kg of predicted body weight every 12 hrs for 7 days, and then the dose was tapered. The study drug was tapered over 4 days if 21 days of treatment had been completed and the patient was unable to breathe without assistance for 48 hrs. Tapering occurred over a 2-day period if disseminated fungal infection or septic shock developed or the patient could breathe without assistance for 48 hrs. Control group: placebo (50 ml of 5% dextrose in water), 50 ml of 5% dextrose in water at a dose of 0.5 mg/kg.	Corticosteroid arm: LIS, mean (SD): 3.3 (0.9), PaO_2/FiO_2, LIS, mean (SD): 126 (42) Control group: LIS, mean (SD): 3 (1.1), PaO_2/FiO_2, LIS, mean (SD): 126 (40)	Both arms reported multiple trauma, sepsis, multiple transfusions, aspiration, pneumonia, among others, and both groups were roughly balanced as to the predisposing cause 54% of patients in the treatment group and 56% of those in the control group had direct lung injury	Of note, there was a higher number of serious adverse events (neuromyopathy) in the corticosteroid group than in the control group (9 versus 0 events).
Meduri et al,[20] United States, multicenter	Randomized: 91; 63; 28 Per-protocol analysis: 79; 55; 24	51.6	Intubated adult patients receiving mechanical ventilation, meeting the criteria for ARDS according to the AECC definition[33] within 72 hrs	Up to 28 days	2:1 randomization protocol, with per-protocol analysis Within 72 hrs after the diagnosis of ARDS Corticosteroid methylprednisolone; a loading dose of 1 mg/kg, then infusion of 1 mg/kg/d from day 1 to day 14; 0.5 mg/kg/d on days 15 to 21; 0.25 mg/kg/d on days 22 to 25; then 0.125 mg/kg/d from days 26 to 28 (all administered in 240 ml of normal saline infused daily at a rate of 10 ml/h) Control group: 240 ml of normal saline administered daily as infusion at a rate of 10 ml/h	Corticosteroid arm: LIS, mean (SD): 3.21 (0.41); PaO_2/FiO_2, LIS, mean (SD): 118.4 (51.2) Control group: LIS, mean (SD): 3.11 (0.41); PaO_2/FiO_2, LIS, mean (SD): 125.9 (38.6)	Both arms reported multiple trauma, sepsis, aspiration, pancreatitis, multiple transfusions; both groups were roughly balanced as to the predisposing cause	Sepsis in both intervention and control arms; 66% of the study patients developed sepsis
Liu et al,[18] China, single-center	Per Lewis et al[2]: Randomized: 26; 12; 14	73	Per Lewis et al[2]: "Inclusion criteria: 18 to 80 years of age; fulfils the criteria for ARDS according to the AECC (Bernard 1994); ARDS diagnosis within 3 days of admission; fulfils CIRCI diagnosis according to Society of Critical Care Medicine Guidelines 2006"	Unclear	Per Lewis et al[2]: Within 72 hrs after the diagnosis of ARDS: "hydrocortisone 100 mg IV 3 times a day for 7 days" Control group: "normal saline; 0.9% IV 100 mg 3 times a day for 7 days"	Unclear	Unclear	Unclear

TABLE 1 Characteristics of the studies included in the review and meta-analysis (continued from the previous page)

Study	Sample size[a]	Male sex, %	Inclusion criteria	Follow-up	Treatment intervention arm, dose versus treatment control arm, dose	Degree of hypoxemia or lung injury	Reported cause of ARDS	Notable comorbidities
Rezk et al,[17] Kuwait, single-center	27; 18; 9	85.2	Inclusion criteria: 1) fulfilled criteria of ARDS; 2) receiving mechanical ventilation; 3) methylprednisolone started randomly in the first 48 hrs. Exclusion criteria: 1) PaO_2/FIO_2 >200; 2) not receiving mechanical ventilation	Up to 28 days	2:1 randomization protocol, with per-protocol analysis Within 48 hrs after the diagnosis of ARDS Corticosteroid: methylprednisolone; a loading dose of 1 mg/kg, then infusion of 1 mg/kg/d from day 1 to day 14; 0.5 mg/kg/d on days 15 to 21; 0.25 mg/kg/d on days 22 to 25; then 0.125 mg/kg/d from day 26 to day 28 Control group: normal saline administered in the same manner as methylprednisolone	Corticosteroid group: FiO_2, LIS, mean (SD): 91.67 (12.49); PEEP, LIS, mean (SD): 11 (3.14) Control group: FiO_2, LIS, mean (SD): 77.78 (22.79); PEEP, LIS, mean (SD): 8.44 (2.55)	Unclear	Unclear
Zhao et al,[21] China, single-center	Per Lewis et al[2]: Randomized: 53; 24; 29	Unclear	Unclear	Unclear	Within uncertain time after the diagnosis of ARDS Per Lewis et al[2]: "inhaled budesonide 2 mg twice a day for 12 days alongside ARDS management algorithm according to the 2006 Chinese Society for Critical Care Medicine Guidelines" Control group: "ARDS management algorithm according to the 2006 Chinese Society for Critical Care Medicine Guidelines"	Unclear	Unclear	Unclear
Tongyoo et al,[19] Thailand, single-center	197; 98; 99	51.5	Hospitalized patients aged ≥18 y, meeting the criteria for severe sepsis or septic shock, receiving mechanical ventilation for hypoxemic respiratory failure; if, within 12 hrs of the study entry, they met the diagnostic criteria for acute lung injury based on the 2012 Berlin criteria for the diagnosis of ARDS[34]	60 days	Within 12 hrs after the diagnosis of ARDS Hydrocortisone given daily as an intravenous bolus (50 mg in 10 ml of normal saline) every 6 hrs for 7 days Control group: a comparable volume of normal saline on the same time schedule	LIS, mean (SE): 2.2 (0.9) in the hydrocortisone group; 2.2 (1) in the control group PaO_2/FiO_2, mean (SE): 175.4 (6.9) in the hydrocortisone group; 172.4 (6.7) in the control group LIS ranged from 0 to 4; 0.1–2.5 was considered mild lung injury, and >2.5 severe. ARDS was diagnosed based on the 2012 Berlin definition.[34]	Severe sepsis–associated ARDS or septic shock Most patients (n = 135) met the criteria for moderate to severe ARDS	Hypertension, diabetes mellitus, CAD, stroke, CKD, chronic lung disease, cancer/immuno-suppression

TABLE 1 Characteristics of the studies included in the review and meta-analysis (continued from the previous page)

Study	Sample size[a]	Male sex, %	Inclusion criteria	Follow-up	Treatment intervention arm, dose versus treatment control arm, dose	Degree of hypoxemia or lung injury	Reported cause of ARDS	Notable comorbidities
Villar et al,[4] Spain, multicenter	277; 139; 138	68.9	Hospitalized patients aged ≥18 y, intubated and mechanically ventilated, with a history of acute onset of ARDS (defined by the 2012 Berlin criteria[34] as moderate-to-severe ARDS), including patients having an initiating clinical condition (eg, pneumonia, aspiration, inhalation injury, sepsis, trauma, or acute pancreatitis) within 1 week after the known clinical insult, or new or worsening respiratory symptoms; bilateral pulmonary infiltrates on chest imaging (X-ray or CT scan)	60 days	Within 7 days after the onset of ARDS: Dexamethasone at a dose of 20 mg administered intravenously once daily from day 1 to day 5, reduced to a dose of 10 mg once daily from day 6 to day 10 Control group: continued routine intensive care Patients in both groups were ventilated with lung-protective mechanical ventilation.	Treatment group: moderate ($100 < PaO_2/FiO_2 \leq 200$; n = 118); severe ($PaO_2/FiO_2 \leq 100$), n= 21) Control group: moderate ($100 < PaO_2/FiO_2 \leq 200$; n= 121); severe ($PaO_2/FiO_2 \leq 100$; n = 17)	Pneumonia, sepsis, aspiration, trauma, others More than 75% of patients had ARDS associated with pneumonia or sepsis.	Patients with major comorbidities (antibiotic therapy and hemodynamic support) were excluded.

a Data are presented as total number of study patients; number of patients in the intervention arm; number of patients in the control arm

Abbreviations: AECC, American-European Consensus Conference; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; CT, computed tomography; FiO_2, fraction of inspired oxygen; IV, intravenous; LIS, lung injury score; PaO_2, partial oxygen pressure; PEEP, positive end-expiratory pressure

the interaction of steroid therapy timing (Supplementary material, *Figure S2*) showed no difference ($P = 0.13$) for this outcome. An additional subgroup analysis by corticosteroid classes demonstrated that this variable had no impact on mortality ($P = 0.94$).

Duration of mechanical ventilation Five trials (including 645 patients) reported on the duration of mechanical ventilation and showed that the use of corticosteroids reduced ventilation times (MD, −4.93 days; 95% CI, −7.81 to −2.06; $P = 0.0008$; $I^2 = 87\%$; low certainty) (FIGURE 2). The MD was 4.93 fewer days (from 7.81 to 2.06 fewer days) (Supplementary material, *Table S2*).

We performed a sensitivity analysis by excluding studies at high risk of bias,[4,16,20] and the results were robust and consistent (MD, −4.09 days; 95% CI, −7.76 to −0.42; $P = 0.03$; $I^2 = 86\%$). Substantial heterogeneity was identified in the pooled data, and various sensitivity analyses could not explain this based on possible methodological or clinical differences among studies.

Ventilator-free days up to day 28 The 5 trials (including 771 patients) that examined ventilator-free days up to day 28 revealed a significant increase in the mean number of ventilator-free days with corticosteroid treatment (MD, 4.28 days; 95% CI, 2.67–5.88; $P < 0.001$; $I^2 = 21\%$; moderate certainty) (FIGURE 3). The MD was 4.28 (95% CI, 2.67–5.88) more ventilator-free days (Supplementary material, *Table S2*).

We conducted a sensitivity analysis by excluding a study at high risk of bias,[4,17] and found the pooled estimate to be robust and consistent with an MD increase of 4.37 (95% CI, 1.69–7.04; $P = 0.001$). The subgroup test of interaction (Supplementary material, *Figure S3*) of steroid therapy timing showed no difference ($P = 0.94$) for this outcome.

Hyperglycemia In 3 trials (including 565 patients) that reported on hyperglycemia, 229 of 300 patients (76.3%) in the corticosteroid group had hyperglycemia compared with 182 of 265 patients (68.7%) in the control group (RR, 1.12; 95% CI, 1.01–1.24; $P = 0.03$; $I^2 = 0\%$; moderate certainty) (FIGURE 4). The absolute effect was 82 (95% CI, 7–165) more events per 1000 affected individuals (Supplementary material, *Table S2*).

Infections The data on infections, where reported, were unclear and could not be pooled for meaningful interpretation.

Neuromuscular weakness In 2 trials (including 270 patients) that examined neuromuscular weakness, 30 of 151 patients (19.9%) in the corticosteroid group had neuromuscular adverse events compared with 22 of 119 patients (18.5%) in the control group (RR, 1.3; 95% CI, 0.8–2.11; $P = 0.28$; $I^2 = 0\%$; very low certainty) (FIGURE 5). The absolute effect was 55 (95% CI, 37–205) more events per 1000 affected individuals.

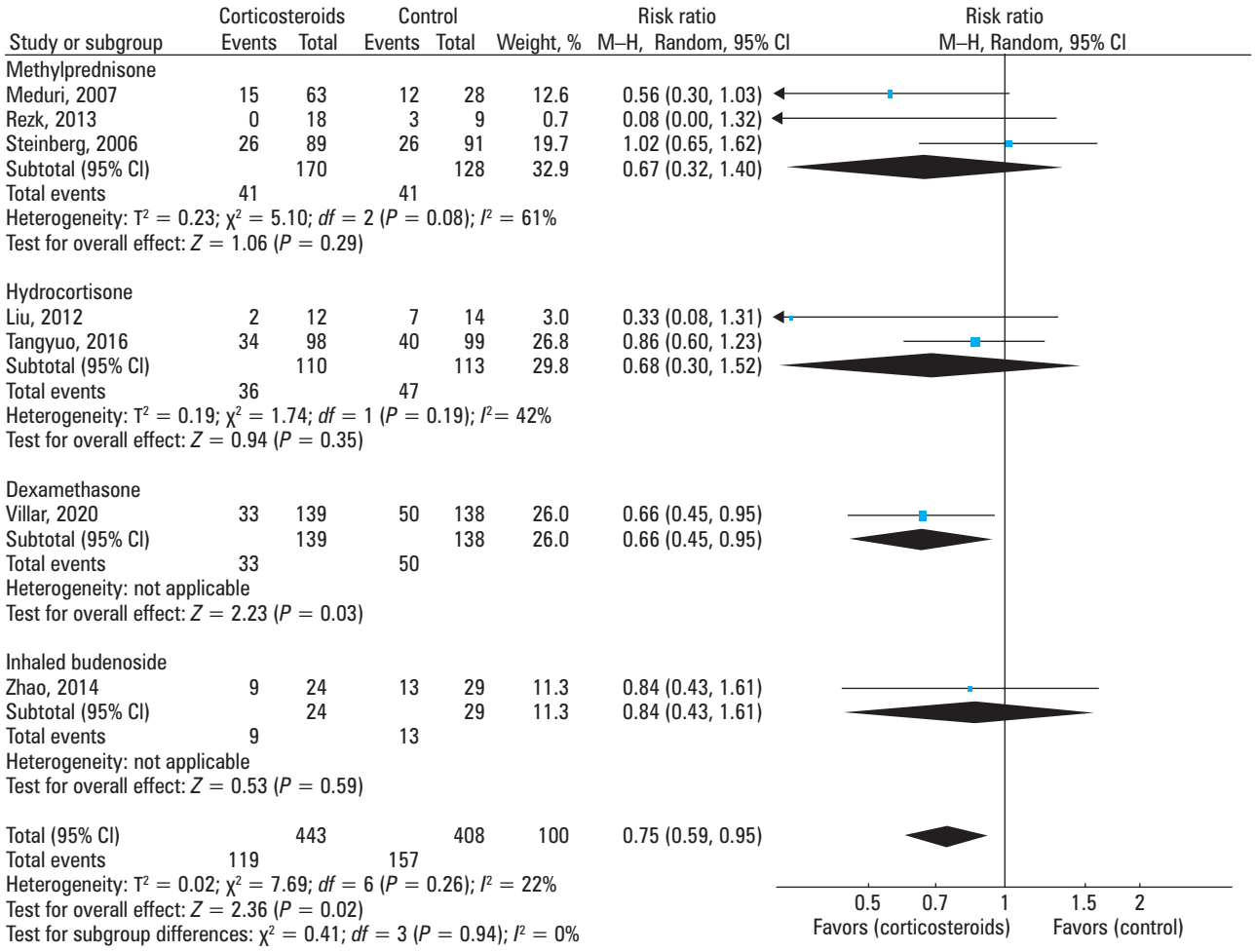

FIGURE 1 Effect of corticosteroids on all-cause mortality

DISCUSSION Our systematic review and meta-analysis examined the effect of corticosteroid use in hospitalized patients with ARDS. We found significantly reduced mortality, shortened mechanical ventilation times, and an increased number of ventilator-free days. However, an increased number of hyperglycemic events was observed, whereas the effect on neuromuscular weakness was uncertain. The previous 2019 Cochrane systematic review[2] reported on low-certainty evidence that corticosteroids may reduce mortality at 3 months after the onset of ARDS, and their 95% CI suggested both an increase and a reduction in the number of deaths. Benefits and adverse effects of mechanical ventilation occurred with similar frequency. However, our improved power and precision found CI boundaries on the benefit side for both mortality and the duration of mechanical ventilation.Despite the significant findings, most of the outcomes were rated down to low or moderate certainty of evidence using the GRADE methods. The GRADE system rates certainty of evidence based on the risk of bias, imprecision, and heterogeneity. The low certainty of evidence implies that one should have low confidence that the effect estimates of an outcome are true for a particular intervention. The low certainty of evidence also suggests that there is a potential for future research to change the effect estimates of an outcome for a particular treatment. The estimates generated in our review were more precise and yielded a significant treatment effect for several outcomes. The moderate certainty of evidence suggests one should have moderate confidence that the direction and magnitude of the effect estimates of an outcome would change significantly with additional research.

Specifically, based on our findings, we have moderate certainty that there is an absolute risk reduction of 9.3% fewer deaths in adults with ARDS treated with corticosteroids (FIGURE 1; Supplementary material, *Table S2*). We also have low certainty that, in this patient population, the duration of in-hospital mechanical ventilation was reduced by approximately 5 days on average (FIGURE 2; Supplementary material, *Table S2*) and moderate certainty that the mean number of ventilator-free days increased by 4 days on average (FIGURE 3; Supplementary material, *Table S2*). The review also found, with moderate certainty, an 8% absolute increase in hyperglycemic adverse events in patients treated with corticosteroids (FIGURE 4; Supplementary material, *Table S2*). However, there was a very low certainty of a plausible yet nonsignificant 5.5% increase in the events of neuromuscular weakness (FIGURE 5;

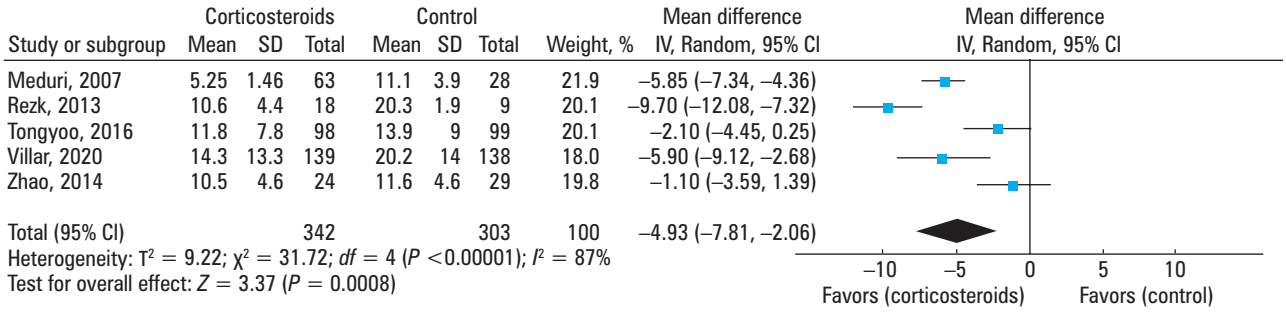

FIGURE 2 Effect of corticosteroids on the duration of mechanical ventilation

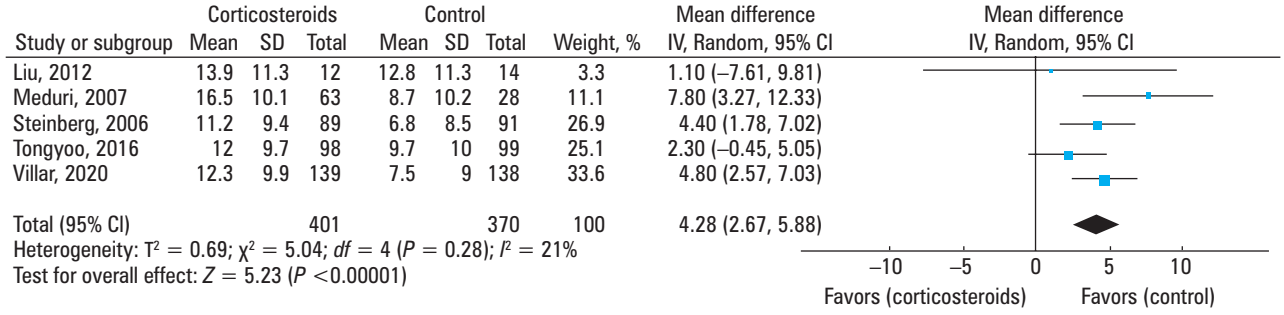

FIGURE 3 Effect of corticosteroids on the number of ventilator-free days (up to 28 days)

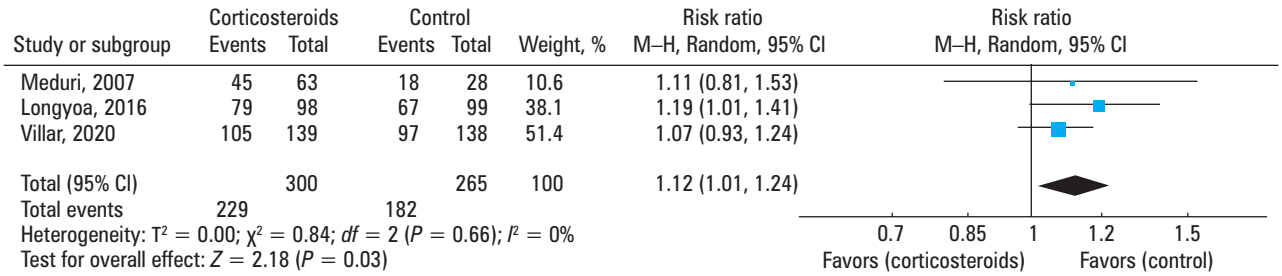

FIGURE 4 Effect of corticosteroids on adverse events and complications (hyperglycemia)

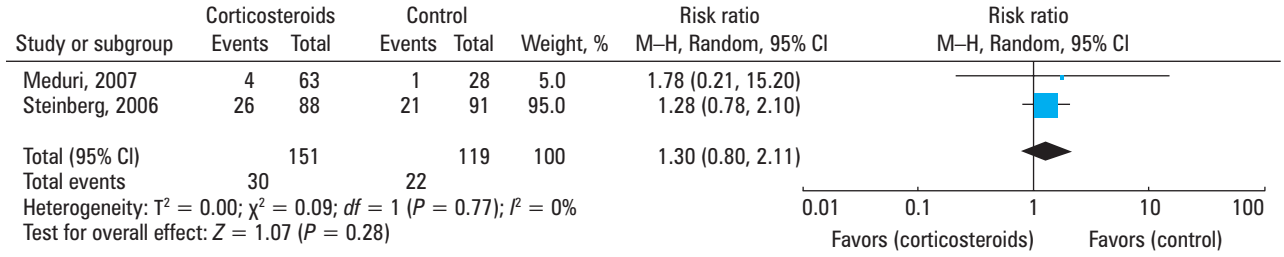

FIGURE 5 Effect of corticosteroids on adverse events and complications (neuromuscular weakness)

Supplementary material, *Table S2*). The timing of corticosteroid therapy may be a factor accounting for its benefits. Our subgroup analysis revealed increased mortality at 60 days with the use of corticosteroids initiated after 14 days from the diagnosis of ARDS or later (RR, 4.35; 95% CI, 1.03–18.39; $P = 0.05$ for therapy initiated later than 14 days after the diagnosis) (Supplementary material, *Figure S4*).

Our study has several strengths. First, we developed explicit eligibility criteria based on the management of patients with ARDS and conducted a comprehensive search of 4 electronic databases. Moreover, we assessed the eligibility of all studies and the risk of bias both in replicate and independently, addressing essential outcomes, and performed several plausible subgroup and sensitivity analyses. In addition, we used the GRADE approach to assess the certainty of evidence. As compared with the previous Cochrane review, we included 7 RCTs (as opposed to 6 included in the Cochrane review), which improved the precision, sample size, and the number of events and led to detecting relevant differences.

This translated to increased confidence in the effect estimates. The results of our sensitivity analysis were robust and consistent, as we excluded studies at high risk of bias. Therefore, we did not rate down for the risk of bias for all-cause mortality, the duration of mechanical ventilation, and the number of ventilator-free days. Additionally, we modified responses in the tool assessing the risk of bias so that it assigned either a "probably no" or "probably yes" response instead of "uncertain." This is in contrast to the Cochrane review, which described the risk of bias as "uncertain" in some studies and, therefore, did rate the high risk of bias for their outcomes; furthermore, the authors did not perform a sensitivity analysis after excluding studies at high risk of bias to assess the robustness of results. We also reported on additional outcomes regarding adverse events, such as hyperglycemia and neuromuscular weakness, which were not covered in the previous review.

Our review also has limitations worth mentioning, which include the use of various corticosteroid agents at different doses, leaving the optimal choice of agents and dosing open to question. Moreover, we could not search the gray literature or conference abstracts for pragmatic reasons and, thus, we may have missed unpublished studies. Furthermore, we noted significant heterogeneity in the pooled estimates of mechanical ventilation times. We could not explain the differences by any methodological or overt clinical heterogeneity between the 5 studies, except for the outlier study by Rezk and Ibrahim,[16] which differed from other studies with regard to numerous outcomes, examined the smallest patient sample, reported on the least duration of mechanical ventilation, and was at high risk of biased estimates. The exploration of heterogeneity was limited due to the suboptimal reporting overall.

Whereas infectious pneumonia is the most common inciting factor leading to ARDS, ARDS is a heterogeneous disease with other possible etiologies including severe sepsis, gastric aspiration, trauma, severe acute pancreatitis, transfusion-associated lung injury, and drug reactions.[1,21] The various etiologies leading to ARDS result in progressive inflammatory damage to the lung tissue. In the acute phase (at 1 day to 6 days), increased interstitial and alveolar edema is observed. In the subacute phase (at 7 to 14 days), there is a proliferation of alveolar epithelial type II cells and fibroblasts, along with collagen deposition. In the chronic phase (after 14 days), fibrosis is intensified and epithelial repair is continued.[21] Corticosteroids may more effectively reduce inflammation occuring in the acute and subacute phases than ameliorate the fibrotic changes in the chronic phase.[6,19,21]

Medical professionals have different opinions regarding the use of corticosteroids for the treatment of ARDS. A 2013 survey of North American intensivists (including 103 responses), which investigated the use of corticosteroids in ARDS, found that responses varied depending on disease severity and etiology: 12% of the respondents acknowledged using corticosteroids "sometimes" or "most always" in ARDS, 22% "sometimes" or "most always" in severe ARDS, and 90% "sometimes" or "most always" in ARDS of unknown etiology.[22] A systematic review of community-acquired pneumonia in hospitalized adults suggests that corticosteroid treatment reduces mortality, the need for mechanical ventilation, and length of hospital stay.[23] The guidelines published by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine suggest, with moderate certainty, using corticosteroids in patients with moderate to severe ARDS within 14 days of disease onset.[24]

The evidence on the use (benefits) of corticosteroids in patients with ARDS is highly ambivalent, complex, and based largely on observational nonrandomized studies. For example, a recently published multicenter retrospective cohort study by Tsai et al,[25] which included intensive care units at medical centers across Taiwan, sought to assess the effectiveness of corticosteroids in patients presenting with influenza-associated ARDS. The study revealed that, among the 241 patients included, those receiving corticosteroids early had a significantly higher in-hospital mortality rate than those who did not (43.5% [37/85] vs 19.2% [30/156]; P <0.001). Early corticosteroid treatment was independently associated with increased in-hospital mortality overall (adjusted odds ratio [OR], 5.02; 95% CI, 2.39–10.54; P <0.001) and in all the examined subgroups. The researchers found that a higher dose and earlier treatment were linked to greater in-hospital mortality. Moreover, they found that earlier treatment was related to a significantly increased OR of subsequent bacteremia (adjusted OR, 2.37; 95% CI, 1.01–5.56).

The study by Tsai et al[25] raises important questions and emphasizes the urgent need for robust comparative research to clarify the issue, since these findings are based on observational evidence, which is confounded by selection bias. This suggests that although estimates may be potentially biased (even when using adjusted analysis estimates), they do underscore the potential adverse events of corticosteroids in the population with influenza-associated ARDS. Similarly, a meta-analysis, which focused on influenza pneumonia and included 10 observational studies (including 6548 patients), revealed an increased mortality risk in patients who received corticosteroids (RR, 1.75; 95% CI, 1.3–2.4; P <0.001).[26]

A retrospective study adjusted for known confounders examined a coronavirus-linked syndrome, the Middle East Respiratory Syndrome (MERS), and showed that corticosteroid use was associated with delayed clearance of the viral RNA without a difference in mortality.[27]

Similarly, Zhou et al[28] carried out a meta-analysis on mortality (including 14 observational studies and 1 RCT, with a total of 6427

patients) and examined the use of corticosteroids in influenza-associated ARDS and severe pneumonia. They found that corticosteroid treatment was associated with significantly higher mortality (OR, 1.53; 95% CI, 1.16–2.01) and incidence of nosocomial infection (OR, 3.15; 95% CI, 1.54–6.45).

Moreover, Baek et al[29] looked at the impact of corticosteroid therapy in the early phase of ARDS by employing a propensity-matched cohort study design. In this Korean study, the researchers compared 404 patients treated with methylprednisolone at a dose of 40 to 180 mg/d or equivalent with 161 patients who did not receive steroids and found that the overall mortality at 28 days did not significantly differ between the corticosteroid-treated and control groups (43.8% vs 41%; $P = 0.54$). At 90 days, the overall mortality rate was higher in the corticosteroid-treated group than in the control group (59.2% vs 48.4%; $P = 0.02$). However, on propensity score matching, corticosteroid therapy was associated with neither a higher 28-day mortality rate (OR, 1.031; 95% CI, 0.657–1.618; $P = 0.895$) nor a higher 90-day mortality rate (OR, 1.435; 95% CI, 0.877–2.348; $P = 0.151$).

Additionally, a recent well-conducted Cochrane review by Lansbury et al,[30] which explored the use of corticosteroids as adjunctive therapy in the treatment of influenza, raised further concerns regarding corticosteroid use in influenza-like diseases. Researchers found increased ORs of mortality (OR, 3.9; 95% CI, 2.31–6.6) and hospital-acquired infection (unadjusted OR, 2.74; 95% CI, 1.51–4.95) in patients treated with corticosteroids.

A very recent study,[31] conducted in a hospital in Wuhan, China, sought to describe the clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) pneumonia who developed ARDS or died. The authors retrospectively examined 201 patients with confirmed COVID-19 pneumonia, who were admitted up to January 26, 2020, with follow-up to mid-February. The median (interquartile range) age was 51 (43–60) years, and 128 patients (63.7%) were men. Eighty-four patients (41.8%) developed ARDS, and 44 (52.4%) of them died. In the 84 individuals who developed ARDS, compared with those who did not, more patients presented with dyspnea (59.5% vs 25.6%, respectively) and had comorbidities such as hypertension (27.4% vs 13.7%, respectively). Moreover, 19% of the patients with ARDS had diabetes compared with 5.1% of those without ARDS. The researchers employed a bivariate Cox regression analysis and found that the risk factors associated with developing ARDS and progressing from ARDS to death included older age (hazard ratio [HR], 3.26; 95% CI, 2.08–5.11 and HR, 6.17; 95% CI, 3.26–11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09–1.19 and HR, 1.08; 95% CI, 1.01–1.17, respectively), and organ dysfunction and coagulation disorder, eg, higher levels of lactate dehydrogenase (HR, 1.61; 95% CI, 1.44–1.79 and HR, 1.3; 95% CI, 1.11–1.52, respectively) and D-dimers (HR, 1.03; 95% CI, 1.01–1.04 and HR, 1.02; 95% CI, 1.01–1.04, respectively). High fever (39 °C) was associated with a higher likelihood of developing ARDS (HR, 1.77; 95% CI, 1.11–2.84) and a lower likelihood of death (HR, 0.41; 95% CI, 0.21–0.82). The researchers also found that the use of methylprednisolone significantly decreased the mortality risk (HR, 0.38; 95% CI, 0.2–0.72), which suggested a potential benefit.

Comparative effectiveness research performed on particular patient populations is urgently required, since the evidence accumulated thus far is weak and, overall, argues against corticosteroids in virus-induced ARDS. We also urge caution in extrapolating the use of corticosteroids to other virus-linked ARDS without additional evidence on this issue. For example, although the use of corticosteroids for COVID-19–induced (caused by the severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) ARDS is controversial, it is estimated that currently approximately 40%–50% of patients with COVID-19 are receiving corticosteroid treatment.[32]

The findings of our systematic review on critically ill patients with ARDS do provide some evidence and show promise for the use of corticosteroids in patients with ARDS. We argue that our review of RCTs strengthened the hypothesis that corticosteroids are beneficial for patients with ARDS. One may also speculate on the evidence being indirect and potentially applicable to COVID-19, but caution is needed here, especially in the context of observational research examining corticosteroids in virus-induced ARDS.

Furthermore, steroid dosing and administration should be critically reviewed, as adverse effects are known to occur with higher doses and prolonged use. This demands urgent, robust, trustworthy, and direct evidence on the effectiveness of corticosteroid use in patients with COVID-19, which would be useful in clinical practice and for public health guidance. We urge caution in interpreting any of these results as directly applicable to patients with COVID-19. Moreover, we are largely dealing with a small number of studies, small sample sizes, and, thus, much uncertainty.

Conclusion In this updated systematic review and meta-analysis of RCTs, we found that the early use of systemic corticosteroids in patients with ARDS may improve mortality, shorten the duration of mechanical ventilation, and reduce the number of ventilator-free days. However, the overall evidence landscape, driven mainly by weaker, nonrandomized observational studies, is very conflicting. Adequately powered, well-designed, and robust RCTs with longer follow-ups and reported adverse effects are needed to confirm or refute the findings of our systematic review. Until then, clinicians may consider the balance between

potential desirable and undesirable effects of corticosteroids when managing patients with ARDS. Caution is urged with regard to potential harms of corticosteroid use and, particularly, in extrapolating these findings beyond patients with ARDS included in this analysis. Specifically, careful reflection is needed when considering the use of corticosteroids in COVID-19 although observational evidence suggests its benefits. Such nonrandomized evidence is plagued by confounders.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

NOTE The authors work on guideline development as well as are members of the GRADE Working Group. Whereas global experts have been acknowledged due to their invaluable input, the views, opinions, and discussion are solely attributable to the principle author and the senior author.

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CONTRIBUTION STATEMENT MJM, WA, and PEA contributed to study design, performed statistical analyses, and interpreted the data. MJM, KA, and PEA abstracted data and assessed the risk of bias. All authors participated in drafting the manuscript and approved its final version.

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