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SYSTEMATIC REVIEW

Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis

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Abstract

Purpose: Corticosteroids are now recommended for patients with severe COVID-19 including those with COVID-related ARDS. This has generated renewed interest regarding whether corticosteroids should be used in non-COVID ARDS as well. The objective of this study was to summarize all RCTs examining the use of corticosteroids in ARDS.

Methods: The protocol of this study was pre-registered on PROSPERO (CRD42020200659). We searched online databases including MEDLINE, EMBASE, CDC library of COVID research, CINAHL, and COCHRANE. We included RCTs that compared the effect of corticosteroids to placebo or usual care in adult patients with ARDS, including patients with COVID-19. Three reviewers abstracted data independently and in duplicate using a pre-specified standardized form. We assessed individual study risk of bias using the revised Cochrane ROB-2 tool and rated certainty in outcomes using GRADE methodology. We pooled data using a random effects model. The main outcome for this review was 28-day-mortality.

Results: We included 18 RCTs enrolling 2826 patients. The use of corticosteroids probably reduced mortality in patients with ARDS of any etiology (2740 patients in 16 trials, RR 0.82, 95% CI 0.72–0.95, ARR 8.0%, 95% CI 2.2–12.5%, moderate certainty). Patients who received a longer course of corticosteroids (over 7 days) had higher rates of survival compared to a shorter course.

Conclusion: The use of corticosteroids probably reduces mortality in patients with ARDS. This effect was consistent between patients with COVID-19 and non-COVID-19 ARDS, corticosteroid types, and dosage.

Keywords: Corticosteroids, ARDS, COVID-19, Mechanical ventilation

Introduction

The role of corticosteroids in acute respiratory distress syndrome (ARDS) remains controversial [1]. Although there are a number of randomized control trials (RCTs) [2, 3] that have shown benefit of corticosteroids in ARDS,

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practice remains variable [1]. Also, observational data, although limited by confounding and imbalances in baseline characteristics, suggest that in certain subtypes of ARDS, such as viral ARDS caused by influenza, corticosteroids may be associated with increased mortality [4]. Furthermore, short-term steroid use has been associated with opportunistic infections, even in immunocompetent hosts [5, 6]. Ongoing questions related to optimal dosage, duration, initiation of treatment, and type of corticosteroids likely also contribute variation in use.

The emergence of data suggesting corticosteroids improve survival in severe coronavirus disease 2019 (COVID-19) has led to renewed interest in the overall effects of corticosteroids in ARDS [7]. Pooled results from recent RCTs in critically ill patients with COVID-19 show a reduction in mortality with the use of systemic corticosteroids (odds ratio [OR] 0.66, 95% confidence interval [CI] 0.53–0.82) [7]. These results informed a WHO clinical practice guideline which provided a strong recommendation for corticosteroids in patients with severe COVID-19 [8]. This new evidence has led experts to hypothesize that the results of these COVID studies may be generalizable to ARDS of non-COVID etiology [1]. Given that all ARDS is in part a result of a hyperinflammatory response to a direct injury [9], data derived from COVID-19 studies may also inform the care of non-COVID ARDS patients.

The objective of this systematic review and meta-analysis was to summarize the RCT data examining the use of corticosteroids in ARDS of any cause. We hypothesized that corticosteroid administration would be beneficial in all patients with ARDS regardless of cause. In addition, we examined whether the effects of corticosteroids are consistent across COVID-19 and non-COVID 19 ARDS, corticosteroid dosing regimes, time of corticosteroid initiation, duration of therapy and amongst different types of corticosteroid molecules.

Methods

Protocol and registration

The protocol of this study was pre-registered on PROSPERO (CRD42020200659) and findings are reported using the PRISMA checklist (e-Table 1).

Search and information sources

Authors of this manuscript (MJM, PE, WA, BR, ZY, LCL, FL) have previously published three systematic reviews addressing a similar clinical question [4, 10, 11]. We made sure to incorporate all the eligible studies from these systematic reviews as part of our analysis and then proceeded to update the previous searches from February 15, 2020 to September 6, 2020.

Take-home message

Corticosteroids probably reduce mortality and duration of mechanical ventilation and these results were consistent in both COVID and non-COVID ARDS. Corticosteroids should likely be used in most patients with ARDS, regardless of etiology.

For the update, we performed a comprehensive search of relevant databases (MEDLINE, EMBASE, Centre for Disease Control (CDC) library of COVID research, CINAHL and COCHRANE centre for trials). We limited our search to humans, but included any language. A copy of our search strategy can be found in our online Supplementary Materials. We screened reference lists of relevant systematic reviews and meta-analysis and also contacted experts in the field to ensure we were not missing any additional articles.

Study selection

We screened all citations in duplicate (DC, SS) in two stages. First, we screened titles and abstracts, and then for any citation selected in this first stage, we screened the full texts. We captured reasons for exclusion during full text review. A third reviewer (BR) adjudicated disagreements, when necessary.

Eligibility criteria

We included RCTs that compared corticosteroids to placebo or usual care in adult patients with ARDS (as defined by the American-European Consensus Conference (AECC) criteria [12] or the Berlin criteria for ARDS [13]). As some of the potentially eligible studies were not explicit about ARDS diagnosis, we made the decision to include studies of COVID-19 patients if they were receiving mechanical ventilation, as these were felt to most likely represent a population or subpopulation consistent with ARDS. We excluded case series, case studies, cohort studies, case reports and other observational studies. We focused on the following outcomes of interest: mortality (if multiple time points were provided, we chose the time point closest to 28 day mortality), duration of mechanical ventilation, intensive care unit (ICU) length of stay, hospital length of stay, incidence of opportunistic infections (as defined by the study authors), muscle weakness (as defined by the study authors), gastrointestinal bleeding and hyperglycemia (both as defined by study authors).

Data collection process and data items

Three reviewers (DC, AK, KS) abstracted data independently and in duplicate using a pre-specified standardized data abstraction form. A fourth reviewer (BR)

adjudicated disagreements. We collected data on trial characteristics, demographic data, intervention and control procedures, and outcomes of interest. In the case of missing data, we contacted the study authors.

Risk of bias assessment in individual studies

We assessed risk of bias independently and in duplicate using the Cochrane Risk of Bias 2.0 tool for RCTs. We used the tool to assess for risk of bias (ROB) in the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We rated each domain as "low", "some concerns" or "high". We determined overall ROB for each trial based on the highest risk attributed to any one domain. We assessed certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [14]. In keeping with GRADE methods, we use terminology consistent with the overall certainty of evidence. This includes stronger language for high certainty evidence, and less certain language ('probably' or 'may') for moderate or low certainty evidence.

Summary measures and synthesis of results

We used the DerSimonnian–Laird random effects model with inverse-variance weighting to generate pooled treatment effects across studies. We assessed heterogeneity between trials using a combination of the Chi^2 test, the I^2 statistic, and visual inspection of the forest plots. We present results of dichotomous outcomes using relative risk (RR) and continuous outcomes as mean difference (MD), both with 95% confidence intervals (CIs). We have also provided absolute differences with 95% CIs which we used for GRADE ratings. If medians and interquartile ranges (IQR) were reported instead of mean and standard deviation (SD), we assumed normality in data distribution and converted IQR to SDs by dividing the IQR by 1.35 [15].

Subgroup analysis and trial sequential analysis (TSA)

We considered a number of a priori subgroup analyses for the outcome of mortality, including: type of corticosteroid used (methylprednisolone vs dexamethasone vs hydrocortisone), timing of corticosteroid initiation after diagnosis of ARDS (early $\leq$ 72 h vs late corticosteroid initiation > 72 h), protocolize duration of corticosteroid therapy ($\leq$ 7 vs > 7 days), corticosteroid dose (below median daily dose (< 88 mg/day of methylprednisolone equivalent) used in included trials vs above median daily dose used in included trials), ARDS etiology (COVID-19 ARDS vs. non COVID-19 ARDS), and ROB (high ROB studies vs low ROB). For ROB, all studies deemed at high ROB or having some concerns regarding ROB were analyzed as part of the high ROB subgroup, with the remainder being analyzed as part of the low ROB subgroup. We also performed three post-hoc subgroup analyses which were requested by peer reviewers: (1) studies published before 2015 as compared to those published on or after 2015, examining the impact in care evolution (such increased use of low tidal volume ventilation); (2) studies that had a placebo arm as compared to those that used standard or usual care and (3) studies that included patients who met formal ARDS criteria as per AECC or Berlin and studies that did not.

For all subgroup analysis, if the p value for the Chi-squared test was < 0.05, we used the ICEMAN tool [16] to assess for credible subgroup effects. This tool considers factors such as the following: whether effect modification is based on comparisons within rather than between trials; whether the effect modification was correctly hypothesized a priori; whether the effect modification was supported by prior evidence; how many subgroups were investigated; and whether random or fixed effects model were used. In all other cases, we assumed that the subgroup differences are not important enough in influence to change our conclusions regarding the effect size or are due to chance.

Additionally, we performed meta-regression subgroup analysis assessing whether dose of corticosteroid (as a continuous variable) had an effect on 28-day mortality. For this analysis, we used methylprednisone dose (mg/d) or equivalent, excluding the loading dose in studies that gave a larger initial day 1 corticosteroid dose. We hypothesized that there would be no significant difference between corticosteroid types, that early corticosteroid initiation would be more beneficial than late corticosteroid initiation, longer duration corticosteroid therapy would be more beneficial than shorter duration corticosteroid therapy, low-dose corticosteroid use would be superior to moderate–high dose corticosteroid use, that there would be no difference in effect between COVID-19 patients with ARDS and non COVID-19 patients with ARDS, and that studies with high ROB would show greater benefit with corticosteroids than low ROB studies. We also hypothesized that there would be no difference in studies conducted before and after 2015 or in studies that included formal ARDS criteria versus those that did not and that studies with a placebo would show a smaller effect than studies used usual care as comparator. Finally, we conducted sensitivity analyses excluding studies that reported mortality at endpoints other than 28 days and two additional posthoc sensitivity analyses requested by peer review excluding studies that did not explicitly have ARDS as part of their inclusion criteria and studies that initiated corticosteroids late.

We conducted TSA [17] using the random effects model for trials reporting mortality. For the TSA, we used a statistical significance level of 5%, a power of 80%, and a relative risk reduction (RRR) of 15% to represent a clinically important difference. Given the 20% risk of a false negative result with the first TSA, and at the request of peer reviewers, we also conducted a second posthoc sensitivity analysis TSA using a power of 90%. We performed TSA analysis using Trial Sequential Analysis version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, www.ctu.dk/tsa). For all other statistical analysis, we used RevMan 5.3 (Cochrane Collaboration, Oxford) software.

Results

We included six RCTs ($n=833$) from previously published meta-analyses [4, 10] addressing the topic [3, 18–22]. The updated search found 759 new citations, from which we included 12 additional RCTs ($n=1993$) [7, 23–29] (e-Fig. 1) for a total of 18 RCTs ($n=2826$) that met eligibility criteria. A recent meta-analysis published in JAMA [4] included seven RCTs examining the role of corticosteroids in patients with COVID-19. As not all of these patients were mechanically ventilated or had ARDS, we used data only from the subgroup of patients that received invasive mechanical ventilation (eFigure 1 from the JAMA report) or when not available, contacted individual trial authors for these subgroup results.

Table 1 shows characteristics of all included RCTs which randomized between 11 and 1007 patients. Five studies were conducted in the USA [18, 21, 23, 30], four in China [7, 22, 25, 26], two in Spain [3, 7], two in France [24], two in the UK [29], two in Brazil [27, 28], and one each in Denmark [7], Kuwait [20], Thailand [19], Australia [30], Canada [30], Ireland [30], the Netherlands [30], and New Zealand [30]. All patients included in the review were invasively ventilated, 12 of the RCTs included 1403 patients with AECC or Berlin-criteria ARDS [3, 7, 18–27], and 6 included 1423 patients with COVID-19 [7, 28, 29]. Additionally, while most non COVID-19 studies provided a breakdown of ARDS etiologies in their demographics, they did not provide outcome-based subgroup data based on specific aetiologies. Six trials used hydrocortisone [7, 19, 22, 24], eight used methylprednisolone [18, 20, 21, 23, 25, 26, 28], and four used dexamethasone [3, 7, 27, 29]. Two of the RCTs [21, 23] initiated corticosteroids late in the course of ARDS (defined as 1 week after diagnosis), whereas the other 16 RCTs initiated corticosteroids within the first week of diagnosis. Eight of the trials provided 7 days or less of corticosteroid therapy [7, 19, 22, 24–26, 28], while the rest provided 10 days or more. The median dose of corticosteroid used was 88 mg of methylprednisolone (equivalent to 400 mg of hydrocortisone) per day and seven of the included trials used a dose less than this [7, 19, 22, 24–26, 28, 29], while the other 11 used a dose higher than 88 mg. The lowest daily dose used was 30 mg of methylprednisolone [28, 29] while the highest was 120 mg of methylprednisolone [21, 23, 25, 26]. 10 RCTs administered a placebo to their control group [7, 18–24, 28] while the remainder only provided standard care.

We judged three RCTs to be at high ROB, one due to concerns regarding randomization and selection of the reported results [20] and another two due to incomplete reporting regarding randomization, descriptions of interventions, and selection of the reported results [25, 26]. The remainder of the trials were judged either at low ROB or some concern. e-Table 2 summarizes the ROB for each individual trial for the outcome of mortality. Table 2 and e-Table 3 depict the pooled outcomes with associated GRADE certainty of evidence.

Corticosteroids probably reduce 28-day mortality in patients with ARDS (2740 patients in 16 trials, RR 0.82, 95% CI 0.72–0.95, random effects model, absolute risk reduction (ARR) 8.0%, 95% CI 2.2–12.5% reduction, number needed to treat (NNT) 12.5, 95% CI 8.0–45.5, moderate certainty, Fig. 1). Both the initial TSA and posthoc TSA were consistent in that they showed that the optimal information size was not reached ($n=4690$, 80% power; $n=6275$, 90% power, Supplementary Materials). We rated this outcome down once due to a combination of borderline indirectness as eight of the studies included mechanically ventilated patients with COVID-19 respiratory failure, which were not explicitly defined as ARDS, and for borderline imprecision as although the 95% confidence interval only included benefit with corticosteroids, the optimal information size based on TSA was not met. When including trials that only enrolled patients meeting formal AECC/Berlin ARDS criteria, this conclusion and certainty of evidence did not change (1317 patients in 10 trials, RR 0.77, 95% CI 0.63–0.94, ARR 10.7%, 95% CI 2.8–17.3% reduction, NNT 9.3, 95% CI 5.8–35.7, moderate certainty, Fig. 2). Subgroup analysis based on COVID-19 status (Fig. 1), steroid type (e-Fig. 2), steroid initiation time (e-Fig. 3), steroid dosage (e-Fig. 4), and ROB (e-Fig. 5) did not demonstrate any credible subgroup effects. Meta-regression based on dosage of steroid as a continuous variable also showed no subgroup effect ($p=0.41$, e-Fig. 6). Patients who received a longer course of corticosteroids (over 7 days) had higher rates of survival than those who received a shorter course (7 days or less) (p-value for subgroup interaction $=0.04$, moderate credibility) (Fig. 3). We performed sensitivity analyses excluding the five studies that reported a mortality endpoint other than at 28 days [3, 20, 21, 23, 30] (e-Fig. 7),

Table 1 Characteristics of included studies

Author, date, single vs multi-center, location	Total number of patients (*n*)	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Steinberg et al. 2006; multi-center; USA [21]	180	Adult patients (intubated and receiving mechanical ventilation; 7 to 28 days after onset of ARDS, on day of study entry PaO_2/FiO_2 had to be < 200 mmHg *Age (mean, SD), Gender (Female)*: Placebo: 49.2, 16.5; Methyl prednisone: 49.0, 19.0; 82/180	Trauma 23/180 Sepsis36/180 Multiple transfusions 2/180 Aspiration 30/180 Pneumonia 68/180 other 20/180	Methylprednisolone sodium succinate diluted in 50 mL of 5% dextrose in water; single IV dose of 2 mg/kg of PBW; followed by 0.5 mg/kg of PBW every 6 h for 14 days; then dose of 0.5 mg/kg of PBW every 12 h for 7 days, then tapering of dose	*Primary outcome*: Overall mortality at 60 days post enrollment *Secondary outcomes*: Ventilator-free days; early mortality; length of ICU stay; length of hospital stay; days of mechanical ventilation; neuromuscular weakness; superinfection
Meduri et al. 2007; multi-center; USA [18]	91	Adult patients receiving mechanical ventilation; meeting criteria for ARDS according to AECC (Bernard et al. [12]); within 72 h *Age (mean, SD), Gender (Female)*: Placebo: 53.2, 15.3, Methyl prednisone: 50.1, 15.3, 44/91	Pneumonia 38/91 Aspiration of gastric content 18/91 Sepsis 15/91 other 20/91	Methylprednisolone; loading dose of 1 mg/kg, followed by infusion of 1 mg/kg/day from day 1 to day 14; 0.5 mg/kg/day on days 15 to day 21; 0.25 mg/kg/day on days 22 to day 25; then 0.125 mg/kg/day from day 26 to day 28	*Primary outcomes*: 1-point reduction in LIS score or successful extubation by day 7 *Secondary outcomes*: Early mortality; ICU mortality; hospital mortality; length of ICU stay; length of hospital stay; days of mechanical ventilation; hyperglycemia; neuromuscular weakness; infection
Liu et al. 2012; single center; China [22]	26	Adults 18 to 80 years of age; fulfils criteria of ARDS according to the AECC (Bernard et al. [12]); ARDS diagnosis within 3 days of admission; fulfils CIRCI diagnosis according to Society of Critical Care Medicine of PLAs Guidelines 2006 *Age (mean, SD), Gender (Female)*: Placebo: 55.9, 15.3, Corticosteroids: 69.8, 14.9; 7/26	Pneumonia 11/26 Trauma 2/26 other organs infection 7/26 severe pancreatitis 3/26 other 3/26	Stress dose glucocorticoid; hydrocortisone 100 mg IV 3 times a day for 7 days	*Primary outcome*: Overall mortality day 28 *Secondary outcomes*: Length of ICU stay
Rezk,and Ibrahim 2013; single center; Kuwait [20]	27	Patients receiving mechanical ventilation; meeting ARDS criteria (AECC, Bernard et al. 1994) [12]; within 48 h *Age (mean, SD), Gender (Female)*: Placebo: 50.44, 13.99, Corticosteroids: 42.67, 13.95; 4/27	Trauma 8/27 hospital-acquired pneumonia 11/27 community-acquired pneumonia 8/27	Methylprednisolone; loading dose of 1 mg/kg followed by infusion of 1 mg/kg/day on days 1 to 14, 0.5 mg/kg/day from day 15 to day 21, 0.25 mg/kg/day from day 22 to day 25, 0.125 mg/kg/day from day 26 to day 28	*Primary outcome*: Mortality at day 14 *Secondary outcomes*: Days of mechanical ventilation

Table 1 (continued)

Author, date, single vs multi-center, location	Total number of patients (*n*)	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Tongyoo et al. 2016; single center; Thailand [19]	104	Patients 18 years or older; with severe sepsis or septic shock; mechanical ventilation; within 12 h of study entry; meeting criteria for ARDS (AECC definition, Bernard et al. 1994) [12] *Age (mean, SD), Gender (Female)*: Placebo: 64.3, 16.0; Corticosteroids: 64.5, 17.3; 92/197	NR	Hydrocortisone; IV bolus, 50 mg in 10 mL of normal saline, every 6 h for 7 days	*Primary outcome*: Secondary outcomesverall mortality at day 28 *Secondary outcome*: Survival without organ support on day 28; days of mechanical ventilation until day 28; mortality at day 60; hyperglycemia; GI bleed; infection
Villar et al. 2020; multi-center; Spain [3]	277	Patients aged 18 years or older; intubated and mechanically ventilated; had acute onset of ARDS, as defined by the American–European Consensus Conference criteria for ARDS,11 or by the Berlin criteria as moderate-to-severe ARDS,12 which includes having an initiating clinical condition (eg, pneumonia, aspiration, inhalation injury, sepsis, trauma, or acute pancreatitis) within 1 week of the known clinical insult, or new or worsening respiratory symptoms; bilateral pulmonary infiltrates on chest imaging (X-ray or CT scan); absence of left atrial hypertension, pulmonary capillary wedge pressure of less than 18 mmHg, or no clinical signs of left heart failure; and hypoxemia, as defined by a ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO_2/FiO_2) of 200 mmHg or less on positive end-expiratory pressure (PEEP) of 5 cmH_2O or more, regardless of FiO_2 *Age (mean, SD), Gender (Female)*: Placebo: 58, 15; Dexamethasone: 56, 14; 86/277	Pneumonia 96/197 Urinary tract infection 37/197 Skin and soft tissue infection 27/197 Intra-abdominal infection 22/197 Hemoculture-positive 56/197	Dexamethasone plus conventional treatment; Patients in the dexamethasone group received an intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. Treatment with dexamethasone was maintained for a maximum of 10 days after randomization or until extubation (if occurring before day 10)	*Primary outcomes*: Number of ventilator-free days at 28 days, number of days alive and free of mechanical ventilation until day 28 post randomization *Secondary outcomes*: All-cause mortality at 60 days; ICU mortality; Hospital mortality; serious hyperglycemia; superinfection

Table 1 (continued)

Author, date, single vs multi-center, location	Total number of patients (*n*)	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Meduri et al. 1998; multi-center; USA [23]	24	Patients 18 years or older; meeting ARDS criteria (AECC definition, Bernard et al. 1994) [12]; 7 days of mechanical ventilation with an LIS of 2.5 or greater and less than a 1-point reduction from day 1 of ARDS; no evidence of untreated infection *Age (mean, SD), Gender (Female)*: Control: 51, 6.6; Methylprednisolone: 47, 3.9; 15/24	Pneumonia 147/277 Sepsis 67/277 Aspiration 33/277 Trauma 21/277 Others 9/277	Methylprednisolone; loading dose 2 mg/kg for first 14 days, then 1 mg/kg for day 15–21, then 0.5 mg/kg for day 22–28, 0.25 mg/kg for day 28–30 then 0.125 mg/kg for day 31 and 32. If patient extubated before day 14, then therapy advanced directly to day 15	*Primary outcomes*: Improvement in LIS (> 1 point) at 10 days of treatment, ICU survival *Secondary outcomes*: Hospital mortality; days of mechanical ventilation; hyperglycemia; GI bleeds; superinfection
Annane et al. 2006; multi-center; France [24]	177	Selected Septic shock Patients (subgroup of septic shock trial) with septic-shock associated ARDS (AECC definition, Bernard et al. 1994) [12] *Age (mean, SD), Gender (Female)*: Placebo: 59, 18; Steroids: 61, 16; 56/177	Pneumonia 11/24; Aspiration 3/24; Blasto 1/24; Sepsis 5/24; Postoperative 2/24; Drug reaction 2/24	Hydrocortisone 50 mg IV q6h or fludrocortisone 50 ug daily for 7 days	*Primary outcome*: Overall mortality on day 28 *Secondary outcomes*: ICU mortality; hospital mortality; gastrointestinal bleeding; superinfection
Zhou, 2015; single center; China [26]	46	Patients with Severe ARDS (AECC definition, Bernard 1994); SBP 90 mmHg and above; Oxygenation index less than 250 mmHg; Multi-lobe lung lesions; Caused by severe CAP *Age (mean, SD), Gender (Female)*: 50.2, 2.3; 16/46	NR	Methylprednisolone; 120 mg IV daily for 7 days	*Primary outcomes*: Length of hospital stay; Days of mechanical ventilation
Zhifang, 2016; single center; China [25]	40	Patients with ARDS diagnosis based on the Europa League in 1994 (AECC definition, Bernard 1994) [12]; *Age (mean, SD), Gender (Female)*: Control: 55.1, 18.7; Steroids: 53.8, 16.2; 15/40	Pneumonia	Methylprednisolone 1–2 mg/kg for 3–14 days	*Primary outcomes*: Length of ICU stay; days of mechanical ventilation

Table 1 (continued)

Author, date, single vs multi-center, location	Total number of patients (*n*)	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Angus et al. 2020; multi-center; Australia, Canada, France, Ireland, the Netherlands, New Zealand, the United Kingdom, and the United States [30]	403	Patients 18 years or older; presumed or confirmed SARS-CoV-2 infection; ICU for respiratory or cardiovascular organ support *Age (mean, SD), Gender (Female)*: No HC: 59.9, 14.6; Fix Dose HC: 60.4, 11.6; Shock HC: 59.5, 12.7; 111/384	COVID-19	Hydrocortisone; Fixed dose of hydrocortisone 50 mg or 100 mg IV q6h for 7 days; OR Shock-dependent course with hydrocortisone 50 mg IV q6h while in shock for up to 28 days	*Primary outcomes*: Organ-support free days up to 21 days (days alive and free of ICU-based respiratory or cardiovascular support) *Secondary outcomes*: In- Hospital mortality; length of ICU stay; length of hospital stay; composite outcome of progression to invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO) or death among those not ventilated at baseline; WHO ordinal scale (range, 0–8, where 0 = no illness, 1–7 = increasing level of care, and 8 = death) assessed at day 14.19,20
Dequin 2020; multi-center; France [7]	149	Patients at least 18 years admitted to one of the nine participating French ICUs for acute respiratory failure could be included if they had a biologically confirmed (reverse transcriptase–polymerase chain reaction) or suspected (suggestive chest computed tomography scan result in the absence of any other cause of pneumonia) COVID-19 *Age (median, IQR), Gender (Female)*: Placebo 66.3 (53.5–72.7); HC: 63.1 (51.5–70.8); 45/149	COVID-19	IV infusion at 200 mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days. If the patient's respiratory and general status had sufficiently improved by day 4, a short treatment regimen was used (200 mg/d for 4 days, followed by 100 mg/d for 2 days and then 50 mg/d for the next 2 days, for a total of 8 days)	*Primary outcome*: Treatment failure on day 21 (defined as death or persistent dependency on mechanical ventilation/high-flow oxygen therapy) *Secondary Outcomes*: Use of tracheal intubation; Use of prone position; Extracorporeal membrane oxygenation or inhaled nitric oxide; PaO_2:FIO_2 ratio (days 1–7, 14, 21); Proportion of patients with nosocomial infections recorded during the ICU stay up to day 28
Horby, 2020; multi-center; UK [29]	1007	Hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection *Age (mean, SD), Gender (Female)*: Usual Care: 65.8, 15.8; Dex: 66.9, 15.4; 2338/6425	COVID-19	Dexamethasone; 6 mg PO/IV daily for up to 10 days	*Primary outcome*: 28-day all-cause mortality *Secondary outcomes*: Time until hospital discharge; subsequent receipt of invasive mechanical ventilation, ECMO, death

Table 1 (continued)

Author, date, single vs multi-center, location	Total number of patients (*n*)	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Tomazini et al. 2020; multi-center; Brazil [27]	299	Patients at least 18 years old, had confirmed or suspected COVID-19 infection, and were receiving mechanical ventilation within 48 h of meeting criteria for moderate to severe ARDS with PaO_2:FIO_2 of 200 or less *Age (mean, SD), Gender (Female)*: Control: 62.7, 13.1; Dex: 60.1, 15.8; 112/299	COVID-19	Dexamethasone 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge, whichever occurred first	*Primary outcome*: Ventilator-free days during the first 28 days (alive and free of mechanical ventilation) *Secondary Outcomes*: All-cause mortality during 28 days; ICU-free days up to day 28; Mechanical ventilation duration at 28 days; SOFA scores (48 h, 72 h, 7 days)
DEXA-COVID19; multi-center; Spain	19	Patients 18 years or older; Mechanical ventilation; Moderate to severe ARDS per Berlin criteria; Confirmed COVID-19 *Age (median, IQR), Gender (Female)*: Control: 60 (52–69); Dex: 62 (48–68); 6/19	COVID-19	Dexamethasone; 20 mg/d IV for 5 days and then 10 mg/d IV for 5 days	*Primary outcome*: 60-day mortality *Serious adverse Events*: Secondary infections of pneumonia, sepsis, or other similar; Pulmonary Embolism
COVID STEROID; multi-center; Denmark	29	Patients 18 years or older; Oxygen supplementation (≥ 10 L/min) or mechanical ventilation or continuous CPAP; Confirmed COVID-19 *Age (mean, SD), Gender (Female)*: Control: 62 (55–71); HC: 57 (52–75); 6/29	COVID-19	Hydrocortisone 200 mg/d intravenously × 7 d (continuous infusion or bolus injection every 6 h)	*Primary outcome*: Days alive without life-support at 28 days *Secondary outcomes/serious adverse events*: Mortality at 28 days; New episodes of septic shock (Sepsis 3 criteria); Invasive fungal infection; GI bleeding
Steroids-SARI; multi-center; China	47	Patients admitted to ICU; PaO_2:FIO_2 < 200 mmHg on positive pressure ventilation or high-flow nasal canulae > 45 L/min; Confirmed COVID-19 *Age (mean, SD), Gender (Female)*: Control: 62 (54–68); Methylpred: 67 (61–74); 12/47	COVID-19	Methylprednisolone 40 mg IV every 12 h for 5 days	*Primary Outcome*: Lower LIS score at 7d and 14d *Secondary Outcomes*: Mortality at 30 days; Secondary bacterial infections; barotrauma; Severe hyperglycemia; GI bleed requiring transfusion; Acquired weakness

Table 1 (continued)

Author, date, single vs multi-center, location	Total number of patients (*n*)	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Jeronimo et al 2020; single center; Brazil [28]	393	Hospitalized patients were included if they had clinical AND/OR radiological suspicion of COVID-19, aged 18 years or older at the time of inclusion, with $SpO_2 \leq 94\%$ at room air OR in use of supplementary oxygen OR under IMV *Age (mean, SD), Gender (Female)*: Placebo: 57, 15; MP: 54,15; 139/393	COVID-19	Methylprednisolone 0.5 mg/kg × 5 days	*Primary outcome*: 28-day mortality *Secondary outcomes*: early mortality (Days 7 and 14); orotracheal intubation by Day 7; patients with $PaO_2/FiO_2 < 100$ by Day 7

and the two studies that initiated corticosteroids late [21, 23] (e-Fig. 17), none of which substantially altered the pooled estimates or conclusions. None of our post-hoc subgroup analyses showed credible subgroup effects (e-Figs. 15, 16, 19).

Corticosteroid use may reduce ICU mortality (RR 0.61, 95% CI 0.38–0.99, ARR 18.6%, 95% CI 0.5–29.6% reduction, low certainty, e-Fig. 8) and probably reduce hospital mortality (RR 0.67, 95% CI 0.46–0.96, ARR 16.6%, 2.0–27.2% reduction, moderate certainty, e-Fig. 9) in critically ill patients with ARDS. The use of corticosteroids may lead to fewer days of mechanical ventilation (MD 4.04 days fewer, 95% CI 2.53–5.53 days fewer, low certainty, e-Fig. 18) and a shorter hospital length of stay (MD 8.05 days fewer, 95% CI 3.12–12.98 days fewer, low certainty, e-Fig. 10). There was an uncertain effect on ICU length of stay with corticosteroids (MD 0.78 days more, 95% CI 4.11 days more to 5.68 days fewer, very low certainty, e-Fig. 11).

There are unclear differences in rates of neuromuscular weakness (271 patients in 2 trials, RR 0.85, 95% CI 0.62–1.18, e-Fig. 12) and gastrointestinal bleeding (436 patients in 5 trials, RR 1.20, 95% CI 0.43–3.34, e-Fig. 13) with corticosteroids although these were all based on low or very low certainty evidence. There was probably an increase in hyperglycemia (915 patients in six trials, RR 1.11, 95% CI 1.01–1.23, moderate certainty evidence, e-Fig. 14) with corticosteroids; however, this outcome was rated down for indirectness, given the variability in definitions of hyperglycemia used across studies. Superinfections due to corticosteroid use are summarized as in e-Table 4. Since some studies individually counted multiple infections in one individual as separate data points and others did not, we opted not to pool this data. Although we could not pool data for this outcome, and understanding these limitations, it did not appear as though there was any signal for increase in superinfection (221 infections in corticosteroid group, 244 infections in control group).

Discussion

ARDS is in part the result of an innate immune-cell mediated inflammatory response that causes damage to the alveoli of the lung in response to a direct injury [9]. It has long been hypothesized that treatment with corticosteroids, as a potent anti-inflammatory agent, may benefit patients with ARDS, regardless of etiology [21, 23]. The results of our systematic review and meta-analysis is the first to support this hypothesis, indicating that corticosteroids may reduce mortality and the duration of mechanical ventilation in all patients with ARDS. Furthermore, corticosteroids likely cause few side effects, except for an increase in hyperglycemia. This effect on mortality appears to be consistent across COVID-19

Table 2 Summary of findings table

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
16[a]	Randomised trials	Not serious	Not serious[b]	Borderline serious[v]	Borderline serious[w]	None	437/1220 (35.8%)	678/1520 (44.6%)	RR 0.82 (0.72 to 0.95)	80 fewer per 1000 (from 125 to 22 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL[x]
Mortality (Strict AECC/Berlin criteria only)												
10[z]	Randomised trials	Not serious	Not serious	Not serious	Serious[w]	None	244/678 (36.0%)	298/639 (46.6%)	RR 0.77 (0.63 to 0.94)	107 fewer per 1000 (from 173 to 28 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL[x]
Mechanical ventilation												
9[c]	Randomised trials	Serious[d]	Not serious[e]	Serious[v]	Not serious	None	614	633	–	MD 4.04 lower (5.53 lower to 2.53 lower)	⊕⊕◯◯ LOW	CRITICAL[x]
Length of ICU stay												
4[h]	Randomised trials	Serious[i]	Serious[j]	Serious[v]	Serious [k]	None	184	153	–	MD 0.78 higher (4.11 lower to 5.68 higher)	⊕◯◯◯ VERY LOW	IMPORTANT[y]
Length of Hospital stay												
4[l]	Randomised trials	Serious[m]	Not serious[e]	Serious[v]	Not serious	None	188	156	–	MD 8.05 lower (12.98 lower to 3.12 lower)	⊕⊕◯◯ LOW	IMPORTANT[y]
Neuromuscular weakness												
2[n]	Randomised trials	Not serious	Serious[o]	Serious[v]	serious [k]	None	41/152 (27.0%)	46/119 (38.7%)	RR 0.85 (0.62 to 1.18)	58 fewer per 1000 (from 147 fewer to 70 more)	⊕◯◯◯ VERY LOW	IMPORTANT[y]
Gastrointestinal bleeding												
5[p]	Randomised trials	Not serious	Not serious	Serious[v]	Serious [k]	None	9/217 (4.1%)	7/219 (3.2%)	RR 1.20 (0.43 to 3.34)	6 more per 1000 (from 18 fewer to 75 more)	⊕⊕◯◯ LOW	IMPORTANT[y]

Table 2 (continued)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
Serious hyperglycemia												
6[s]	Randomised trials	Not serious	Not serious	Serious[t,v]	Not serious	None	282/480 (58.8%)	229/435 (52.6%)	RR 1.11 (1.01 to 1.23)	58 more per 1000 (from 5 to 121 more)	⨁⨁⨁◯ MODERATE	IMPORTANT[y]

CI Confidence interval, *RR* Risk ratio, *MD* Mean difference

Question: Corticosteroids compared to control for Acute Respiratory Distress Syndrome

Setting: ICU

Explanations

[a] Annane et al. [24], Liu et al. [22], Meduri et al. [23], [18], Rezk and Ibrahim [20], Steinberg et al. [21], Tongyoo et al. [19], Villar et al. [3], COVID STEROID 2020 [7], DEXA-COVID19 [7], Horby [29], Jeronimo et al. [28], Tomazini et al. [27], Steroids-SARI [7], Dequin [7], Derek [7}

[b] Isquared is mildly high, however, however, the majority of studies favour corticosteroids with only two very small unpublished studies showing a non-significant benefit with placebo

[c] Meduri et al. [18], Rezk and Ibrahim [20], Steinberg et al. [21], Tongyoo et al. [19], Villar et al. [3], Tomazini et al. [27], Zhifang [25], Zhou [26], Steroids-SARI [7]

[d] Of the 10 included studies, three are at high risk of bias (Rezk and Ibrahim [20], Zhou [26], Zhi-fang [25] and one has some concerns (Steroids-SARI [7])

[e] High isquared, however, all studies favour corticosteroids

[h] Liu et al. [22], Meduri et al. [18], Steinberg et al. [21], Zhi-fang [25]

[i] Out of the four included studies, one had high risk of bias (Zhi-fang [25]) and the other had some concerns (Liu et al. [22])

[j] High isqaured with variable effects across studies

[k] Wide confidence intervals that do not exclude serious benefit or harm

[l] Meduri et al. [18], Steinberg et al. [21], Zhou [26], Steroids-SARI [7]

[m] Out of the 4 included studies, one had high risk of bias (Zhou 2014) and two had some concerns (Steroids-SARI [7])

[n] Meduri et al. [18], Steinberg et al. [21]

[o] Low isquared, however variable effects across studies

[p] Annane et al. [24], Meduri et al. [23], Tongyoo et al. [19], COVID-STEROID [7], Steroids-SARI [7]

[q] Annane et al. [24], Liu et al. [22], Meduri et al. [23], Meduri et al. [18], Rezk and Ibrahim [20], Steinberg et al. [21], Tongyoo et al. [19], Villar et al. [3], COVID STEROID [7], Tomazini et al. [27]

[r] Different studies measured superinfection differently

[s] Meduri et al. [23], [18], Tongyoo et al. [19], Villar et al. [3], Tomazini et al. [27], Steroids-SARI [7]

[t] Defined differently across studies. Meduri et al. [18] defined as requiring insulin, whereas other studies had different glucose cutoffs (150 vs. 180 mg/dl)

[u] Wide confidence interval doesn't exclude no effect

[v] Not all included studies had ARDS as inclusion criteria (COVID-19 studies, Annane et al. [24]). However, we did not downgrade one whole level because there was no subgroup differences and effect sizes were similar between studies that strictly defined ARDS and studies that did not

[w] Optimal information size not reached by TSA

[x] Rated as critically important from patient perspective

[y] Rated as important from patient perspective

[z] Annane et al. [24], Liu et al. [22], Meduri et al. [23], Meduri et al. [18], Rezk and Ibrahim [20], Steinberg et al. [21], Tongyoo et al. [19], Villar et al. [3], DEXA-COVID19 2020, Tomazini et al. [27]

ARDS (regardless of strict ARDS criterion) and non-COVID-19 patients, and between corticosteroid type, timing and dose, although a longer duration of therapy may be more beneficial compared to a shorter course. Given the consistency of the results between ARDS etiology, this analysis supports the hypothesis that corticosteroids should be considered in all patients with ARDS, assuming no contraindications.

The 2017 SCCM and ESICM guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients [31] made a conditional recommendation for corticosteroid use in patients with ARDS and a PaO_2/FiO_2 ratio < 200. Prior meta-analyses examining this topic [4, 10, 32] have also demonstrated a consistent finding of decreased mortality and decreased duration of mechanical ventilation with corticosteroid when used in patients with ARDS. Now with the addition of COVID-19 RCTs, estimates of effect in ARDS are more precise and based on a larger number of patients. In addition, more comprehensive subgroup analyses are possible in order to address lingering questions regarding populations of interest and optimal steroid administration regimes. Unfortunately, while no definitive conclusions could be made, this meta-analysis did indicate that longer duration corticosteroids may be more beneficial than a shorter course. Furthermore, while we cannot comment on late administration of corticosteroids given that almost all our included RCTs initiated corticosteroids within the first week of ARDS diagnosis, starting corticosteroids more than 2 weeks after ARDS diagnosis may be harmful, as illustrated by Steinberg et al. [21] as the exudative/inflammatory phase of ARDS has passed. Given the findings of this updated review, clinical practice guidelines addressing ARDS, including the SCCM/ESICM CIRCI guideline, will need to be re-evaluated. Despite the increased clarity, residual questions remain regarding the most beneficial corticosteroid regime. In addition, limitations of trial level data do not allow for a more granular assessment beyond considering single subgroups at once when it is possible that multiple variables could explain the differences or lack of differences in effect sizes. Conducting an individual patient level meta-analysis may allow for a more comprehensive exploration of these subgroups of interest. Specific factors affecting the response to corticosteroid treatment in patients with ARDS were the subject of a recent review addressing the role of dosage, timing of initiation, mode of administration, duration, and tapering in achieving optimal response to corticosteroid treatment in ARDS [33].

Recent RCTs examining the treatment of COVID-19 respiratory failure have shown consistent benefit with corticosteroids, especially in the critically ill [7]. This has led to multiple clinical practice guidelines strongly recommending the use of corticosteroids for the treatment of critically ill COVID-19 patients, including those on mechanical ventilation [8, 34]. Although still relatively early in our understanding of COVID-19 ARDS, most treatment regimes for COVID-induced ARDS mimic those of non-COVID-ARDS including low tidal volumes, optimal positive end expiratory pressure (PEEP), and prone positioning for severe cases [35]. The results of this review further demonstrate the consistency of ARDS when it comes to treatment. While six of the included trials did not include patients who met Berlin/AECC criteria for ARDS, the similarity of treatment effect and lack of subgroup differences between studies that meet strict criteria and studies that do not suggest that patients in all these studies can be treated similarly in the context of corticosteroids. Furthermore, given the somewhat arbitrary and imprecise nature of the AECC/Berlin criteria [36], our study suggests that following the strict definition criteria itself to inform treatment with corticosteroids of patients with ARDS may miss patients who may benefit from this therapy. Additionally, we have demonstrated that corticosteroids have very similar effects on mortality in both the COVID-19 ARDS subgroup (RR 0.89, 95% CI 0.76–1.05) and the non-COVID-19 ARDS (RR 0.70, 95% 0.55–0.89). This consistency suggests that COVID-19 ARDS may be treated similarly to non-COVID-19 ARDS when it comes to corticosteroids.

This is the largest and most comprehensive meta-analysis to date examining corticosteroids in ARDS of any cause. Furthermore, unlike previous meta-analyses [4, 10, 11], this is the only review to combine both COVID − ARDS and COVID + ARDS patients in the same meta-analysis. Strengths of this review include the comprehensive search, pre-registration of the protocol, careful evaluation of subgroups of interest including COVID-19 versus non-COVID, and including meta-regression to evaluate the impact of corticosteroid dose, assessment of ROB using Cochrane 2.0, TSA and certainty of evidence using the GRADE approach. This review also has limitations. First, as mentioned above, while most studies included patients with ARDS as defined by the AECC [12] or Berlin criteria [13], 6 RCTs of COVID did not strictly enroll patients with ARDS as per Berlin. Given that patients with COVID-19 respiratory failure significant enough to require invasive mechanical ventilation usually present with bilateral infiltrates [37], we felt that this population was similar enough to the ARDS population to be included. It is possible that we may have missed patients that would have met ARDS criteria but who were not intubated, e.g. those on non-invasive ventilation or included patients who did not meet ARDS criteria e.g. COVID-19 patients

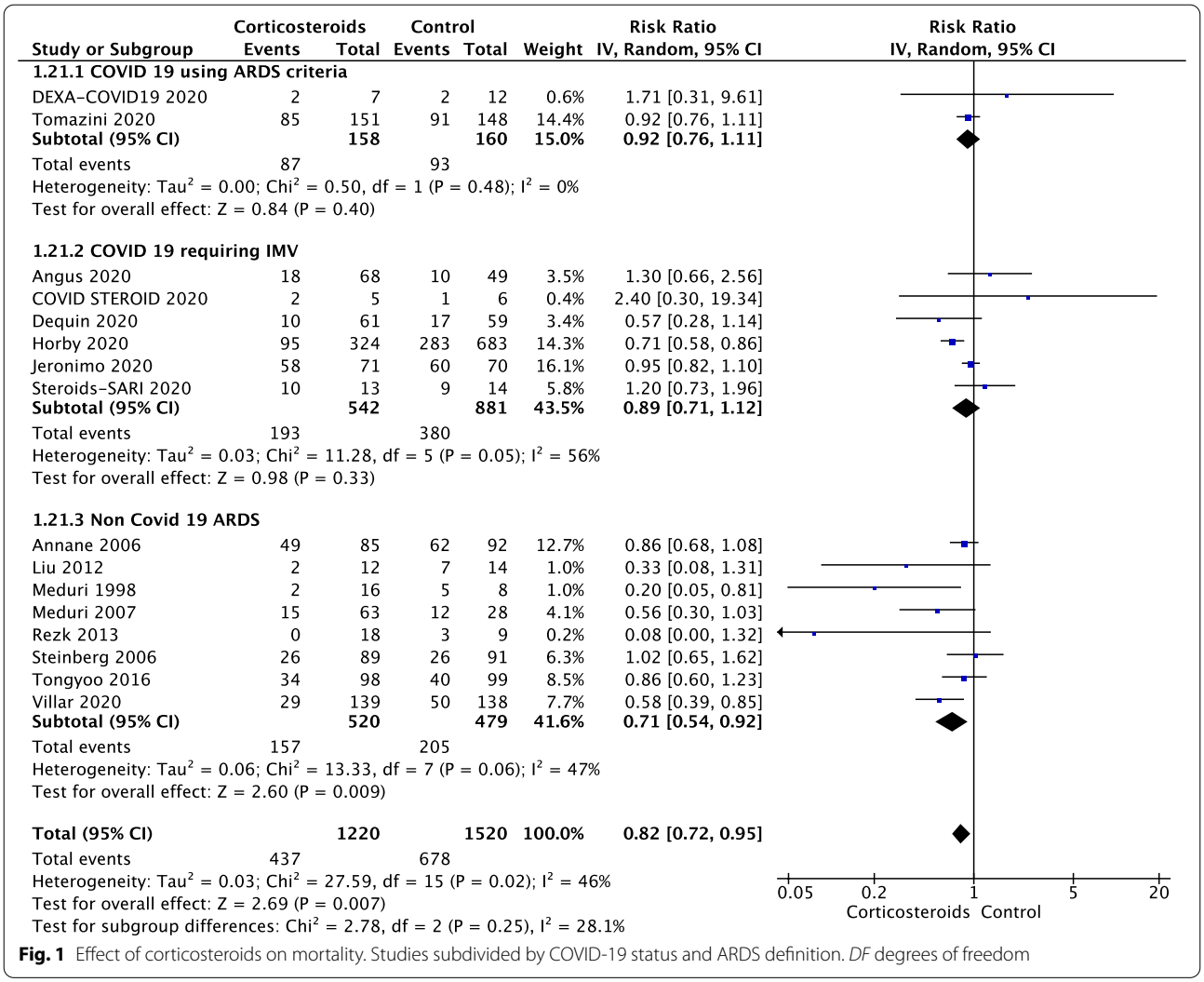
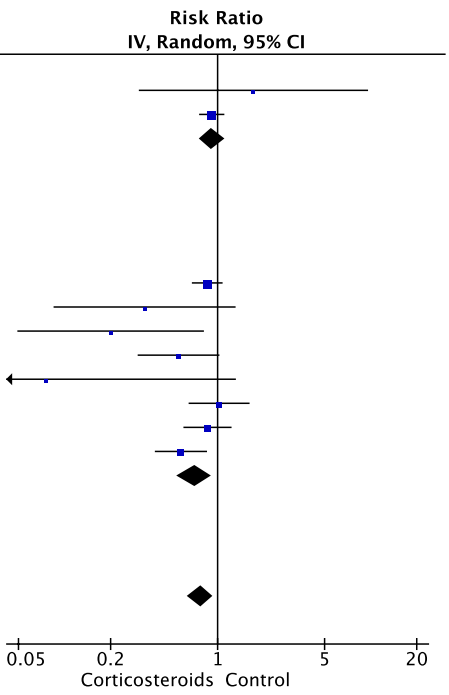


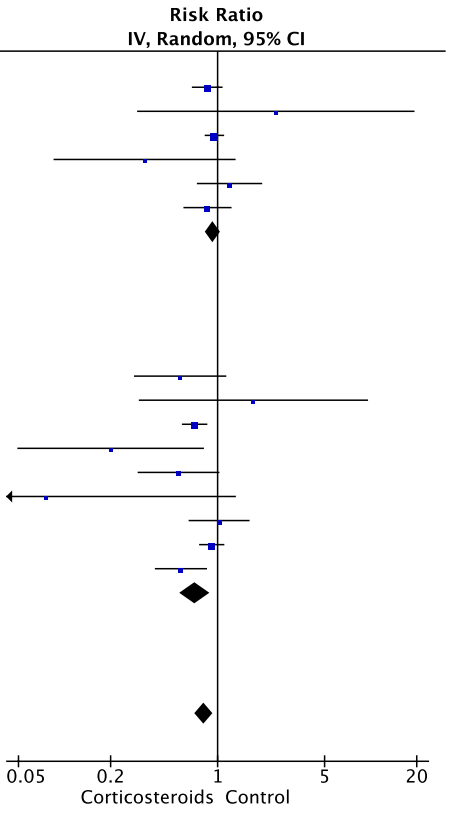
Fig. 1 Effect of corticosteroids on mortality. Studies subdivided by COVID-19 status and ARDS definition. *DF* degrees of freedom

without bilateral infiltrates or PF < 200; however, this would likely represent a small proportion of total ARDS patients. Further, when we conducted analyses excluding all trials that did not meet strict AECC/Berlin criteria or separated these trials out as their own subgroup, treatment effect sizes remained similar, there was a lack of significant subgroup effects and the overall certainty of our conclusions remained unchanged. However, we recognize that the lack of formal ARDS criteria for all studies provides a potential source of indirectness in our results and have accordingly downgraded the certainty of outcomes to reflect this. We also recognize that not all studies used the same criteria to define ARDS, with some studies using the AECC criteria and others using the Berlin criteria. However, as we only included patients that required mechanical ventilation, studies that used the Berlin criteria only included patient with moderate-to-severe ARDS [3, 7, 27]. This makes the criteria (AECC and Berlin) functionally the same for the purposes of this review. Second, the underlying etiology of ARDS in these studies was heterogenous and most non-COVID studies were small. However, it is reassuring that the effect of corticosteroids was consistent across included studies (regardless of etiology or size of the trial) with low levels of statistical heterogeneity. Some of the trials included in this meta-analysis are older, including one which is more than 20 years old [23], and since then, standard of care has changed; however, again we did not observe high degrees of statistical heterogeneity to suggest this may have influenced the certainty of our results. Moreover, when using the GRADE methodology to rate outcomes, we rated importance of outcomes through consensus of the co-author group. In an ideal world, a wider survey including actual patients would have provided a more robust rating. Finally, we were unable to find evidence addressing long-term survival, as well as data on children or in low and middle income countries—all important areas for future research.



Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.20.1 COVID 19						
DEXA-COVID19 2020	2	7	2	12	1.3%	1.71 [0.31, 9.61]
Tomazini 2020	85	151	91	148	23.7%	0.92 [0.76, 1.11]
Subtotal (95% CI)		**158**		**160**	**25.1%**	**0.92 [0.76, 1.11]**
Total events	87		93			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0\%$						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.20.2 Non Covid 19						
Annane 2006	49	85	62	92	21.6%	0.86 [0.68, 1.08]
Liu 2012	2	12	7	14	2.0%	0.33 [0.08, 1.31]
Meduri 1998	2	16	5	8	1.9%	0.20 [0.05, 0.81]
Meduri 2007	15	63	12	28	7.9%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	0.5%	0.08 [0.00, 1.32]
Steinberg 2006	26	89	26	91	11.8%	1.02 [0.65, 1.62]
Tongyoo 2016	34	98	40	99	15.3%	0.86 [0.60, 1.23]
Villar 2020	29	139	50	138	14.0%	0.58 [0.39, 0.85]
Subtotal (95% CI)		**520**		**479**	**74.9%**	**0.71 [0.54, 0.92]**
Total events	157		205			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 13.33$, df = 7 (P = 0.06); $I^2 = 47\%$						
Test for overall effect: Z = 2.60 (P = 0.009)						
Total (95% CI)		**678**		**639**	**100.0%**	**0.77 [0.63, 0.94]**
Total events	244		298			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 15.93$, df = 9 (P = 0.07); $I^2 = 44\%$						
Test for overall effect: Z = 2.51 (P = 0.01)						
Test for subgroup differences: $Chi^2 = 2.63$, df = 1 (P = 0.11), $I^2 = 61.9\%$						

Fig. 2 Effect of corticosteroids on mortality including studies with strict ARDS definition. *DF* degrees of freedom



Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.15.1 7 days or less of corticosteroid therapy						
Annane 2006	49	85	62	92	13.2%	0.86 [0.68, 1.08]
COVID STEROID 2020	2	5	1	6	0.5%	2.40 [0.30, 19.34]
Jeronimo 2020	58	71	60	70	16.8%	0.95 [0.82, 1.10]
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]
Steroids-SARI 2020	10	13	9	14	5.9%	1.20 [0.73, 1.96]
Tongyoo 2016	34	98	40	99	8.8%	0.86 [0.60, 1.23]
Subtotal (95% CI)		**284**		**295**	**46.1%**	**0.93 [0.83, 1.04]**
Total events	155		179			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.76$, df = 5 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 1.33 (P = 0.18)						
1.15.2 Greater than 7 days of corticosteroid therapy						
Dequin 2020	10	61	17	59	3.5%	0.57 [0.28, 1.14]
DEXA-COVID19 2020	2	7	2	12	0.7%	1.71 [0.31, 9.61]
Horby 2020	95	324	283	683	14.9%	0.71 [0.58, 0.86]
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]
Meduri 2007	15	63	12	28	4.2%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]
Steinberg 2006	26	89	26	91	6.5%	1.02 [0.65, 1.62]
Tomazini 2020	85	151	91	148	14.9%	0.92 [0.76, 1.11]
Villar 2020	29	139	50	138	8.0%	0.58 [0.39, 0.85]
Subtotal (95% CI)		**868**		**1176**	**53.9%**	**0.72 [0.57, 0.90]**
Total events	264		489			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 16.25$, df = 8 (P = 0.04); $I^2 = 51\%$						
Test for overall effect: Z = 2.92 (P = 0.003)						
Total (95% CI)		**1152**		**1471**	**100.0%**	**0.81 [0.70, 0.94]**
Total events	419		668			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 26.10$, df = 14 (P = 0.03); $I^2 = 46\%$						
Test for overall effect: Z = 2.88 (P = 0.004)						
Test for subgroup differences: $Chi^2 = 4.03$, df = 1 (P = 0.04), $I^2 = 75.2\%$						

Fig. 3 Effect of corticosteroids on mortality. Studies subdivided by duration of corticosteroid therapy

Conclusion

The use of corticosteroids probably reduces mortality and may reduce the duration of mechanical ventilation in patients with ARDS. This effect was consistent between patients with COVID-19 and non-COVID-19 ARDS and between different corticosteroid types, and dosage.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06394-2.

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Author contributions

DC, BR and GUM came up with the idea for the study. DC, MJM, ZY, PA, LL and SS performed study screening. DC, KS, ZY, LL, MJM and AK performed dual data abstraction. BR adjudicated for any potential disagreements. DC performed the statistical analysis. LM provided statistical assistance with the meta-regression. KL, MWM, AP, BD, WA, SP, JM, FL, DA, DC and BR helped write the first draft. All other authors helped with editing the subsequent manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability

Available upon request.

Declarations

Conflicts of interest

AP is the sponsor and MWM the coordinating investigator of the COVID STEROID trial, which is funded by the Novo Nordisk Foundation and supported by Pfizer Inc. WA is the chair of the Surviving Sepsis COVID guideline. BR was the methodologist for the 2017 CIRCI SCCM guidelines and on the methods team for the WHO corticosteroid in COVID guideline. SP served as co-chair of the SCCM/ESICM 2017 Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients. DA has been the co-chair of the SCCM/ESICM guidelines on the diagnosis and management of CIRCI 2017 (PMID: 29095205; PMID: 29090327; PMID: 28940017 ; PMID: 28940011; PMID: 28938253; PMID: 28938251). He was a member of WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group which has published a prospective meta-analysis on the use of corticosteroids for COVID-19 (PMID: 32876694; PMID: 32831155); and a member of the steering committee of BMJ/GRADE rapid recommendations for corticosteroids for sepsis (PMID: 30097460; PMID: 29979221). DA is coordinating the individual patient data meta-analysis on hydrocortisone for septic shock (PMID: 33268422) and has coordinated the Cochrane trial-level meta-analysis on the use of corticosteroids for children and adults with sepsis (PMID: 31808551). DA has been the PI of the following trials on corticosteroids for sepsis (and or ARDS) PMID: 20103758; PMID: 18184957; PMID: 16374152; PMID: 12186604; PMID: 29490185. DA was the member of the steering committee of the following trials of corticosteroids for COVID-19: PMID: 32876697; PMID: 32876689. DA has received no personal rewards for any of the above mentioned academic activities. LM does paid consulting work for Bayer (oncology), AstraZeneca (biologics for asthma) and Janseen (TB drugs). GUM served as a member of the SCCM/ESICM 2017 Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients. MJM serves as a co-author on the Surviving Sepsis COVID guideline. FL contributed to systematic reviews and clinical trials of evaluating the effects of corticosteroids in ARDS and pneumonia and chaired the WHO corticosteroid in COVID guideline.

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