




Steroid treatment in patients with acute respiratory distress syndrome: a systematic review and network meta-analysis

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Abstract

Purpose Although the most recent systematic review and meta-analyses on acute respiratory distress syndrome (ARDS) have shown that the use of steroids decreases mortality in adult patients, its benefits and risks may differ depending on the type and dosage of the steroid. Therefore, we conducted a network meta-analysis (NMA) to compare the differences in the efficacy among different doses and types of steroids.

Methods We searched MEDLINE, CENTRAL, ICHUSHI, ClinicalTrials.gov, and WHO ICTRP databases from the earliest records to March 2021 for randomized control trials, which compared steroids with placebo or conventional therapy for ARDS. Using the random-effects model, we compared various categories of steroids (high-dose methylprednisolone, low-dose methylprednisolone, hydrocortisone, dexamethasone, and no steroid) concerning hospital mortality, incidence of infection, and ventilator-free days (VFD).

Results We analyzed nine studies involving adult patients ($n = 1212$). Although there were no significant differences between the groups in terms of the mortality and incidence of infection, the number of VFD were greater when using low-dose methylprednisolone than when not using any steroids (Mean difference: 6.06; 95% confidence intervals: [2.5, 10.5]). Moreover, the rank probability showed that low-dose methylprednisolone might be the optimal treatment, whereas using no steroid or high-dose methylprednisolone may be inferior to other treatments in terms of mortality, infection, and VFD.

Conclusion This NMA suggested that the effect of steroids on the outcome in patients with ARDS might depend on the type of the steroid drug administered. Moreover, further studies are needed to identify the optimal type and dosage.

Keywords Systematic review · Critical care · Respiratory insufficiency · Steroids · Network meta-analysis

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Introduction

Acute respiratory distress syndrome (ARDS) is defined as acute respiratory failure due to non-hemodynamic pulmonary edema caused by inflammatory cytokines, and it is associated with a high mortality rate [1, 2]. Inflammatory cytokines were modulated by a pro-inflammatory transcription factor, nuclear factor-kappa B (NF- κ B) [3, 4]. Steroids are expected to treat ARDS by attenuating NF- κ B by the action of the glucocorticoid receptor α .

The most recent systematic review and meta-analyses (SR/MA) on ARDS have shown that the use of steroids decreases mortality and increases ventilator-free days (VFD) [5]. Another recent SR/MA suggested that early and longer administration of steroids in patients with ARDS might reduce mortality [6]. In these SR/MA, different types and dosages of steroids, such as high-dose methylprednisolone [7], low-dose methylprednisolone [8–10], hydrocortisone [11], and dexamethasone [12, 13] were used. In addition, the biological half-life and anti-inflammatory potency of steroids vary depending on its type. Though the differences in the type and dosage of steroids might affect outcomes, the optimal steroid regimen in terms of the benefit-risk ratio in ARDS remains unclear because these pairwise SR/MA assessed over all efficacy and outcomes of steroid by comparing groups of patients that did and did not use steroids.

We hypothesized that the steroid type influences the outcome in ARDS patients and sought to verify this by performing a network meta-analysis (NMA). Therefore, we conducted this systematic review and NMA to identify the optimal steroid therapy among patients with ARDS.

Methods

Protocol

We conducted this SR according to the Preferred Reporting Items for Systematic review and Meta-Analyses extension statement for reviews incorporating network meta-analyses (Online Resource 1) [14].

Eligibility criteria

We included randomized control trials (RCTs) that compared steroids for established ARDS. We did not search for quasi-randomized studies, cohort studies, case–control studies, and case series. ARDS was diagnosed according to the American European Consensus Conference (AECC) [15] definition (1994) or Berlin (2012) diagnostic criteria [16]. During our search for studies published before the establishment of the

AECC, we included patients with acute respiratory failure, which was defined as follows: an acute onset of hypoxemia with a PaO₂ to FiO₂ ratio (*P/F* ratio) of ≤ 200 mmHg, bilateral noncardiogenic pulmonary edema, no clinical evidence of increased left atrial hypertension, and a pulmonary artery wedge pressure ≤ 18 mmHg in the presence of a pulmonary artery catheter. Patients who had been previously treated with corticosteroids and immunosuppressive drugs or had cardiogenic pulmonary edema and hypercapnia without hypoxia were excluded. As we investigated the effects of steroids in established ARDS patients, we excluded patients with oxygenation of $200 < P/F \text{ ratio} \leq 300$ and no ventilation. We also excluded patients who were administered inhaled steroids because of the limited effects on the lungs without collapse.

We categorized interventions according to the received four types of steroids based on previous studies [7–10, 12, 13, 17, 18] and compared the results obtained from the following five groups: high-dose methylprednisolone, low-dose methylprednisolone, hydrocortisone, dexamethasone, and no steroid. We defined high-dose methylprednisolone as ≥ 1000 mg/day on the first day, 1000 mg/day on the second and third day, and tapering from the fourth day. We defined low-dose methylprednisolone as a methylprednisolone dose of 1.0–2.0 mg/kg/day after loading dose of 1.0–2.0 mg/kg/day from the first day to 14th day, which was administered for at least 3 weeks with tapering. We defined hydrocortisone as 200–300 mg/day for 7 days. We defined dexamethasone as any dosage for 10 days. We defined no steroid as a placebo or conventional therapy.

The primary outcome of this SR was hospital mortality. The secondary outcomes were incidence of infection and number of VFD. When data on hospital mortality were not available, we collected data on the longest mortality within 28–60 days after randomization.

Information sources, search strategy, study selection, and data collection process

The searched databases were MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and Iqaku Chuo Zasshi (ICHUSHI). The ICHUSHI Web is the largest database of Japanese medical journals, containing approximately 10 million manuscripts from 6000 journals. We comprehensively searched these databases for relevant studies published from the earliest records to March 2021. We also searched for ongoing and unpublished trials in the following trial registers: ClinicalTrials.gov and the World Health Organization International Clinical Trials Platform Search Portal (WHO ICTRP) in March 2021. The list of search terms is shown in Online Resource 2. Additionally, we manually searched reference lists of included studies,

previous SR/MA [6, 19–22], and articles citing these studies (based on citation information from the Web of Science).

When the screened records did not contain the necessary information, we inquired the authors for details. Two or more reviewers independently screened the titles and abstracts of the studies in the first screening. Articles included in the first screening were assessed for eligibility according to the inclusion criteria by reading the full texts. When the reviewers disagreed with the inclusion, conflicts were resolved by consensus. Two or more reviewers independently extracted data from full manuscripts. We extracted data pertaining to study characteristics such as study design, locations of the study center, sample size, information of participants (age, diagnostic criteria, and main etiology of ARDS), interventions, comparisons, low tidal ventilation as conventional therapy, and outcomes. We contacted the authors of the studies to collect sufficient information if necessary. The relevant data of the included studies were summarized using Microsoft Excel and Cochrane Statistical Package Review Manager (version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

Geometry of the network

We constructed network plots for each outcome in this NMA. Each node corresponded to a treatment strategy. The edge presented direct comparisons between interventions and comparators and added to the number of included studies.

Abstraction of data and assessment of the risk of bias

Two or more reviewers independently classified the risk of bias for each included study as high, low, or unclear. We assessed the following seven domains for risk of bias using the Cochrane risk of bias assessment tool [23]: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete data outcome, selective reporting, and other bias. When reviewers disagreed with the decision on the risk of bias, conflicts were resolved by discussing with a third reviewer.

Data synthesis

We conducted a pairwise meta-analysis using the random-effects method to assess for direct associations between interventions and outcomes. We integrated the dichotomous variables as risk ratios (RR) with 95% confidence intervals (CI) and continuous variables as mean differences (MD) with 95% CI. We assessed heterogeneity using visual inspection of forest plot and I^2 statistics. We assessed indirectness

by checking patient characteristic of each included studies. We assessed publication bias by checking the number of studies that had not been published on ClinicalTrials.gov and WHO ICTRP.

We conducted an NMA using the Bayesian random-effects method to derive direct and indirect estimates comparing all interventions and comparisons. We integrated the dichotomous variables as odds ratios (OR) with 95% credible intervals (CrIs) and continuous variables as MD with 95% CrIs. We assessed intransitivity by checking patient characteristic of each direct comparison as the source for indirect estimates. We assessed imprecision by each 95% CrIs crossing clinically important intervals of OR defined as 0.8–1.25. We assessed incoherence using the node-splitting method [24]. We derived rank probability for each intervention and comparison from the results of the NMA within a Bayesian framework and decided treatment hierarchy using surface under the cumulative ranking curve (SUCRA) [25].

We assessed the certainty of evidence (CoE) for each estimate using the Grades of Recommendation, Assessment, Development, and Evaluation Working Group (GRADE) approach for NMA [26, 27]. First, we assessed the CoE for direct estimate using five considerations (risk of bias, heterogeneity, indirectness, publication bias, and imprecision). Second, we assessed the CoE for the indirect estimate by considering the CoE for the direct estimate of the common comparator related to the indirect estimate and using two considerations (intransitivity and imprecision). Finally, we assessed the CoE for network estimate by considering the CoE for direct and indirect estimates and using two considerations (incoherence and imprecision).

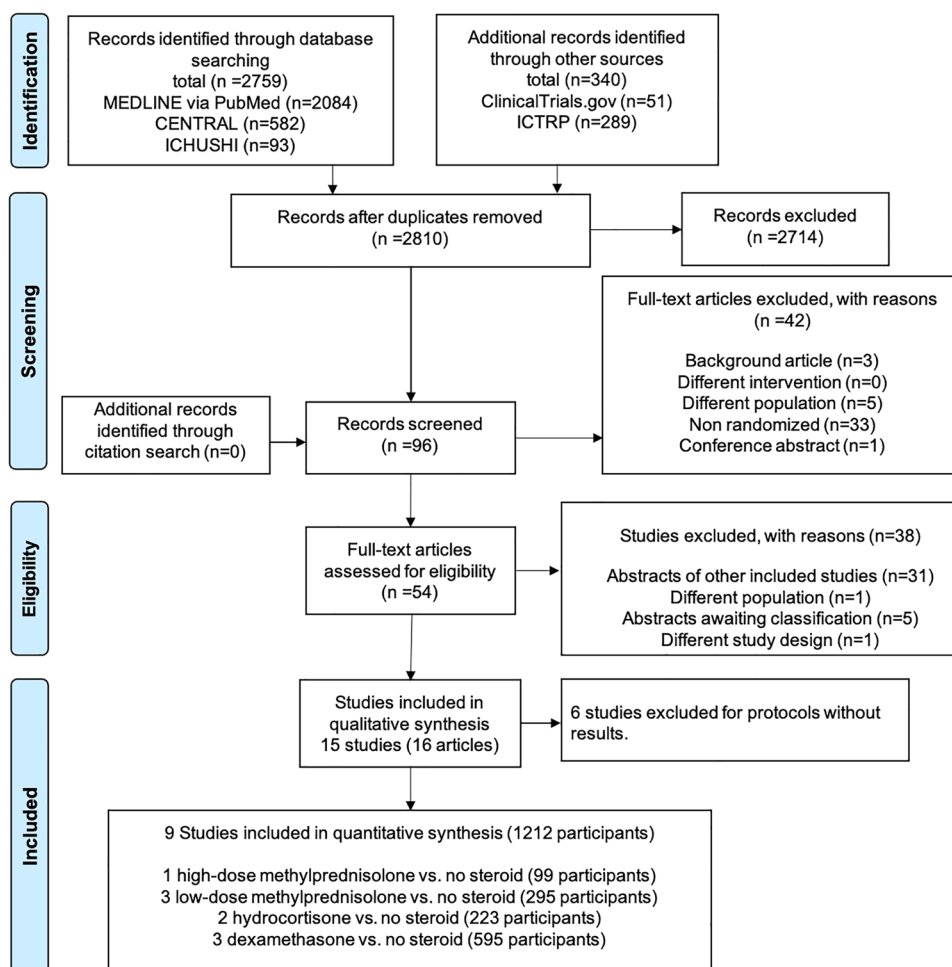
We defined statistical significance as 95% CIs and CrIs that did not cross the value 1.0. We used the Cochrane Statistical Package Review Manager (version 5.3; Cochrane Collaboration, Copenhagen, Denmark) for the pairwise meta-analysis. We performed NMA using JAGS and R (version 4.0.4; The R Foundation, Wien, Austria) software, whereas the *rjags* and *gemtc* packages were used for the Bayesian approach. We then created the table showing the summary of findings [28].

Results

Study selection

A flow diagram of this study is shown in Fig. 1. After eliminating the duplicates, we assessed 2810 records through databases and other source searches. We excluded 2714 records by screening the titles and abstracts and 96 records using full texts. On assessing the remaining 54 records for eligibility, we found two articles [8, 29] published from the same study. Subsequently, we identified 15 eligible studies.

Fig. 1 Flow diagram of this study. CENTRAL Cochrane Central Register of Controlled Trials, ICHUSHI Igaku Chuo Zasshi, ICTRP World Health Organization International Clinical Trials Platform Search Portal



Among the 15 eligible studies, we excluded six studies with unpublished outcomes (Online Resource 3). Two of the six excluded studies had completed recruitment, but we did not get a reply from the authors regarding the outcome data, proportion of ARDS, and diagnostic criteria for ARDS. Finally, we included nine studies ($n = 1212$) for quantitative synthesis, the details of which are provided in Table 1. The network of eligible comparisons for the meta-analysis is shown in Fig. 2.

Study characteristics

One study compared high-dose methylprednisolone with placebo [7]. Three studies compared low-dose methylprednisolone with placebo [8–10], two studies compared hydrocortisone with placebo [11, 30], and three studies compared dexamethasone with no steroid and were not used as placebo [12, 13, 31]. Direct pairwise comparisons are provided in Online Resource 4.

The most common etiology was pneumonia 57.1% (692/1,212). Ventilation strategy of six studies was low tidal ventilation [9, 11–13, 31, 32]. We grouped 28-day mortality

for two studies [12, 30], 60-day mortality for three studies [9, 11, 31], and 45-day mortality for one study [7] to assess hospital mortality. VFD were measured in eight studies, while VFD of one study [8] were obtained from the author. We converted 95% CI of VFD to a standard deviation in one study [12]. Data on infections were collected from nine studies. One study [13] assessed new infections in the ICU, while another study [31] assessed pneumonia in the ICU. The observation period for infection was 28 days in two studies [9, 12], 7 days in one study [7], 1 year in one study [10], and up to discharge in one study [11]. Two studies [8, 30] did not report the observation period for the infection. Two studies [12, 31] did not use a placebo and had unplanned termination of the recruitment of participants. We received no reply about the data on 60-day mortality and infection from the authors of one of the studies [31].

Risk of bias and CoE

We assessed the overall risk of bias of four studies [7–9, 11] as low, that of four studies [10, 12, 30, 31] as unclear, and that of one study [13] as high using the Cochrane risk of bias

Table 1 Details for included studies

Author year Country	No of patients Steroid/control	Age Steroid/control, years	Inclusion criteria of ARDS	Initiation timing of steroid from ARDS onset Early: < 7 days Late: ≥ 7 days	Regimen of steroids	Comparison	Low tidal venti- lation strategy	Main etiology of ARDS	Planned primary outcome
Bernard [7] 1987 USA	50/49	Mean ± SD 55 ± 14.1/56 ± 14	(i) Arterial blood gas oxygen partial pressure ≤ 70 mmHg or arterial blood oxygen partial pressure/alveolar oxygen partial pressure ≤ 0.3 with oxygen inhalation of 40% or more (ii) Bilateral noncardiogenic pulmonary edema (iii) A pulmonary artery wedge pressure ≤ 18 mmHg in the presence of a pulmonary artery catheter	Early	Methylprednisolone Day 1: 30 mg/kg 4 times daily	Placebo (Mannitol)	Study published before 1999 No data	Not detail	No
Meduri ^{a,b} [8] 1998 USA	16/8	Mean ± SD 47 ± 15.6/51 ± 18.7	AECC criteria	Late	Methylprednisolone Loading: 2 mg/kg Day 1–14: 0.5 Day 15–21: 0.25 Day 22–28: 0.125 Day 29–30: 0.0625 Day 31–32: 0.0313 mg/kg 4 times daily	Placebo (0.9% saline)	Study published before 1999 No data	Sepsis 63% (15/24)	No

Table 1 (continued)

Author year Country	No of patients Steroid/control,	Age Steroid/control, years	Inclusion criteria of ARDS	Initiation timing of steroid from ARDS onset Early: < 7 days Late: ≥ 7 days	Regimen of steroids	Comparison	Low tidal venti- lation strategy	Main etiology of ARDS	Planned primary outcome
Steinberg 2006 [9] USA	89/91	Mean ±SD 49.0 ± 19.0/49.2 ± 16.5	AECC criteria	Late	Methylprednisolone Loading: 2 mg/kg Day 1–14: 0.5 mg 4 times daily Day 15–21: 0.5 mg 2 times daily Tapering off over 4 days	Placebo (5% dextrose)	Yes	Pneumonia 42% (76/180) Sepsis 22% (40/180)	Mortality at day 60
Meduri [10] 2007 USA	63/28	Mean ±SD 50.1 ± 15.3/53.2 ± 15.3	AECC criteria	Early	Methylprednisolone Loading: 1 mg/kg Day 1–14: 1 Day 15–21: 0.5 Day 22–25: 0.25 Day 26–28: 0.125 mg/kg/day by continuous infusions	Placebo (0.9% serine)	Yes	Pneumonia 42% (38/91) Sepsis 16% (15/91)	1-point reduction in lung injury score
Liu [30] 2012 China	12/14	Mean ±SD 69.8 ± 14.9/55.9 ± 15.3	AECC criteria	Early	Hydrocortisone Day 1–7: 100 mg 3 times daily	Placebo (0.9% serine)	Not described	Pneumonia 42.3% (11/26)	No
Tongyoo [11] 2016 Thailand	98/99	Mean ±SD 64.5 ± 17.3/64.3 ± 16.0	AECC/Berlin criteria (Included acute lung injury)	Early	Hydrocortisone Day 1–7: 50 mg 6 times daily	Placebo (Not detail)	Yes	Pneumonia 51% (100/197)	No
Tomazini [12] 2020 Brazil	151/148	Mean ±SD 60.1 ± 15.8/62.7 ± 13.1	Berlin criteria as moderate-to-severe ARDS	Early	Dexamethasone Day 1–5: 20 Day 6–10: 10 mg once daily	No placebo	Yes	Pneumonia due to SARS CoV-2	Ventilator-free days to day 28
Villar [13] 2020a Spain	139/138	Mean ±SD 56 ± 14/58 ± 15	AECC/Berlin criteria as P/F ratio 200 or less	Early	Dexamethasone Day 1–5: 20 Day 6–10: 10 mg once daily	No placebo	Yes	Pneumonia 53% (147/277) Sepsis 24% (67/277)	Ventilator-free days to day 28

Table 1 (continued)

Author year Country	No of patients Steroid/control, years	Age Steroid/control, years	Inclusion criteria of ARDS	Initiation timing of steroid from ARDS onset Early: < 7 days Late: ≥ 7 days	Regimen of steroids	Comparison	Low tidal venti- lation strategy	Main etiology of ARDS	Planned primary outcome
Villar ^c [31] 2020b Spain	7/12	Median (IQR) 62 (48–68)/60 (52–69)	Berlin criteria as moderate-to- severe ARDS	Early	Dexamethasone Day1–5: 20 Day6–10: 10 mg once daily	No placebo	Yes	Pneumonia due to SARS CoV-2	Mortality at day 60

ARDS acute respiratory distress syndrome, AEC₂ American European Consensus Conference, IQR interquartile range, SD standard deviation, SARS CoV-2 severe acute respiratory syndrome coronavirus 2, ICU intensive care unit

^aMeduri [8] included two articles

^bWe got information by author contact in Meduri [8]. Meduri [8] REPLY: Data on ventilator-free days to 28 days; Intervention ($n = 16$); Mean \pm SD; 12.4 ± 8.1 days, Control ($n = 8$); 4.0 ± 6.1 days, which referred to all patents randomized before [$n = 14$] or after [$n = 2$] day 14 of ARDS

^cWe got information by author contact in Villar [31]. Villar [31] REPLY: In our analysis of 19 patients, we did not analyze ventilator-free days. All patients were mechanically ventilated at the time of randomization. Mortality at 60 days after randomization was as follows: Dexamethasone group: two deaths from 7 enrolled patients; Control group: two deaths from 12 enrolled patients. Mortality was blinded for all groups. Only the study coordinator knew the number of deaths at 28 and 60 days. Regarding infections—Dexamethasone group: three patients out of seven developed pneumonia during the ICU stay. Control group: 7 patients out of 12 developed pneumonia during ICU stay

assessment tool. Domains of risk of bias for each outcome are shown in Table 2. We showed processes of assessment for CoE in Online Resource 5, and the results concerning CoE in Online Resource 6. As we could not analyze direct comparisons for each steroid, we could not assess incoherence between direct and indirect estimates.

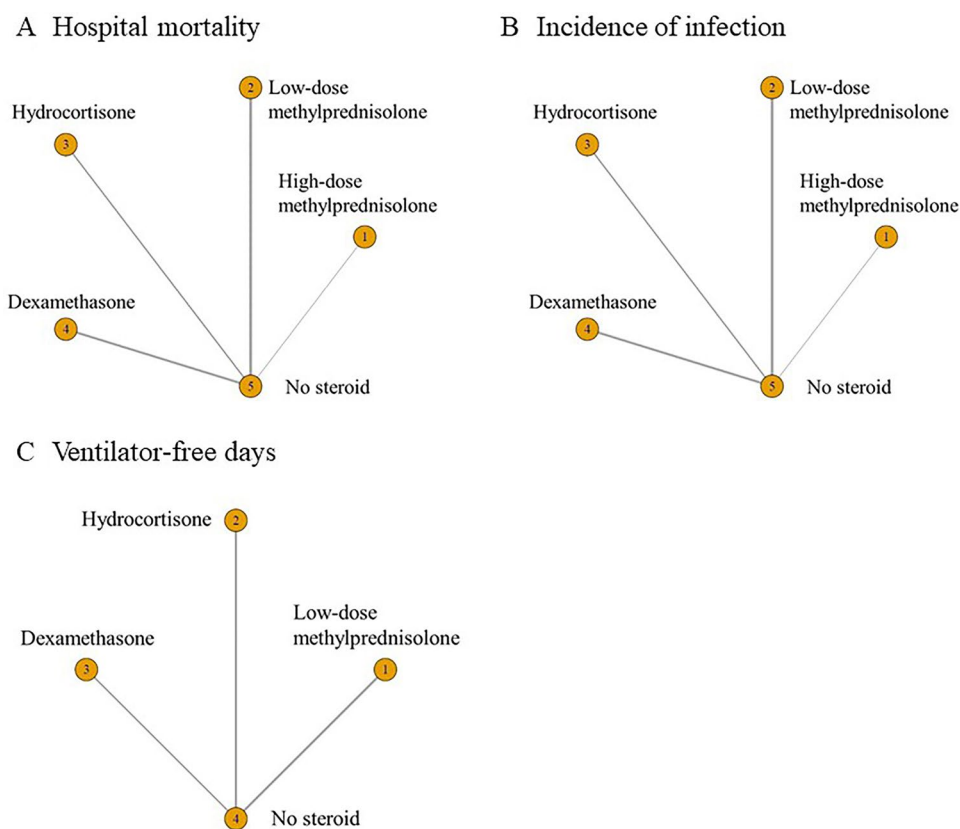
Hospital mortality

Network estimate for hospital mortality was created from nine RCTs including 1212 patients (Table 3). High-dose methylprednisolone, low-dose methylprednisolone, hydrocortisone, and dexamethasone were not associated with a reduction in hospital mortality compared with no steroid. Using dexamethasone as a reference comparator, there was no statistical difference in the association with hospital mortality when comparing high-dose methylprednisolone (OR 1.16 95% CrI [0.08, 12.9], 36 more patients per 1000 patients, CoE: very low). Low-dose methylprednisolone (OR 0.66 95% CrI [0.07, 3.04], 95 less patients per 1000 patients, CoE: very low), and hydrocortisone (OR 0.72 95% CrI [0.06, 4.35], 76 less patients per 1000 patients, CoE: very low) were not associated with the reduction of hospital mortality compared with dexamethasone. Using hydrocortisone as a reference comparator, high-dose methylprednisolone (OR 1.62 95% CrI [0.13, 31.0], 113 more patients per 1000 patients, CoE: very low) was not associated with increasing hospital mortality. There was no statistical difference in the association with hospital mortality when comparing low-dose methylprednisolone with hydrocortisone (OR 0.93 95% CrI [0.11, 7.42], 16 less patients per 1000 patients, CoE: low). Using low-dose methylprednisolone as a reference comparator, high-dose methylprednisolone (OR 1.74 95% CrI [0.18, 30.0], 118 more patients per 1000 patients, CoE: very low) was not associated with increasing hospital mortality. The rank probability of hospital mortality was in the order of low-dose methylprednisolone, hydrocortisone, dexamethasone, high-dose methylprednisolone, and no steroid (Fig. 3).

Incidence of infection

Network estimate for incidence of infection was created from nine RCTs including 1212 patients (Table 3). High-dose methylprednisolone, low-dose methylprednisolone, hydrocortisone, and dexamethasone were not associated with a reduction in the incidence of infection compared with no steroid. Using dexamethasone as a reference comparator, high-dose methylprednisolone (OR 2.26 95% CrI [0.55, 10.2], 174 more patients per 1000 patients, CoE: very low), and hydrocortisone (OR 1.32 95% CrI [0.49, 3.84], 53 more patients per 1000 patients, CoE: very low) were not associated with increasing incidence of infection compared with

Fig. 2 Network plot. **A** Hospital mortality **B** incidence of infection **C** Ventilator-free days. Each node corresponded to a treatment strategy. The edge presented direct comparisons between interventions and comparators and added to the number of included studies



dexamethasone. There was no statistical association when the reduction of incidence of infection compared low-dose methylprednisolone with dexamethasone (OR 0.74 95% CrI [0.32, 1.77], 49 less patients per 1000 patients, CoE: very low). Using hydrocortisone as a reference comparator, high-dose methylprednisolone (OR 1.73 95% CrI [0.33, 8.45], 95 more patients per 1000 patients, CoE: very low) was not associated with increasing incidence of infection. There was no statistical association when the reduction of incidence of infection compared low-dose methylprednisolone with hydrocortisone (OR 0.56 95% CrI [0.19, 1.60], 71 less patients per 1000 patients, CoE: low). Using low-dose methylprednisolone as a reference comparator, high-dose methylprednisolone (OR 3.06 95% CrI [0.70, 14.1], 272 more patients per 1000 patients, CoE: very low) was not associated with increasing incidence of infection. The rank probability of the incidence of infection was in that order of low-dose methylprednisolone, dexamethasone, hydrocortisone, no steroid, and high-dose methylprednisolone (Fig. 3).

VFD

Network estimate for VFD was created from seven RCTs including 1094 patients (Table 3). Low-dose methylprednisolone was associated with increasing VFD compared with no steroid (MD 6.00, 95% CI [3.39, 8.61]; CoE: high).

Other comparisons with no steroid showed that the other treatments were not associated with increasing VFD. Using dexamethasone as a reference comparator, low-dose methylprednisolone (MD 2.40 95% CrI [- 2.87, 8.70], CoE: very low) was not associated with increasing VFD. There was no statistical difference in association with VFD when hydrocortisone was compared with dexamethasone (MD - 1.54 95% CrI [- 8.34, 4.87], CoE: very low). Using hydrocortisone as a reference comparator, low-dose methylprednisolone (MD 3.99 95% CrI [- 1.90, 11.1], CoE: moderate) was not associated with increasing VFD. The rank probability of VFD was in the order of low-dose methylprednisolone, dexamethasone, hydrocortisone, and no steroid (Fig. 3).

Discussion

The present study revealed that although there were no significant differences in hospital mortality and incidence of infection among all comparisons, including steroids and no steroid, low-dose methylprednisolone resulted in a greater improvement of VFD compared with no steroid. Though the CoE of most comparisons was very low, the anticipated absolute effect and rank probability indicated that the effect of steroids on the outcome in ARDS patients might vary depending on the type and/or dose of steroids.

Table 2 Risk of bias summary

Study	Random sequence generation	Allocation concealment	Blinding for participants and personnel	Blinding for outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
<i>a. Risk of bias summary of hospital mortality</i>							
Bernard 1987 [7]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Meduri 1998 [8]	Low risk	Low risk ^a	Low risk ^a	Low risk ^a	Low risk	Unclear risk	Low risk
Steinberg 2006 [9]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Meduri 2007 [10]	Low risk	Low risk	Low risk ^a	Low risk ^a	Low risk	High risk ^a	Low risk
Liu 2012 [30]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk
Tongyoo 2016 [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Tomazini 2020 [12]	Low risk	Low risk	High risk ^b	Low risk	Low risk	Low risk	Low risk
Villar 2020a [13]	Low risk	Low risk	High risk ^b	Low risk	Low risk	High risk ^c	Low risk
Villar 2020b [31]	Low risk	Low risk	High risk ^b	Low risk	Low risk	Low risk	Low risk
<i>b. Risk of bias summary of incidence of infection</i>							
Bernard 1987 [7]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Meduri 1998 [8]	Low risk	Low risk ^a	Low risk ^a	Low risk ^a	Low risk	Unclear risk	Low risk
Steinberg 2006 [9]	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Meduri 2007 [10]	Low risk	Low risk	Low risk ^a	Low risk ^a	Low risk	High risk ^a	Low risk
Liu 2012 [30]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk
Tongyoo 2016 [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Tomazini 2020 [12]	Low risk	Low risk	High risk ^b	Unclear risk	Low risk	High risk ^c	Low risk
Villar 2020a [13]	Low risk	Low risk	High risk ^b	Low risk	Low risk	High risk ^c	Low risk
Villar 2020b [31]	Low risk	Low risk	High risk ^b	Unclear risk	Low risk	Low risk	Low risk
<i>c. Risk of bias summary of ventilator-free days</i>							
Meduri 1998 [8]	Low risk	Low risk ^a	Low risk ^a	Low risk	Low risk	Unclear risk	Low risk
Steinberg 2006 [9]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Meduri 2007 [10]	Low risk	Low risk	Low risk ^a	Low risk	Low risk	Low risk ^a	Low risk
Liu 2012 [30]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk
Tongyoo 2016 [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Tomazini 2020 [12]	Low risk	Low risk	High risk ^b	Low risk	Low risk	Low risk	High risk ^d
Villar 2020a [13]	Low risk	Low risk	High risk ^b	Low risk	Low risk	Low risk	High risk ^d

^aWe got information by author contact in Meduri [8] and Meduri [10]. Meduri [8] REPLY: Central randomization by a third party in order to conceal the allocation; Physicians and all medical personnel were blinded. Meduri [10] REPLY: The randomization is double blind and will remain blind throughout therapy to physicians, nursing care teams, research investigators, outcome assessor, participants and their family members. The primary objective of this prospective double blind, randomized clinical trial is to assess the effects of prolonged methylprednisolone therapy on the following response by days 7 and 28 of therapy: improvement in lung injury score, number of ventilator-free days, mortality

^bThese studies did not use placebo in control group

^cNot planned outcomes in pre-published protocol

^dThe study was stopped earlier than planned

The analysis of individual patients' data from RCTs showed that low-dose methylprednisolone reduced mortality and VFD compared to placebo, although this SR/MA did not compare each steroid regimen [32]. Prolonging any steroid was suggested to improve mortality of patients with ARDS regardless of the type of steroids [33]. In addition, recent

SR/MAs was demonstrated for early and longer steroids in patients with ARDS and its effectiveness on mortality was verified by synthesizing studies on low-dose methylprednisolone and dexamethasone [6]. One recent retrospective propensity-matched cohort study suggested that the pulsed methylprednisolone therapy worsened the 60-day mortality

Table 3 NMA-SoF table

a. Estimates of effects, credible intervals, and certainty of the evidence for improving hospital mortality in patients with ARDS
Bayesian NMA-SoF table

BENEFITS

Patient or population: Patients with ARDS

Interventions: High-dose methylprednisolone, low-dose methylprednisolone, hydrocortisone, dexamethasone, no steroid

Comparator (reference): One of the other therapies other than the therapy included in intervention

Outcome: Hospital mortality or mortality for 28-60 days

Setting(s): Inpatient

Geometry of the Network*

Total studies: 9 RCT Total Participants: 1222	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking**** (SUCRA)	Interpretation of Findings
		With reference comparator	With intervention	Difference			
1 High-dose methylprednisolone (Direct evidence; 1 RCT; 99 participants)	0.87 (0.10 to 7.58)	633 per 1000 ¹	600 per 1000	33 per 1000 fewer (from 486 fewer to 296 more)	⊕○○○ Very Low Due to Indirectness ² and Imprecision ³	4 (40%)	-
2 Low-dose methylprednisolone (Direct evidence; 3 RCT; 295 participants)	0.49 (0.10 to 1.49)	339 per 1000 ¹	201 per 1000	138 per 1000 fewer (from 290 fewer to 94 more)	⊕⊕○○ Low Due to Imprecision ³	1 (73%)	-
3 Hydrocortisone (Direct evidence; 2 RCT; 223 participants)	0.54 (0.08 to 2.33)	416 per 1000 ¹	278 per 1000	138 per 1000 fewer (from 362 fewer to 198 more)	⊕⊕○○ Low Due to Imprecision ³	2 (67%)	-
4 Dexamethasone (Direct evidence; 3 RCT; 595 participants)	0.75 (0.23 to 3.12)	480 per 1000 ¹	409 per 1000	71 per 1000 fewer (from 305 fewer to 262 more)	⊕○○○ Very Low Due to Risk of bias ⁴ and Imprecision ³	3 (47%)	-
5 No steroid	Reference comparator	No estimable	No estimable	No estimable	Reference comparator	5 (24%)	-
High-dose methylprednisolone (No direct evidence)	1.16 (0.08, 12.9)	404 per 1000 ¹	440 per 1000	36 per 1000 more (from 352 fewer to 493 more)	⊕○○○ Very Low Due to Indirectness ² and Imprecision ³	-	-
Low-dose methylprednisolone (No direct evidence)	0.66 (0.07, 3.04)	404 per 1000 ¹	309 per 1000	95 per 1000 fewer (from 359 fewer to 269 more)	⊕○○○ Very Low Due to Risk of bias ⁴ and Imprecision ³	-	-
Hydrocortisone (No direct evidence)	0.72 (0.06, 4.35)	404 per 1000 ¹	328 per 1000	76 per 1000 fewer (from 365 fewer to 343 more)	⊕○○○ Very Low Due to Risk of bias ⁴ and Imprecision ³	-	-
Dexamethasone (No direct evidence)	Reference comparator	No estimable	No estimable	No estimable	Reference comparator	-	-
High-dose methylprednisolone (No direct evidence)	1.62 (0.13, 31.0)	327 per 1000 ¹	440 per 1000	113 per 1000 more (from 268 fewer to 611 more)	⊕○○○ Very Low Due to Indirectness ² and Imprecision ³	-	-
Low-dose methylprednisolone (No direct evidence)	0.93 (0.11, 7.42)	327 per 1000 ¹	311 per 1000	16 per 1000 fewer (from 276 fewer to 456 more)	⊕⊕○○ Low Due to Imprecision ³	-	-
Hydrocortisone (No direct evidence)	Reference comparator	No estimable	No estimable	No estimable	Reference comparator	-	-
High-dose methylprednisolone (No direct evidence)	1.74 (0.18, 30.0)	256 per 1000 ¹	374 per 1000	118 per 1000 more (from 198 fewer to 656 more)	⊕○○○ Very Low Due to Indirectness ² and Imprecision ³	-	-
Low-dose methylprednisolone (No direct evidence)	Reference comparator	No estimable	No estimable	No estimable	Reference comparator	-	-

ARDS: Acute respiratory distress syndrome; SUCRA: Surface under the cumulative ranking curve
 NMA-SoF table definitions
 * Solid lines represent direct comparisons
 ** Network Meta-analysis (1) estimates are reported as odds ratio. CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals (CI) since a Bayesian analysis has been conducted.
 *** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.
 **** Rank and SUCRA are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.
 † Information is reported from studies included in the network meta-analysis for the comparison displays.

GRADE Working Group grades of evidence (or certainty in the evidence)
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes
¹ Mortality is reported from reference comparators in each comparison.
² Serious indirectness. Ventilation strategy of this direct evidence for this comparison is not low tidal ventilation.
³ Very serious imprecision. Due to wide confidence intervals in these estimates.
⁴ Serious risk of bias. Due to lack of blindness for participants and personnel.

Table 3 (continued)

b. Estimates of effects, credible intervals, and certainty of the evidence for incidence of infection in patients with ARDS

Bayesian NMA-SoF table

HARMS

Patient or population: Patients with ARDS

Interventions: High-dose methylprednisolone, low-dose methylprednisolone, hydrocortisone, dexamethasone, no steroid

Comparator (reference): One of the other therapies other than the therapy included in intervention

Outcome: Incidence of infection

Setting(s): Inpatient

Geometry of the Network*

Total studies: 9 RCT Total Participants: 1222	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of the evidence	Ranking**** (SUCRA)	Interpretation of Findings
		With reference comparator	With intervention	Difference			
1	High-dose methylprednisolone (Direct evidence; 1 RCT; 99 participants) 1.72 (0.46 to 6.88)	102 per 1000 [†]	163 per 1000	61 per 1000 fewer (from 52 fewer to 337 more)	⊕○○○ Very Low Due to Indirectness [‡] and Imprecision [§]	5 (17%)	-
2	Low-dose methylprednisolone (Direct evidence; 3 RCT; 295 participants) 0.56 (0.30 to 1.10)	417 per 1000 [†]	286 per 1000	131 per 1000 fewer (from 240 fewer to 23 more)	⊕⊕○○ Moderate Due to Imprecision [§]	1 (88%)	-
3	Hydrocortisone (Direct evidence; 2 RCT; 223 participants) 1.01 (0.44 to 2.41)	186 per 1000 [†]	188 per 1000	2 per 1000 more (from 95 fewer to 169 more)	⊕⊕○○ Low Due to Imprecision [§]	3 (42%)	-
4	Dexamethasone (Direct evidence; 3 RCT; 595 participants) 0.77 (0.43 to 1.32)	285 per 1000 [†]	235 per 1000	50 per 1000 fewer (from 139 fewer to 60 more)	⊕○○○ Very Low Due to Risk of bias [¶] , Imprecision [§]	2 (67%)	-
5	No steroid Reference comparator	No estimable	No estimable	No estimable	Reference comparator	4 (37%)	-
	High-dose methylprednisolone (No direct evidence) 2.26 (0.55, 10.2)	232 per 1000 [†]	406 per 1000	174 per 1000 more (from 90 fewer to 523 more)	⊕○○○ Very Low Due to Indirectness [‡] , Imprecision [§] , and Risk of bias [¶]	-	-
	Low-dose methylprednisolone (No direct evidence) 0.74 (0.32, 1.77)	232 per 1000 [†]	183 per 1000	49 per 1000 fewer (from 144 fewer to 116 more)	⊕○○○ Very Low Due to Imprecision [§] and Risk of bias [¶]	-	-
	Hydrocortisone (No direct evidence) 1.32 (0.49, 3.84)	232 per 1000 [†]	285 per 1000	53 per 1000 more (from 103 fewer to 305 more)	⊕○○○ Very Low Due to Imprecision [§] and Risk of bias [¶]	-	-
	Dexamethasone (No direct evidence) Reference comparator	No estimable	No estimable	No estimable	Reference comparator	-	-
	High-dose methylprednisolone (No direct evidence) 1.73 (0.33, 8.45)	181 per 1000 [†]	276 per 1000	95 per 1000 more (from 113 fewer to 468 more)	⊕○○○ Very Low Due to Indirectness [‡] and Imprecision [§]	-	-
	Low-dose methylprednisolone (No direct evidence) 0.56 (0.19, 1.60)	181 per 1000 [†]	110 per 1000	71 per 1000 fewer (from 141 fewer to 80 more)	⊕⊕○○ Low Due to Imprecision [§]	-	-
	Hydrocortisone (No direct evidence) Reference comparator	No estimable	No estimable	No estimable	Reference comparator	-	-
	High-dose methylprednisolone (No direct evidence) 3.06 (0.70, 14.1)	351 per 1000 [†]	623 per 1000	272 per 1000 more (from 76 fewer to 533 more)	⊕○○○ Very Low Due to Indirectness [‡] and Imprecision [§]	-	-
	Low-dose methylprednisolone (No direct evidence) Reference comparator	No estimable	No estimable	No estimable	Reference comparator	-	-

ARDS: Acute respiratory distress syndrome; SUCRA: Surface under the cumulative ranking curve

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Metaanalysis (1) estimates are reported as odds ratios. CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals (CI) since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

**** Rank and SUCRA are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

† Information is reported from studies included in the network meta-analysis for the comparison displays.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[†] Incidence of infection is reported from reference comparators in each comparison.

[‡] Serious indirectness. Ventilation strategy of this direct evidence for this comparison is not low tidal ventilation.

[§] Serious imprecision. Due to wide confidence intervals in these estimates.

[¶] Serious imprecision. Due to wide confidence intervals in these estimates.

[¶] Serious risk of bias. Due to lack of blindness for participants, personnel and outcome assessors, and unselective outcomes reporting.

Table 3 (continued)

c. Estimates of effects, credible intervals, and certainty of the evidence for ventilator-free days in patients with ARDS

Bayesian NMA-SoF table

BENEFITS

Patient or population: Patients with ARDS

Interventions: Low-dose methylprednisolone, hydrocortisone, dexamethasone, no steroid

Comparator (reference): One of the other therapies other than the therapy included in intervention

Outcome: Ventilator-free days for 28 days

Setting(s): Inpatient

Geometry of the Network*

Total studies: 7 RCT Total Participants: 1094	Relative effect (95% CrI)	Anticipated absolute effect (95% CrI)**		Certainty of evidence	Ranking*** (SUCRA)	Interpretation of Findings
		Assumed risk control	With intervention			
1 Low-dose methylprednisolone (Direct evidence; 3 RCT; 295 participants)	-	Study population	The mean difference in increasing VFDs was 6.06 higher (2.5 higher to 10.5 higher)	⊕⊕⊕⊕ High	1 (93%)	-
2 Hydrocortisone (Direct evidence; 2 RCT; 223 participants)	-	Study population	The mean difference in increasing VFDs was 2.10 higher (3.15 lower to 7.09 higher)	⊕⊕○○ Low Due to Imprecision ¹	3 (39%)	-
3 Dexamethasone (Direct evidence; 2 RCT; 576 participants)	-	Study population	The mean difference in increasing VFDs was 3.64 higher (0.56 lower to 7.83 higher)	⊕○○○ Very Low Due to Imprecision ¹ and Risk of bias ²	2 (62%)	-
4 No steroid	Reference comparator	No estimable	No estimable	Reference comparator	4 (7%)	-
Low-dose methylprednisolone (No direct evidence)	-	Study population	The mean difference in increasing VFDs was 2.40 higher (2.87 lower to 8.70 higher)	⊕○○○ Very Low Due to Imprecision ¹ and Risk of bias ²		
Hydrocortisone (No direct evidence)	-	Study population	The mean difference in increasing VFDs was 1.54 lower (8.34 lower to 4.87 higher)	⊕○○○ Very Low Due to Imprecision ¹ and Risk of bias ²		
Dexamethasone (No direct evidence)	Reference comparator	No estimable	No estimable	Reference comparator		
Low-dose methylprednisolone (No direct evidence)	-	Study population	The mean difference in increasing VFDs was 3.99 higher (1.90 lower to 11.1 higher)	⊕⊕⊕○ Moderate Due to Imprecision ³		
Hydrocortisone (No direct evidence)	Reference comparator	No estimable	No estimable	Reference comparator		

ARDS: Acute respiratory distress syndrome; VFDs: Ventilator-free days; MD: Mean difference; SUCRA: Surface under the cumulative ranking curve

NMA-SoF table definitions

* Lines in the network graphic represent direct comparisons

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Rank and SUCRA are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

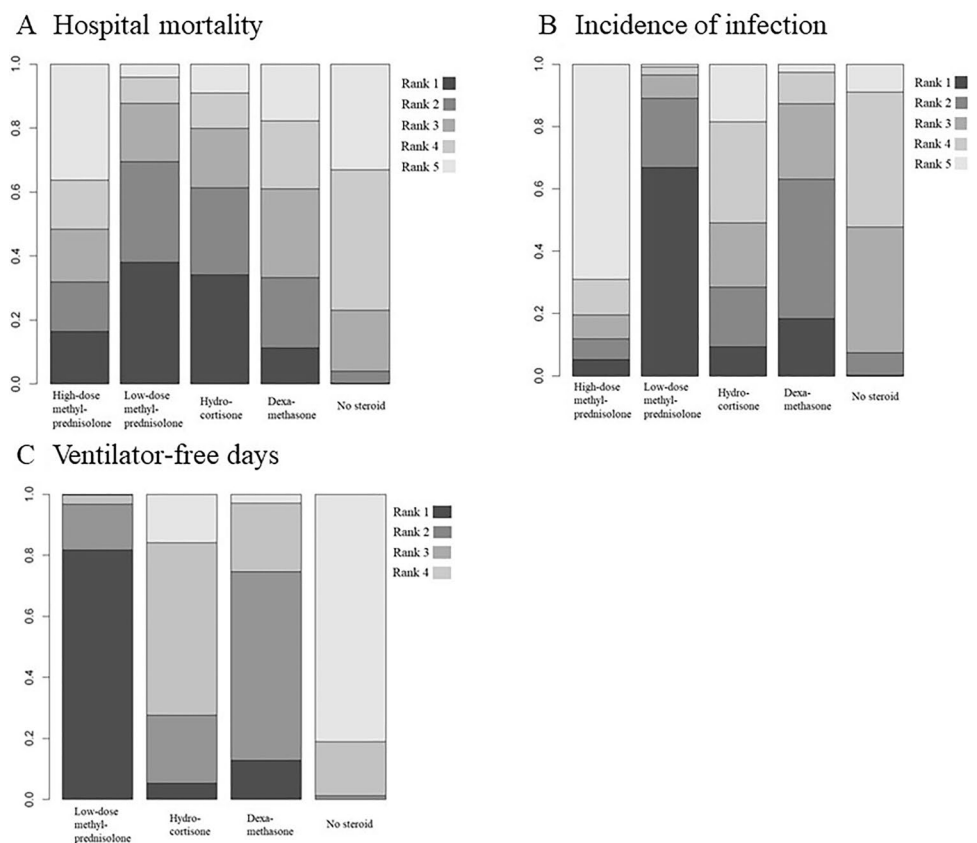
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes.

¹ Very serious imprecision. Due to wide confidence intervals in these estimates, defined two VFDs as clinically meaning deference of VFDs.

² Very serious risk of bias. Due to lack of blindness for participants and personnel, and unplanned discontinuation of trial.

³ Serious imprecision. Due to wide confidence intervals in these estimates, defined two VFDs as clinically meaning deference of VFDs.

Fig. 3 Rank probabilities in the network meta-analysis

and VFD [18]. In contrast to previous SR/MAs, our direct pairwise comparisons show that any of the steroids were not associated with reducing hospital mortality and incidence of infection compared with no steroid. Based on these results, any type of steroids might not build up a steadfast position.

Though previous studies provided results of a pairwise comparison with placebo, we created indirect estimates of comparisons among steroids by NMA and verified estimates of hospital mortality, the incidence of infection, and VFD among each steroid. This NMA for patients with ARDS revealed that low-dose methylprednisolone or hydrocortisone relative to dexamethasone may reduce hospital mortality (95 per 1000 patients fewer, 76 per 1000 patients fewer, respectively), high-dose methylprednisolone relative to hydrocortisone may increase hospital mortality (113 per 1000 patients more), and high-dose methylprednisolone relative to low-dose methylprednisolone may increase hospital mortality (118 per 1000 patients more). Low-dose methylprednisolone relative to hydrocortisone may reduce incidence of infection (71 per 1000 patients fewer), while high-dose methylprednisolone relative to other steroids may increase incidence of infection (95–272 per 1000 patients more). Low-dose methylprednisolone relative to hydrocortisone and dexamethasone may increase VFD (6.06, 2.40 higher, respectively). In addition, the rank probability showed that low-dose methylprednisolone may be the

optimal treatment, whereas high-dose methylprednisolone and no steroid may be the inferior to other treatment in terms of hospital mortality, incidence of infection, and VFD. Though the evidences were uncertain, considering these results and point estimates, our NMA suggested that the effect of steroids on outcome vary depending on the types of steroids.

Our NMA has several limitations. We could not use EMBASE for our database search. However, we consider studies that were included as appropriate, as we manually searched the reference list of the included articles and their reference lists and checked previous SRs/MAs. Although we performed an NMA, each comparison included only a few studies. In addition, NMA for VFD did not include studies using high-dose methylprednisolone. Conventional therapy strategies besides steroids may vary among eligible studies. In particular, compliance with the low tidal ventilation strategy, which was the strategy to improve mortality, was low in 1999 or earlier. Though the definition of infection was not reported in some eligible studies and was discrepant between studies, the definition of each study conformed to the general criteria. There may be an unexplained heterogeneity among eligible studies other than different definitions of infection because a placebo was not used in studies on dexamethasone. However, we made efforts to minimize heterogeneity by including patients with mechanical ventilation and

checking age, diagnosis criteria, and etiology. Finally, we could not deny the possibility that not only the types of steroids but also the duration of administration might affect our results. We have defined the types and protocols of steroids based on previous studies, as previous RCTs did not verify different durations among steroids; however, we could not stratify results by the duration of steroids. Considering past studies, as low-dose methylprednisolone was administered the longest duration among the types of steroids, favorable outcomes of low-dose methylprednisolone may be obtained. Therefore, we could not draw conclusions on the optimal steroid agent. Further studies including these above studies must confirm our results.

In conclusion, our results indicate that the effect of steroids on outcome might vary depending on the type of steroids in ARDS patients. Further studies are needed to identify the optimal type and dosage.

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Data availability The datasets analyzed during the current network meta-analysis are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest All the authors declare that they have no conflicts of interest.

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