Supplementary material

Mammen MJ, Aryal K, Alhazzani W, Alexander PE. Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials. Pol Arch Intern Med. 2020; 130: 276-286. doi:10.20452/pamw.15239

Appendix S1- *Supplemental Methods and Results*

Supplemental Methods

Data Sources and Searches

ARDS definition used for study selection

In the event that data could support sub-group analysis by severity of ARDS (degree of hypoxemia), we used the Berlin definition to define ARDS[1]. This is based on three mutually exclusive categories of ARDS based on the degree of hypoxemia: i) mild (200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg), ii) moderate (100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg), and iii) severe (PaO_2/FIO_2 ≤ 100 mm Hg) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤40 mL/cm H_2O), positive end-expiratory pressure (≥10 cm H_2O), and corrected expired volume per minute (≥10 L/min)

Study Selection

To add robustness to the screening, the reviewers conducted an initial piloting/calibration step of the citations (25 citations) and full texts (2 full-texts) and decided to iterate the step if chance-corrected kappa agreement was less than 0.70 [2].

Search Strategy

MEDLINE search (1996 to February 14th 2020)

Database: Ovid MEDLINE(R) <1996 to February 14, 2020>

Search Strategy:

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1 exp Respiratory Distress Syndrome, Adult/ or Respiratory Distress Syndrome.mp. (25609)

2 (((acute or adult) and (respiratory adj1 distress)) or ards).mp. (23833)

3 exp Acute Lung Injury/ (6011)

4 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. (12217)

5 1 or 2 or 3 or 4 (37142)

6 ((randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or clinical trials as topic.sh. or trial.ti.) not (exp animals/ not humans.sh.) (974959)

7 5 and 6 (3600)

8 corticosteroid*.mp. (64069)

9 7 and 8 (253)

EMBASE search (2018 to February 14th 2020)

Database: EMBASE <1996 to 2020 February 14>

Search Strategy:

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1 exp adult respiratory distress syndrome/ (30472)

2 (((acute or adult) and (respiratory adj1 distress)) or ards).mp. (55493)

3 exp acute lung injury/ (14541)

4 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. (22830)

5 1 or 2 or 3 or 4 (70701)

6 (Acyclovir or Albumin* or Anisodomine* or Beta-agonist* or Corticosteroid* or Dazoxiben or Granulocyte-macrophage colonystimulating factor* or Indomethacin* or Interleukin-10 or Ketoconazole or Levosimendan or Lisofylline or L02-oxothiazolidine-4-carboxylic acid or Mesenchymal stem cell* or N-acetylcysteine or procysteine or Neutrophil elastase inhibitor* or Penehyclidine hydrochloride or Pentoxifylline or Prostaglandin E1 or Sivelestat or Statin* or Surfactant* or Xuebijing or drug* or pharmacological agent*).mp. (8475446)

7 aciclovir/ or albumin/ or exp beta adrenergic receptor stimulating agent/ or exp corticosteroid/ or dazoxiben/ or granulocyte macrophage colony stimulating factor/ or indometacin/ or interleukin 10/ or ketoconazole/ or levosimendan/ or lisofylline/ or exp mesenchymal stem cell/ or acetylcysteine/ or 2 oxo 4 thiazolidinecarboxylic acid/ or exp leukocyte elastase inhibitor/ or exp cholinergic receptor blocking agent/ or pentoxifylline/ or prostaglandin E1/ or exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ or

sivelestat/ or exp surfactant/ or exp drug/ or (drug administration or drug therapy).fs. (5945915)

8 6 or 7 (8744186)

9 5 and 8 (36820)

10 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (1169301)

11 (randomized controlled trial/ or randomization/ or placebo/ or crossover procedure/ or double blind procedure/ or single blind procedure/ or (crossover* or cross over*).ti,ab. or (doubl* adj blind*).ti,ab. or (controlled adj3 (study or design or trial)).ti,ab. or (placebo* or allocat* or trial* or random* or groups).ti,ab.) not ((exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti,ab.)) (3661204)

12 9 and 10 (3755)

13 9 and 11 (6212)

14 9 and 10 (3755)

15 limit 14 to yr="2018 -Current" (433)

16 limit 15 to human (371)

Data Abstraction and Quality Assessment

For all phases of the project, reviewers resolved disagreements by consensus discussion and, if necessary, in consultation with a third adjudicating reviewer. We also employed a calibration step, as described earlier in the study selection.

GRADE Methods

We were also alert to a modified Cochrane instrument as we conducted the risk of bias of the primary studies [3]. We would assess the effect of losses to follow-up (best case, worse case scenarios, the extent of loss and differential loss, and imputation strategies) and decided to consider sensitivity modelling if it was found that included studies were plagued by substantial differential loss to follow-up/data loss [4].

We planned to assess publication bias through visual inspection of funnel plots and possible statistical tests (Egger's test), guided by the threshold of at least 10 studies as part of the analysis[5]. We were also guided by the rule of thumb for optimal information (OIS) size as one objective measure of imprecision for grading evidence [6, 7] (rating down for imprecision if the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial).

All-cause mortality at 60 days based on time from ARDS onset

In three trials (n=659) that examined all-cause mortality at 60 days based on time from ARDS onset, we see no difference in the risk of death based on corticosteroid treatment versus control (RR 0.82, 95% CI 0.54 to 1.25, p=0.36; I^2 = 63%; low certainty) (Figure S4). Absolute effects were 64 fewer deaths per 1,000 affected individuals (from 163 fewer to 88 more) (Table S2).

However, the subgroup analyses suggested that the effect varied according to time from ARDS onset ($\leq$ 12 hours, 1-7, days versus 7-13 days versus more than 14 days). An apparent increased risk of death is seen at greater than 14 days from ARDS onset when receiving corticosteroid (I^2=62%, p=0.05). The increased RR was 4.35 (95% CI 1.03 to 18.39), p=0.05 for > 14 days.

Appendix S2- *Supplemental Tables and Figures*

Figure S1: PRISMA flow diagram

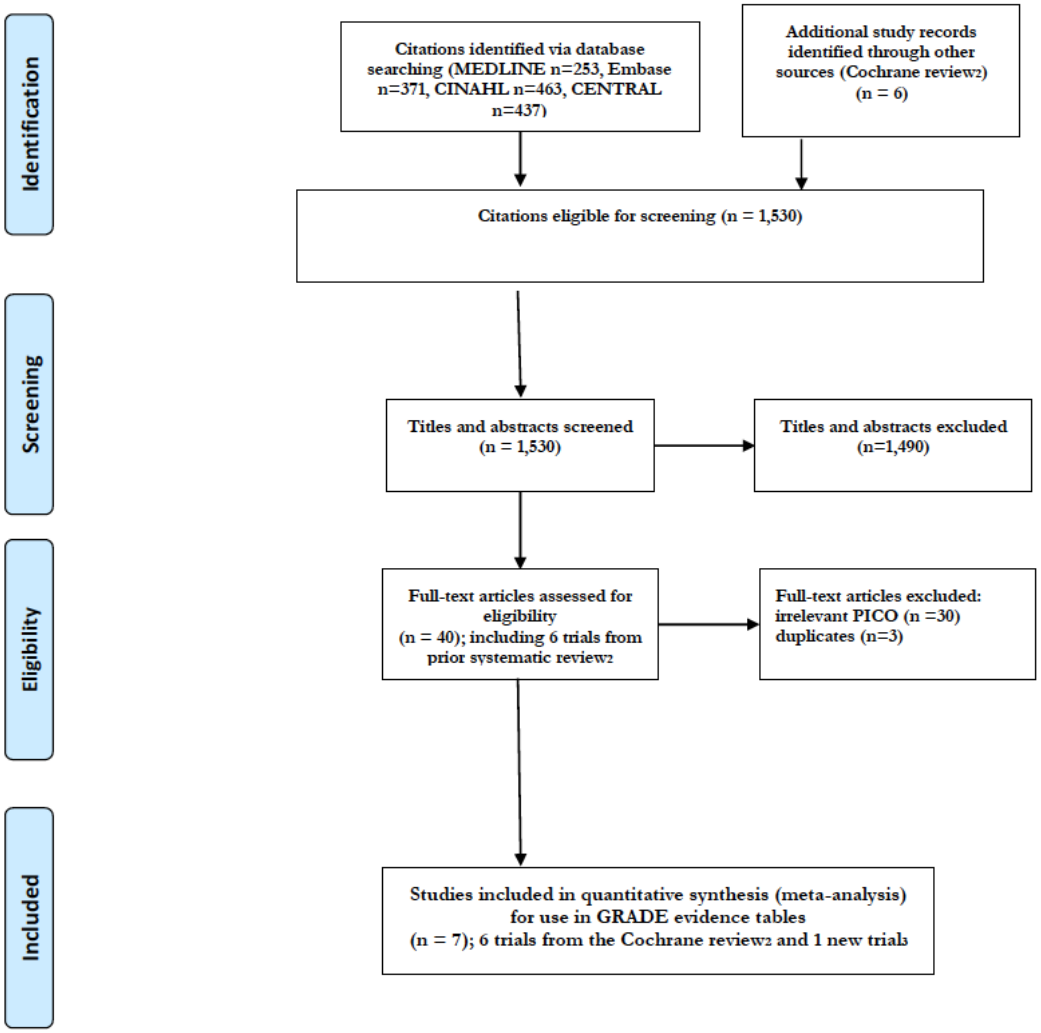

Figure S2: Effect of corticosteroids on all-cause mortality in ARDS patients by subgroups stratified from onset of ARDS in timing of corticosteroid therapy

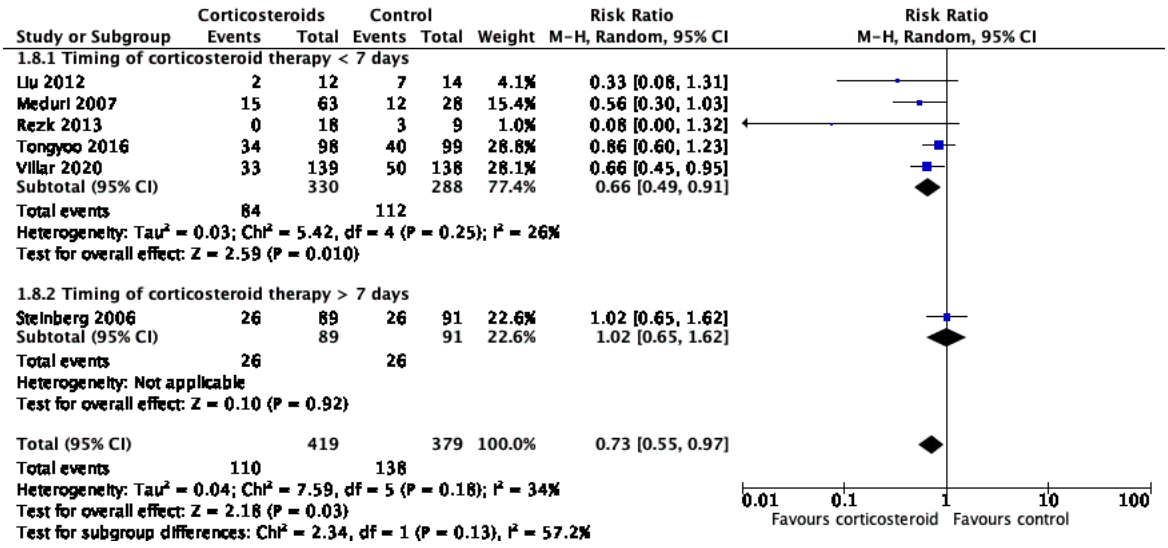

Figure S3: Effect of corticosteroids on ventilator-free days up to 28 days in ARDS patients by subgroups stratified from onset of ARDS in timing of corticosteroid therapy

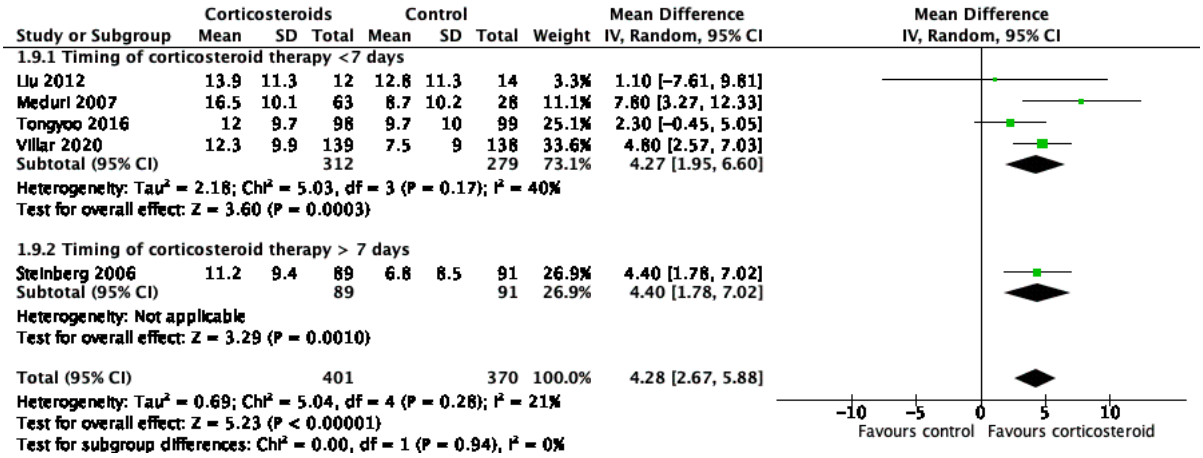

Figure S4: Effect of corticosteroids on all-cause mortality at 60 days based on time from ARDS onset

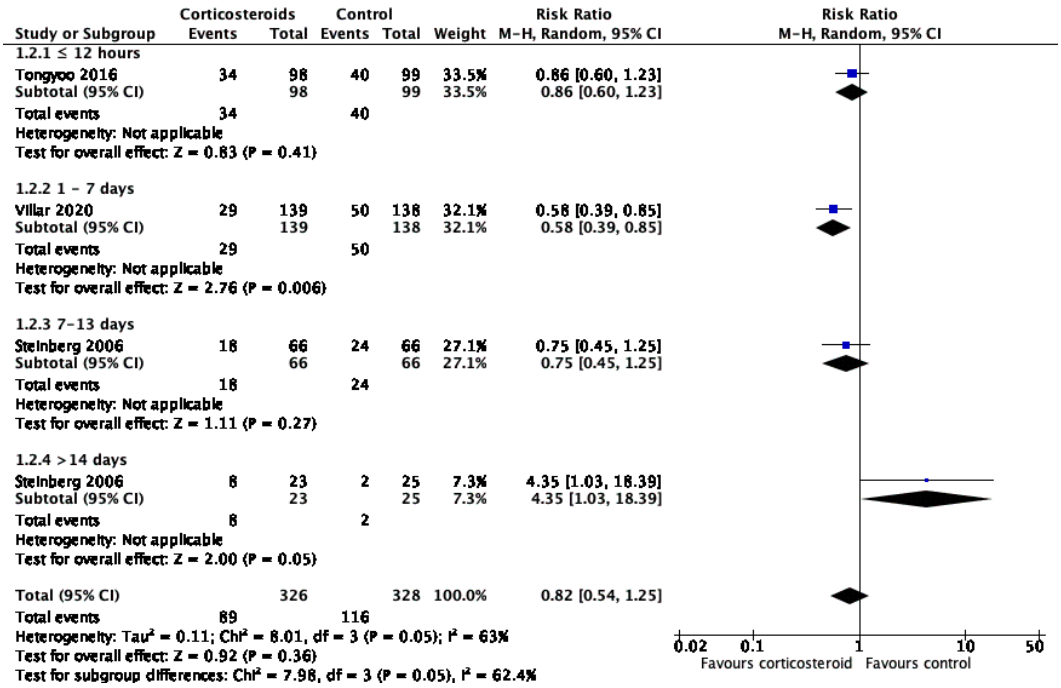

Table S1: Risk of bias assessment of included trials

Study author surname, year	**Randomization and allocation concealment**	**Blinding Patients**	**Blinding Healthcare providers**	**Blinding data collectors**	**Blinding adjudicators**	**Blinding data analysts**	**Selective outcome reporting**	**Attrition**	**Baseline imbalance**	**Stopping for benefit**	**Other bias issues**	**Industry funded**	**Overall risk of bias**
Liu, 2012	Probably Yes 1	Probably No 2	Probably No 2	Probably No 2	Probably No 2,8	Probably No 2	Probably Yes 3	Probably Yes 3	Probably No 7	Probably No 4	Probably No 4	Non-profit	High
Meduri, 2007	Yes 5	Yes 5	Yes 5	Probably Yes 1	Probably No 2,8	Probably No 2,8	Probably No 2	Probably No 6	Probably No 2	No	Probably No 4	Non-profit	Low
Rezk, 2013	Probably No 2	Probably No 2	Probably No 2	Probably No 2	Probably No 2	Probably No 2	Probably Yes 3	Probably No 6	Probably No 7	Probably No 4	Probably No 4	Uncertain	High
Steinberg, 2006	Probably Yes 1	Probably Yes 1	Probably Yes 1	Probably Yes 1	Probably No 2,8	Probably No 2,8	Probably Yes 3	Probably No 6	Probably No 7	Probably No	Probably No 4	Non-profit	Low

Tongyoo, 2016	Yes “computer-generated randomization table”	Yes	Yes research nurse not involved in treatment prepared treamtents	Yes	Probably Yes 1	Probably Yes 1	Probably Yes 3 clinical trial registration occurred after trial started	Probably No 4	Probably No 7	No	Probably No 4	Non-profit	Low
Villar, 2020	Yes 9	Probably Yes (patient likely sedated and not aware of interventions)	No (no placebo)	No (no placebo)	Probably Yes 1	Probably Yes 1	Probably No 2	Probably No 6	Probably No 7	Probably No (it was stopped due to lack of enrollment) 10	Probably No 4	Non-profit	Low for mortality, High for vent-free days, and mechanical

													duration
Zhao 2014	Probably Yes 1	Probably No 2	No	No	No	No	Probably No 2	Probably No 6	Probably No 7	Probably No	Probably No 4	Non-profit	High

1 Lack of full reporting, but we favored the domain being executed.

2 Reporting was not present, therefore not able to make accurate judgement, but we judged the domain was likely not executed.

3 Reporting was not present, therefore not able to make accurate judgement, so we judged the domain having the issue.

4 Reporting was not present, therefore not able to make accurate judgement, so we judged the domain not having the issue (none identified).

5 Sufficient details were provided to confirm enough presence of execution.

6 All data was reported analyzed intention to treat.

7 Reported as no overt imbalance.

8 But likely not applicable to mortality

9 “Patients were randomly assigned to receive conventional treatment (ie, continued routine intensive care; control group) or conventional treatment plus intravenous dexamethasone. Randomisation was based on balanced treatment assignments and stratified for centres using blocks of ten opaque, prenumbered, sealed envelopes”

10 “The trial was stopped following recommendations by the data and safety monitoring board due to low enrolment numbers”

Table S2. GRADE Evidence Profile: Corticosteroids for Patients with ARDS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality (all-cause)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Usual care	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	119/443 (26.9%)	151/408 (37.0%)	**RR 0.75** (0.59 to 0.95)	**93 fewer per 1,000** (from 152 fewer to 19 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Usual care	Relative (95% CI)	Absolute (95% CI)		
Mechanical Ventilation Duration												
5	randomised trials	not serious [a]	serious [c]	not serious	serious [d]	none	342	303	-	MD **4.93 Days fewer** (7.81 fewer to 2.06 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Usual care	Relative (95% CI)	Absolute (95% CI)		
Ventilator-free days up to day 28												
5	randomised trials	not serious [a]	not serious	not serious	serious [e]	none	401	370	-	MD **4.28 Days more** (2.67 more to 5.88 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Usual care	Relative (95% CI)	Absolute (95% CI)		
Hyperglycemia												
3	randomised trials	serious [f]	not serious	not serious	not serious	none	229/300 (76.3%)	182/265 (68.7%)	**RR 1.12** (1.01 to 1.24)	**82 more per 1,000** (from 7 more to 165 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Usual care	Relative (95% CI)	Absolute (95% CI)		
Neuromuscular weakness												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Usual care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [f]	not serious	not serious	very serious [g,h]	none	30/151 (19.9%)	22/119 (18.5%)	**RR 1.30** (0.80 to 2.11)	**55 more per 1,000** (from 37 fewer to 205 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Sensitivity analysis reveals results were robust and consistent with the removal of high-risk studies, therefore, we did not rate down

b. Optimal information size (n=300 events for a dichotomous outcome) was not reached (n=270). Therefore, we downgraded one level.

c. High I2 and [significant] Cochran Q chi-square test warranted a double downgrade (point estimates varied widely. Sensitivity analysis with removal of high risk of bias studies showed reductions of heterogeneity to a moderate-high level but did not explain the heterogeneity.

d. The Optimal information size is reached and the both boundaries of the 95% CI are on the side of benefit. Optimal information size is met. However, the number of studies was low (driven largely by Villar (2020) and we judged that the 95% CI is wide enough to warrant a downgrade for imprecision.

e. The rule of thumb Optimal information size is reached (n=400 for continuous outcomes) and the both boundaries of the 95% CI are on the side of benefit. However, we judged that the 95% CI is wide enough to warrant a downgrade for imprecision. In addition, there is a small number of studies.

f. Due to the low number of studies and sub-optimal reporting, we decided to downgrade one level.

g. The confidence interval crossed harms and benefits

h. Optimal information size not reached and based on a small number of studies and small number of events

Table S3*: Excluded studies*

Author surname, year	**Reason for exclusion***
Baek, 2020 [8]	Propensity matched cohort study design, ineligible PICO and design
Lansbury, 2020 [9]	Review of observational cohort studies and 1 RCT, ineligible PICO and design
Zhou, 2020 [10]	Meta-analysis of 14 observational, 1 RCT, ineligible PICO and design
Tsai, 2020 [11]	Retrospective cohort study, ineligible PICO and design
Sun, 2019 [12]	Systematic review of mainly observational studies, ineligible designs; similar RCTs as Cochrane review but judged of lower methodologically quality
Wu, 2020 [13]	Retrospective analysis, ineligible design

**Our decisions to exclude these studies, were driven mainly by ineligible study designs and PICO we felt did not specifically match our review PICO that focused on RCTs*

References

1. Definition Task Force A, Ranieri V, Rubenfeld G, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526-33.

2. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine. 2009;151:264-9.

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4. Ebrahim S, Akl EA, Mustafa RA, et al. Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers. J Clin Epidemiol. 2013;66:1014-21 e1.

5. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.

6. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64:407-15.

7. Castellini G, Bruschettini M, Gianola S, et al. Assessing imprecision in Cochrane systematic reviews: a comparison of GRADE and Trial Sequential Analysis. Syst Rev. 2018;7:110.

8. Baek MS, Lee Y, Hong SB, et al. Effect of corticosteroid therapy in the early phase of acute respiratory distress syndrome: a propensity-matched cohort study. Korean J Intern Med. 2020.

9. Lansbury LE, Rodrigo C, Leonardi-Bee J, et al. Corticosteroids as adjunctive therapy in the treatment of influenza: An updated Cochrane systematic review and meta-analysis. Critical Care Medicine. 2020;48:e98-e106.

10. Zhou Y, Fu X, Liu X, et al. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. Sci Rep. 2020;10:1-10.

11. Tsai MJ, Yang KY, Chan MC, et al. Impact of corticosteroid treatment on clinical outcomes of influenza-associated ARDS: a nationwide multicenter study. Ann Intensive Care. 2020;10:26.

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