Supplementary Materials

Table S1 Summary of search strategy

Search No	Search strategy*
#1	MeSH descriptor: [steroid] explode all trees
#2	MeSH descriptor: [corticosteroid] explode all trees
#3	steroid* or glucocorticoid* or corticosteroid* or cortisone* or hydrocortisone* or prednisolon* or methylprednisolon* or prednison* or dexamethason* or triamcinolon* in All Text
#4	#1 or #2 or #3
#5	MeSH descriptor: [sepsis] explode all trees
#6	MeSH descriptor: [shock, septic] explode all trees
#7	seps* or septic* in All Text
#8	#5 or #6 or #7
#9	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.)
#10	#4 and #8 and #9

*This search strategy was adopted for following databases: PubMed, MEDLINE, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL).

Table S2 Summary of previous research findings

Title	Study (year)	Publish journal	Included trails	Participants	Subgroup analyse	Primary outcomes	Subgroup analyse outcomes	Adverse events	Conclusions
Safety and Efficacy of Corticosteroids for the Treatment of Septic Shock: A Systematic Review and Meta-Analysis	Sligl W, 2009	Clinical Infectious Diseases	8	Adults with septic shock	Responders and non-responders based on corticotropin stimulation test	28-day all-cause mortality (RR, 1.00; 95% CI, 0.84–1.18,P=0.97) Shock reversal (RR, 1.41; 95% CI, 1.22–1.64, P=)	Responders(RR, 0.95; 95% CI, 0.70- 1.28,P=0.72) Nonresponders(RR, 0.90; 95% CI, 0.75–1.07,P=0.23)	Superinfection(RR, 1.11; 95% CI, 0.86–1.42, P=0.42)	Corticosteroid therapy appears to be safe but does not reduce 28-day all-cause mortality rates
CorticosteroidsintheTreatmentof Severe Sepsis and Septic Shock in Adults	Annane, 2009	The Journal of the American Medical Association	22	Severe Sepsis and Septic Shock in Adults	Long course of low-dose and short courses of high-dose corticosteroids	28-day all-cause mortality (RR,0.84; 95% CI, 0.71-1.00; P=.05). Increased 28-day shock reversal(RR, 1.12; 95% CI, 1.02-1.23, P=.02)	Prolonged low-dose corticosteroid suggests benefit on short-term mortality (RR, 0.84; 95%CI, 0.72- 0.97, P=.02)	No increasing the risk of gastroduodenal bleeding, superinfection and neuromuscular weakness. Hyperglycemia (RR, 1.16; 95% CI, 1.07-1.25, P<001) Hypernatremia (RR, 1.61; 95% CI, 1.26-2.06, P<001)	No clear benefit on mortality.
Low-Dose Hydrocortisone Therapy Attenuates Septic Shock in Adult Patients but Does Not Reduce	Wang, 2014	Society of Critical Care Anesthesiologists	8	Septic Shock in Adult	Subgroup analyses for sample size (< 100 or > 100) and quality score (6 or 7)	28-day all-cause mortality (RR,0.84; 95% CI, 0.71-1.00; P=.05). 7-day and 28-day shock reversal (OR = 2.08, 95% CI, 1.58–2.73, P < 0.0001)	No clear benefit on mortality. Benefit on shock reversal	No increasing the risk of gastroduodenal bleeding and superinfection. Hyperglycemia (OR = 2.143, 95% CI, 1.41–3.26, P < 0.0001)	Ameliorates septic shock at 7 and 28 days, but no benefit 28-day mortality

28-Day Mortality: A Meta-Analysis of Randomized Controlled Trials						and (OR = 1.50, 95% CI, 1.12–1.99, P = 0.006).			
Corticosteroids for treating sepsis	Annane, 2015	The Cochrane Collaboration	33	Patients with sepsis	Based on treatment dose/duration, methodological quality and targeted population (sepsis or only septic shock)	28-day all-cause mortality (RR, 0.88; 95% CI 0.78 to 0.99, P=0.01) 7-day and 28-day shock reversal (OR = 1.31, 95% CI 1.14 to 1.51, P = 0.001) and (OR = 1.11, 95% CI 1.02 to 1.21; P = 0.01).	No information only for septic shock.	No information only for septic shock.	Benefit on mortality.
Corticosteroids in septic shock: a systematic review and network meta-analysis	Gibbison, 2017	Critical Care	Complete data from 22 studies and partial data from 1 study.	Septic Shock in Adult	Based on treatment regimen.	No clear evidence that any intervention or treatment regimen is better than any other across the spectrum of mortality. Benefit on shock reversal.	No.	No clear evidence that any one corticosteroid drug or treatment regimen is more likely to be effective reducing the incidence of gastrointestinal bleeding or superinfection in septic shock.	No clear evidence that any one corticosteroid drug or treatment regimen is more likely to be effective in reducing mortality. Hydrocortisone shows more shock reversal.

Fig. S1 PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3, 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be	Table S1

		repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 and Fig. 1

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10 and Fig. 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13 and Fig. 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: **www.prisma-statement.org**.

Fig. S2 Summary of findings table

corticosteroids for septic shock

Patient or population: patients with septic shock
Settings:
Intervention: corticosteroids

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Corticosteroids	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
28-day all cause mortality Follow-up: 3 months	**Study population**		**RR 0.93** (0.86 to 0.99)	9043 (21 studies)	⊕⊕⊕⊖ **moderate**[1]	
	312 per 1000	**290 per 1000** (274 to 309)				
	Moderate					
	333 per 1000	**310 per 1000** (293 to 330)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

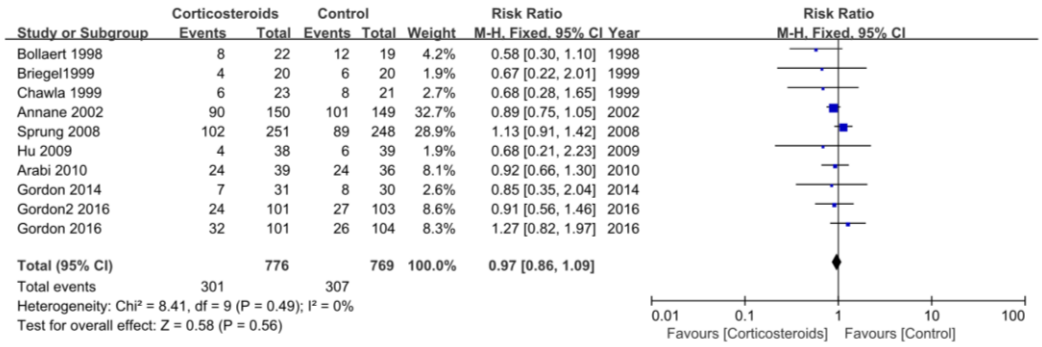
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Benefit-to-riskratio of some studies, remains controversia.

Fig. S3 Forest plots of comparison corticosteroids versus control of ICU mortality(a) and hospital mortality(b).

a.



b.

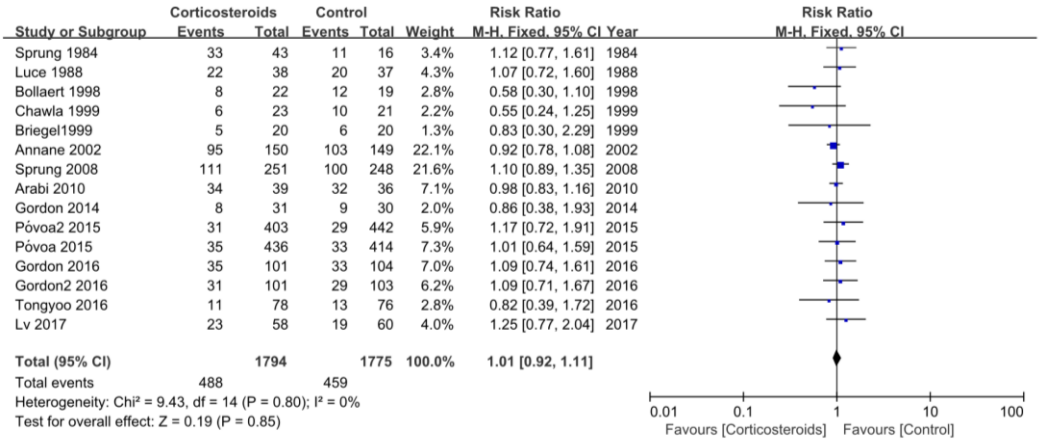
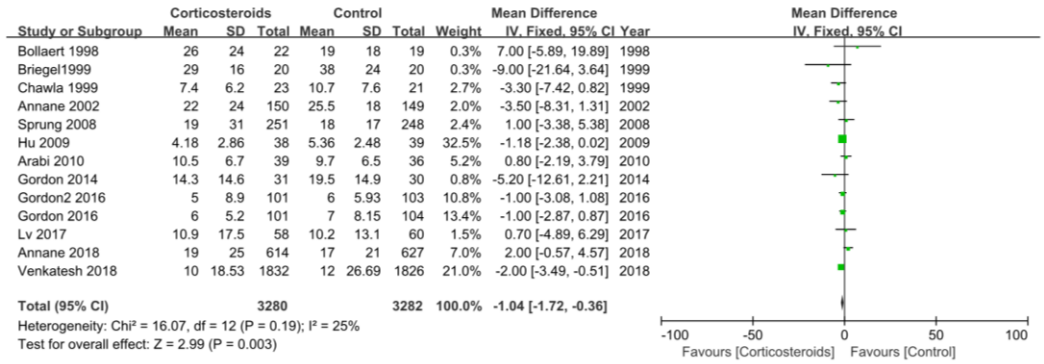


Fig. S4 Forest plots of comparison corticosteroids versus control of length of ICU stay (a) and hospital stay for all participants (b).

a.



b.

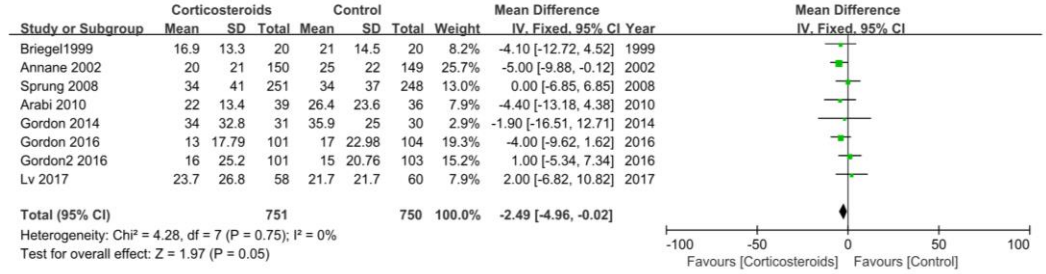
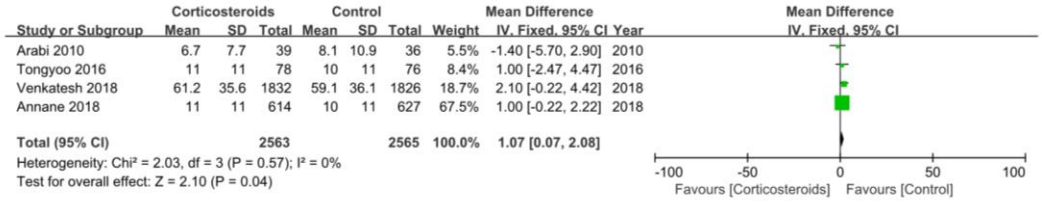


Fig. S5 Forest plots of comparison corticosteroids versus control of mechanical ventilation free days (**a**) and duration of mechanical ventilation (**b**) for all participants.

a.



b.

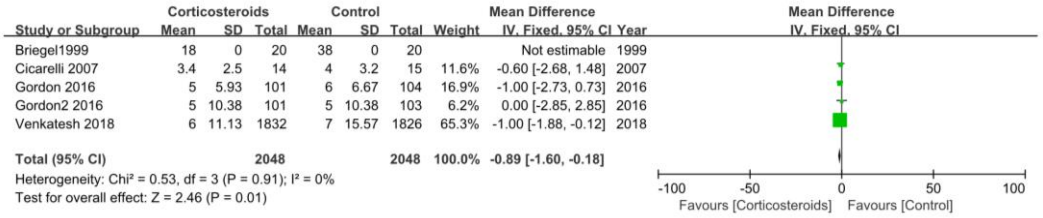
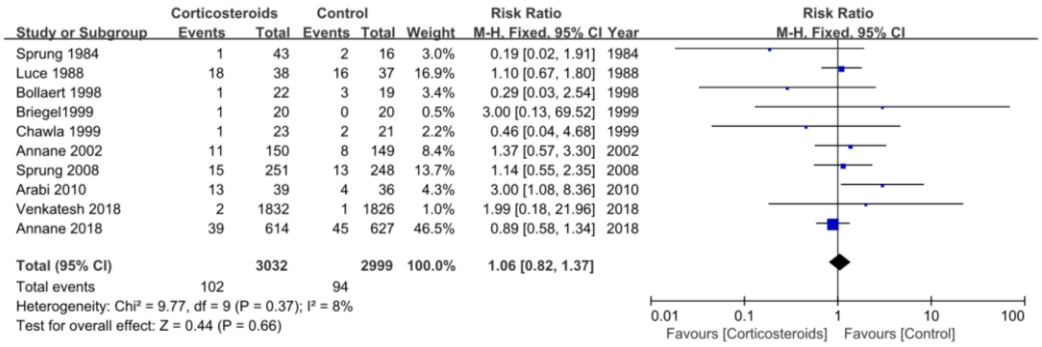
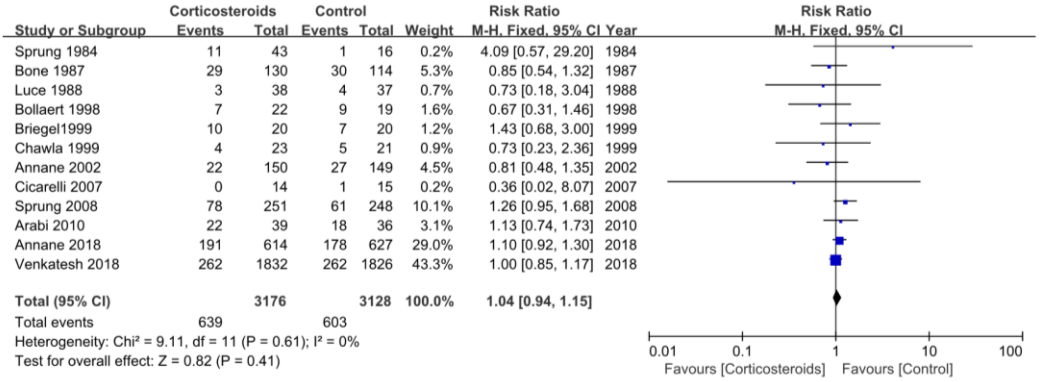


Fig. S6 Forest plots of comparison corticosteroids versus control of adverse events, including gastroduodenal bleeding (**a**), superinfections (**b**) and hyperglycaemia(**c**).

a.



b.



c.

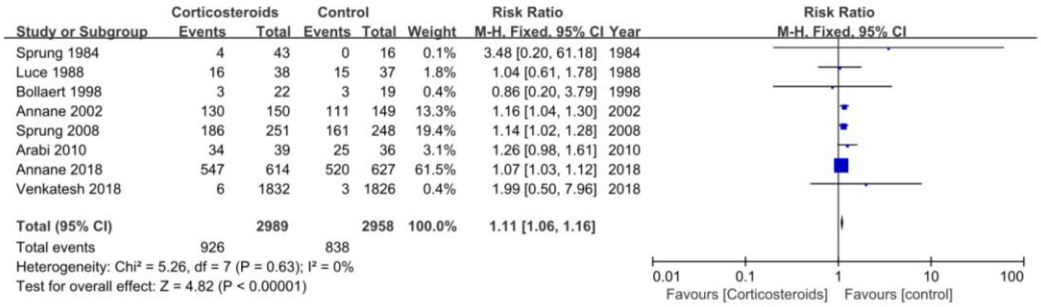
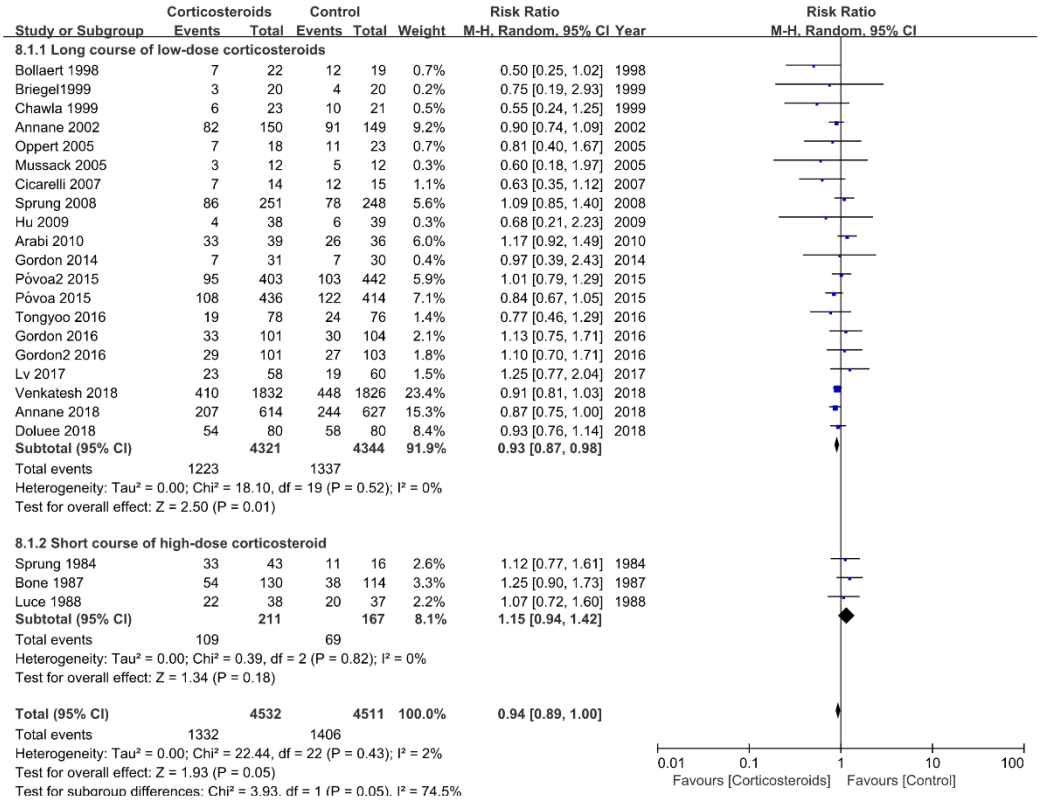
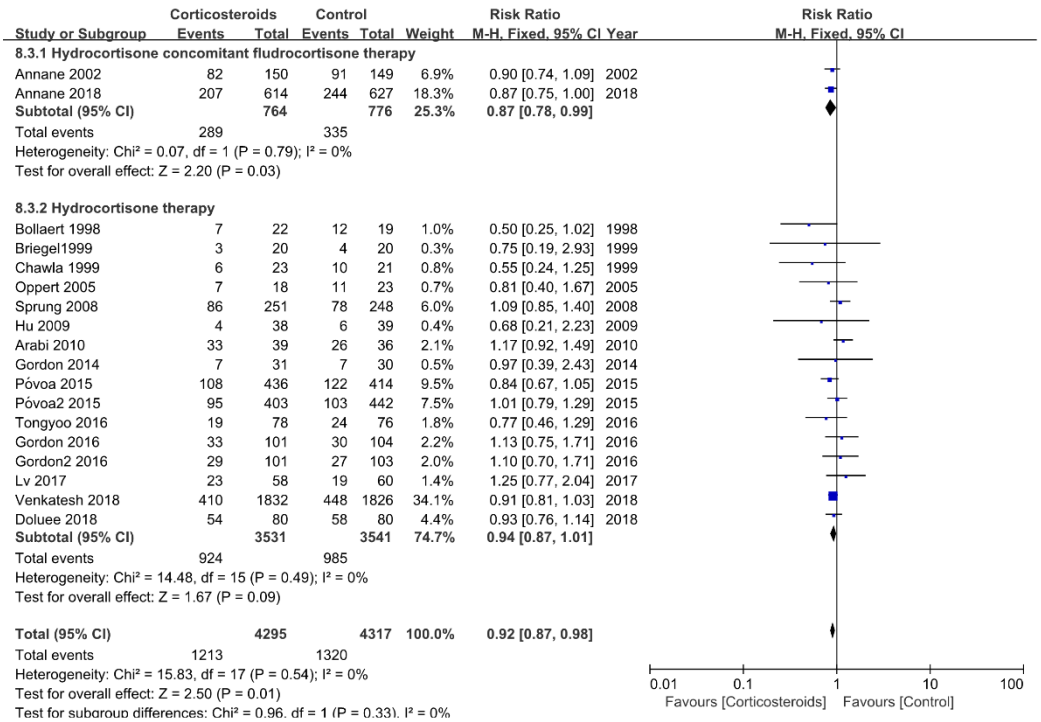


Fig. S7 Forest plots of comparison corticosteroids versus control of 28-day all-cause mortality by subgroups based on treatment dose and course (**a**), whether concomitant mineralocorticoid (**b**), date of publication (**c**), and size sample(**d**).

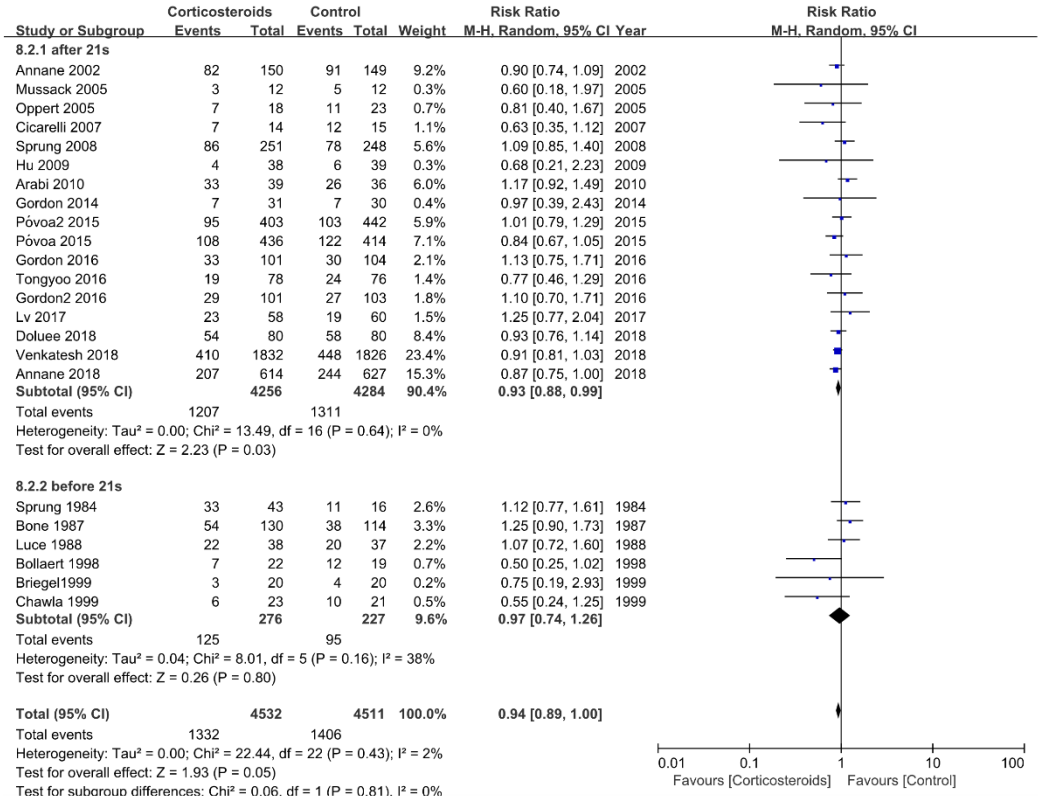
a.



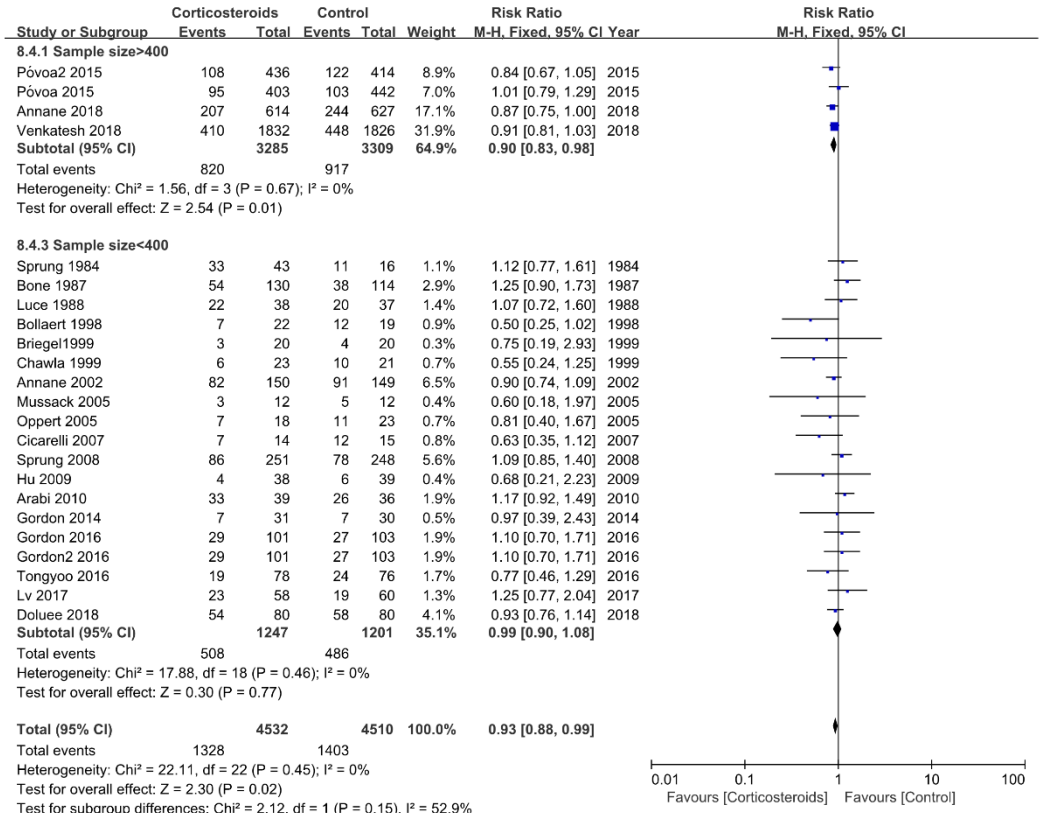
b.


Corticosteroids
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
8.3.1 Hydrocortisone concomitant fludrocortisone therapy
Annane 2002 82 150 91 149 6.9% 0.90 [0.74, 1.09] 2002
Annane 2018 207 614 244 627 18.3% 0.87 [0.75, 1.00] 2018
Subtotal (95% CI) 764 776 25.3% 0.87 [0.78, 0.99]
Total events 289 335
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
8.3.2 Hydrocortisone therapy
Bollaert 1998 7 22 12 19 1.0% 0.50 [0.25, 1.02] 1998
Briegel1999 3 20 4 20 0.3% 0.75 [0.19, 2.93] 1999
Chawla 1999 6 23 10 21 0.8% 0.55 [0.24, 1.25] 1999
Oppert 2005 7 18 11 23 0.7% 0.81 [0.40, 1.67] 2005
Sprung 2008 86 251 78 248 6.0% 1.09 [0.85, 1.40] 2008
Hu 2009 4 38 6 39 0.4% 0.68 [0.21, 2.23] 2009
Arabi 2010 33 39 26 36 2.1% 1.17 [0.92, 1.49] 2010
Gordon 2014 7 31 7 30 0.5% 0.97 [0.39, 2.43] 2014
Póvoa 2015 108 436 122 414 9.5% 0.84 [0.67, 1.05] 2015
Póvoa2 2015 95 403 103 442 7.5% 1.01 [0.79, 1.29] 2015
Tongyoo 2016 19 78 24 76 1.8% 0.77 [0.46, 1.29] 2016
Gordon 2016 33 101 30 104 2.2% 1.13 [0.75, 1.71] 2016
Gordon2 2016 29 101 27 103 2.0% 1.10 [0.70, 1.71] 2016
Lv 2017 23 58 19 60 1.4% 1.25 [0.77, 2.04] 2017
Venkatesh 2018 410 1832 448 1826 34.1% 0.91 [0.81, 1.03] 2018
Doluee 2018 54 80 58 80 4.4% 0.93 [0.76, 1.14] 2018
Subtotal (95% CI) 3531 3541 74.7% 0.94 [0.87, 1.01]
Total events 924 985
Heterogeneity: Chi² = 14.48, df = 15 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Total (95% CI) 4295 4317 100.0% 0.92 [0.87, 0.98]
Total events 1213 1320
Heterogeneity: Chi² = 15.83, df = 17 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%
0.01
0.1
1
10
100
Favours [Corticosteroids]
Favours [Control]

c.


Corticosteroids
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
8.2.1 after 21s
Annane 2002 82 150 91 149 9.2% 0.90 [0.74, 1.09] 2002
Mussack 2005 3 12 5 12 0.3% 0.60 [0.18, 1.97] 2005
Oppert 2005 7 18 11 23 0.7% 0.81 [0.40, 1.67] 2005
Cicarelli 2007 7 14 12 15 1.1% 0.63 [0.35, 1.12] 2007
Sprung 2008 86 251 78 248 5.6% 1.09 [0.85, 1.40] 2008
Hu 2009 4 38 6 39 0.3% 0.68 [0.21, 2.23] 2009
Arabi 2010 33 39 26 36 6.0% 1.17 [0.92, 1.49] 2010
Gordon 2014 7 31 7 30 0.4% 0.97 [0.39, 2.43] 2014
Póvoa2 2015 95 403 103 442 5.9% 1.01 [0.79, 1.29] 2015
Póvoa 2015 108 436 122 414 7.1% 0.84 [0.67, 1.05] 2015
Gordon 2016 33 101 30 104 2.1% 1.13 [0.75, 1.71] 2016
Tongyoo 2016 19 78 24 76 1.4% 0.77 [0.46, 1.29] 2016
Gordon2 2016 29 101 27 103 1.8% 1.10 [0.70, 1.71] 2016
Lv 2017 23 58 19 60 1.5% 1.25 [0.77, 2.04] 2017
Doluee 2018 54 80 58 80 8.4% 0.93 [0.76, 1.14] 2018
Venkatesh 2018 410 1832 448 1826 23.4% 0.91 [0.81, 1.03] 2018
Annane 2018 207 614 244 627 15.3% 0.87 [0.75, 1.00] 2018
Subtotal (95% CI) 4256 4284 90.4% 0.93 [0.88, 0.99]
Total events 1207 1311
Heterogeneity: Tau² = 0.00; Chi² = 13.49, df = 16 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)
8.2.2 before 21s
Sprung 1984 33 43 11 16 2.6% 1.12 [0.77, 1.61] 1984
Bone 1987 54 130 38 114 3.3% 1.25 [0.90, 1.73] 1987
Luce 1988 22 38 20 37 2.2% 1.07 [0.72, 1.60] 1988
Bollaert 1998 7 22 12 19 0.7% 0.50 [0.25, 1.02] 1998
Briegel1999 3 20 4 20 0.2% 0.75 [0.19, 2.93] 1999
Chawla 1999 6 23 10 21 0.5% 0.55 [0.24, 1.25] 1999
Subtotal (95% CI) 276 227 9.6% 0.97 [0.74, 1.26]
Total events 125 95
Heterogeneity: Tau² = 0.04; Chi² = 8.01, df = 5 (P = 0.16); I² = 38%
Test for overall effect: Z = 0.26 (P = 0.80)
Total (95% CI) 4532 4511 100.0% 0.94 [0.89, 1.00]
Total events 1332 1406
Heterogeneity: Tau² = 0.00; Chi² = 22.44, df = 22 (P = 0.43); I² = 2%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%
0.01 0.1 1 10 100
Favours [Corticosteroids] Favours [Control]

d.


Corticosteroids
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
8.4.1 Sample size>400
Póvoa2 2015 108 436 122 414 8.9% 0.84 [0.67, 1.05] 2015
Póvoa 2015 95 403 103 442 7.0% 1.01 [0.79, 1.29] 2015
Annane 2018 207 614 244 627 17.1% 0.87 [0.75, 1.00] 2018
Venkatesh 2018 410 1832 448 1826 31.9% 0.91 [0.81, 1.03] 2018
Subtotal (95% CI) 3285 3309 64.9% 0.90 [0.83, 0.98]
Total events 820 917
Heterogeneity: Chi² = 1.56, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
8.4.3 Sample size<400
Sprung 1984 33 43 11 16 1.1% 1.12 [0.77, 1.61] 1984
Bone 1987 54 130 38 114 2.9% 1.25 [0.90, 1.73] 1987
Luce 1988 22 38 20 37 1.4% 1.07 [0.72, 1.60] 1988
Bollaert 1998 7 22 12 19 0.9% 0.50 [0.25, 1.02] 1998
Briegel1999 3 20 4 20 0.3% 0.75 [0.19, 2.93] 1999
Chawla 1999 6 23 10 21 0.7% 0.55 [0.24, 1.25] 1999
Annane 2002 82 150 91 149 6.5% 0.90 [0.74, 1.09] 2002
Mussack 2005 3 12 5 12 0.4% 0.60 [0.18, 1.97] 2005
Oppert 2005 7 18 11 23 0.7% 0.81 [0.40, 1.67] 2005
Cicarelli 2007 7 14 12 15 0.8% 0.63 [0.35, 1.12] 2007
Sprung 2008 86 251 78 248 5.6% 1.09 [0.85, 1.40] 2008
Hu 2009 4 38 6 39 0.4% 0.68 [0.21, 2.23] 2009
Arabi 2010 33 39 26 36 1.9% 1.17 [0.92, 1.49] 2010
Gordon 2014 7 31 7 30 0.5% 0.97 [0.39, 2.43] 2014
Gordon 2016 29 101 27 103 1.9% 1.10 [0.70, 1.71] 2016
Gordon2 2016 29 101 27 103 1.9% 1.10 [0.70, 1.71] 2016
Tongyoo 2016 19 78 24 76 1.7% 0.77 [0.46, 1.29] 2016
Lv 2017 23 58 19 60 1.3% 1.25 [0.77, 2.04] 2017
Doluee 2018 54 80 58 80 4.1% 0.93 [0.76, 1.14] 2018
Subtotal (95% CI) 1247 1201 35.1% 0.99 [0.90, 1.08]
Total events 508 486
Heterogeneity: Chi² = 17.88, df = 18 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)
Total (95% CI) 4532 4510 100.0% 0.93 [0.88, 0.99]
Total events 1328 1403
Heterogeneity: Chi² = 22.11, df = 22 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Chi² = 2.12, df = 1 (P = 0.15), I² = 52.9%
0.01 0.1 1 10 100
Favours [Corticosteroids] Favours [Control]