CHEST Online Supplement

Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia

A Systematic Review and Meta-Analysis

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CHEST 2016; 149(1):209-219

 DOI: 10.1378/chest.15-1733

e-Appendix 1.

Methods 1

We search Pubmed, Cochrane, and Embase databases, the search strategy is as follows (pubmed as sample).

Search strategy of Pubmed database (from 1950 to May 2015)

Search	Query	Items found
#3	Search (#2) AND #1	296
#2	Search community-acquired pneumonia	9078
#1	Search ((((((steroid) OR glucocorticoid) OR corticosteroid) OR hydrocortisone) OR prednisone) OR methylprednisolone) OR dexamethasone	916028

Other published related systematic review and meta-analysis were also searched to identify additional trials. It is as follows:

1. Chen Y, Li K, Pu H, Wu T. Corticosteroids for pneumonia. *Cochrane Database Syst Rev.* 2011(3):D7720.

2. Cheng M, Pan ZY, Yang J, Gao YD. Corticosteroid therapy for severe community-acquired pneumonia: a meta-analysis. *Respir Care.* 2014;59(4):557-563.

3. Confalonieri M, Annane D, Antonaglia C, Santagiuliana M, Borriello EM, Meduri GU. Is prolonged low-dose glucocorticoid treatment beneficial in community-acquired pneumonia? *Curr Infect Dis Rep.* 2013;15(2):158-166.

4. Nie W, Zhang Y, Cheng J, Xiu Q. Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. *PLoS One.* 2012;7(10):e47926.

5. Salluh JI, Povoa P, Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT. The role of corticosteroids in severe community-acquired pneumonia: a systematic review. *Crit Care.* 2008;12(3):R76.

6. Shafiq M, Mansoor MS, Khan AA, Sohail MR, Murad MH. Adjuvant steroid therapy in community-acquired pneumonia: a systematic review and meta-analysis. *J Hosp Med.* 2013;8(2):68-75.

7. Siempos II, Vardakas KZ, Kopterides P, Falagas ME. Adjunctive therapies for community-acquired pneumonia: a systematic review. *J Antimicrob Chemother.* 2008;62(4):661-668.

e-Appendix 2.

Methods 2

Data were analyzed separately for RCTs and observational studies. Differences were expressed as relative risk (RR) with 95% CI. Heterogeneity across trials was assessed using a standard chi-squared test, with significance being set at $P < 0.10$. Heterogeneity across studies was also tested with the I^2 statistic, which is a quantitative measure of inconsistency across studies[1]. Studies with an I^2 statistic of 25% to 50% were considered to have low heterogeneity, those with an I^2 statistic of 50% to 75% were considered to have moderate heterogeneity, and those with an I^2 statistic of 75% were considered to have high heterogeneity. I^2>50% indicates significant heterogeneity[2]. The Mantel-Haenszel method with random-effects modeling was used to calculate pooled RRs and 95% CIs. Publication bias was assessed by visually inspecting a funnel plot in which the log RRs were plotted against their SEs.

Meta-analyses may result in type I errors owing to an increased risk of random error when sparse data are analysed and due to repeated significance testing when a cumulative meta-analysis is updated with new trials[3]. To assess the risk of type I errors we applied trial sequential analysis to cumulative meta-analysis. Trial sequential analysis combines an estimation of information size (cumulated sample size of included trials) with an adjusted threshold for statistical significance in the cumulative meta-analyses. The latter termed trial sequential monitoring boundaries, adjusts the confidence intervals and reduces type I errors. When the cumulative z curve crosses the trial sequential monitoring boundary, a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed[4]. If the z curve does not cross any of the boundaries and the required information size has not been reached, evidence to reach a conclusion is insufficient. We calculated information size as a diversity adjusted required information size, suggested by the diversity of the intervention effect estimates among the included trials[5]. The required information size was calculated based on a 15% control event rate (the control event rate in our meta-analysis for the severe CAP mortality outcome) and a relative risk reduction of 25% in mortality of severe CAP patients, with an overall type I error of 5%, a power of 80% and a 0.01 two sided α. All statistical analyses were performed using Review Manager (RevMan) version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration) and trial sequential analysis program version 0.9 beta (www.ctu.dk/tsa)(6).

We performed predefined subgroup analyses according to severity of CAP (severe CAP versus mixed CAP), inflammatory response(high versus low CRP level), whether using loading dose(yes

versus no),whether achieve effective serum concentration(yes versus no), duration of corticosteroids treatment(≥7d versus <7d), cumulative dose of corticosteroids(>300mg methylprednisolone versus ≤300 mg methylprednisolone), effect model (random effect versus fixed effect) and we confirm the stability of the results with sensitivity analyses and trial sequential analysis.

References:

1. Higgins J GSE. *Cochrane handbook for systematic reviews of interventions, version 5.1.0 [updated March 2011]*. Cochrane Collaboration 2011. www.cochrane-handbook.org..

2. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-560.

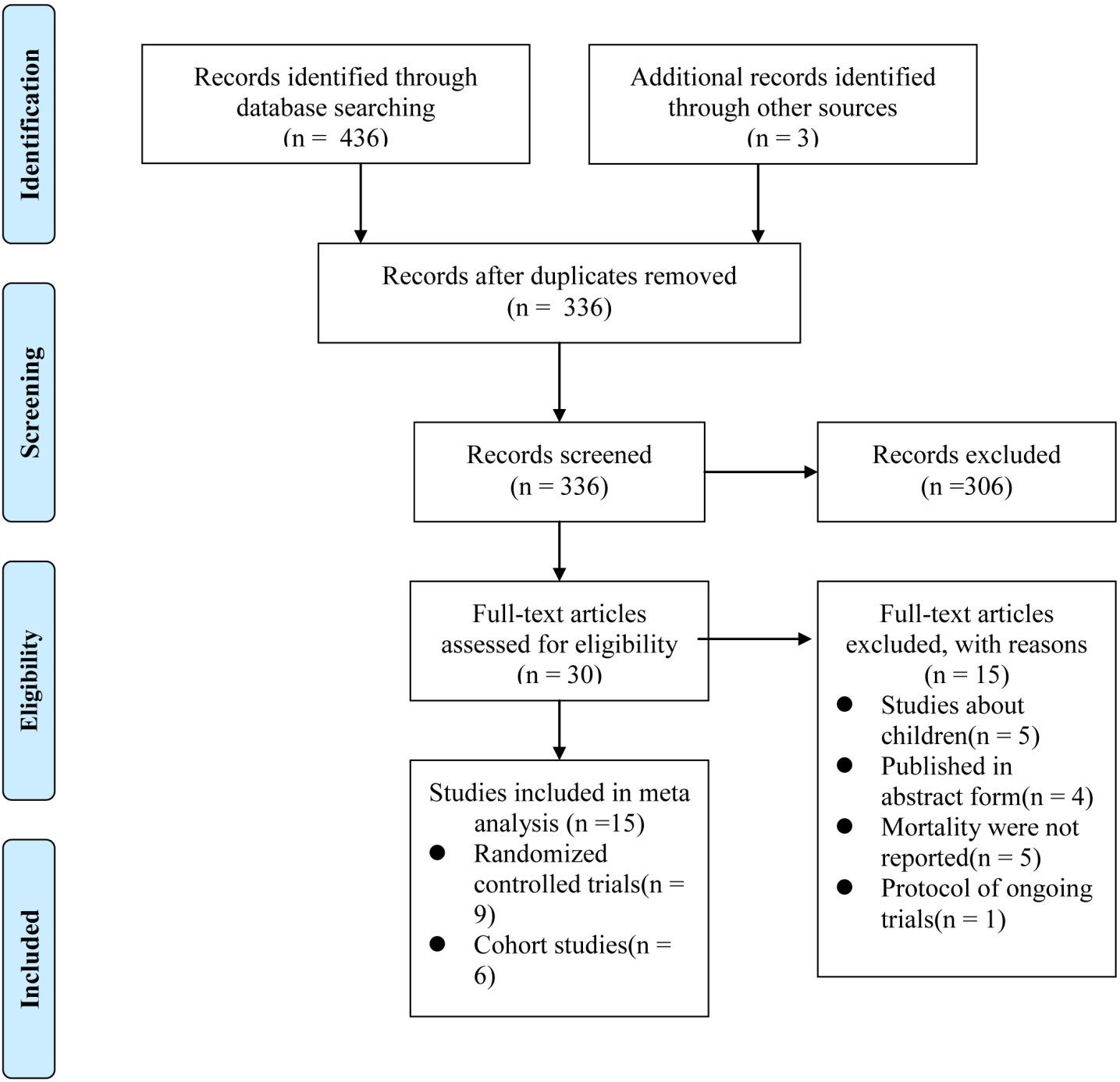
3. Brok J, Thorlund K, Wetterslev J, et al. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol.* 2009;38:287-298.

4. Thorlund K, Devereaux PJ, Wetterslev J, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol.* 2009;38:276-286.

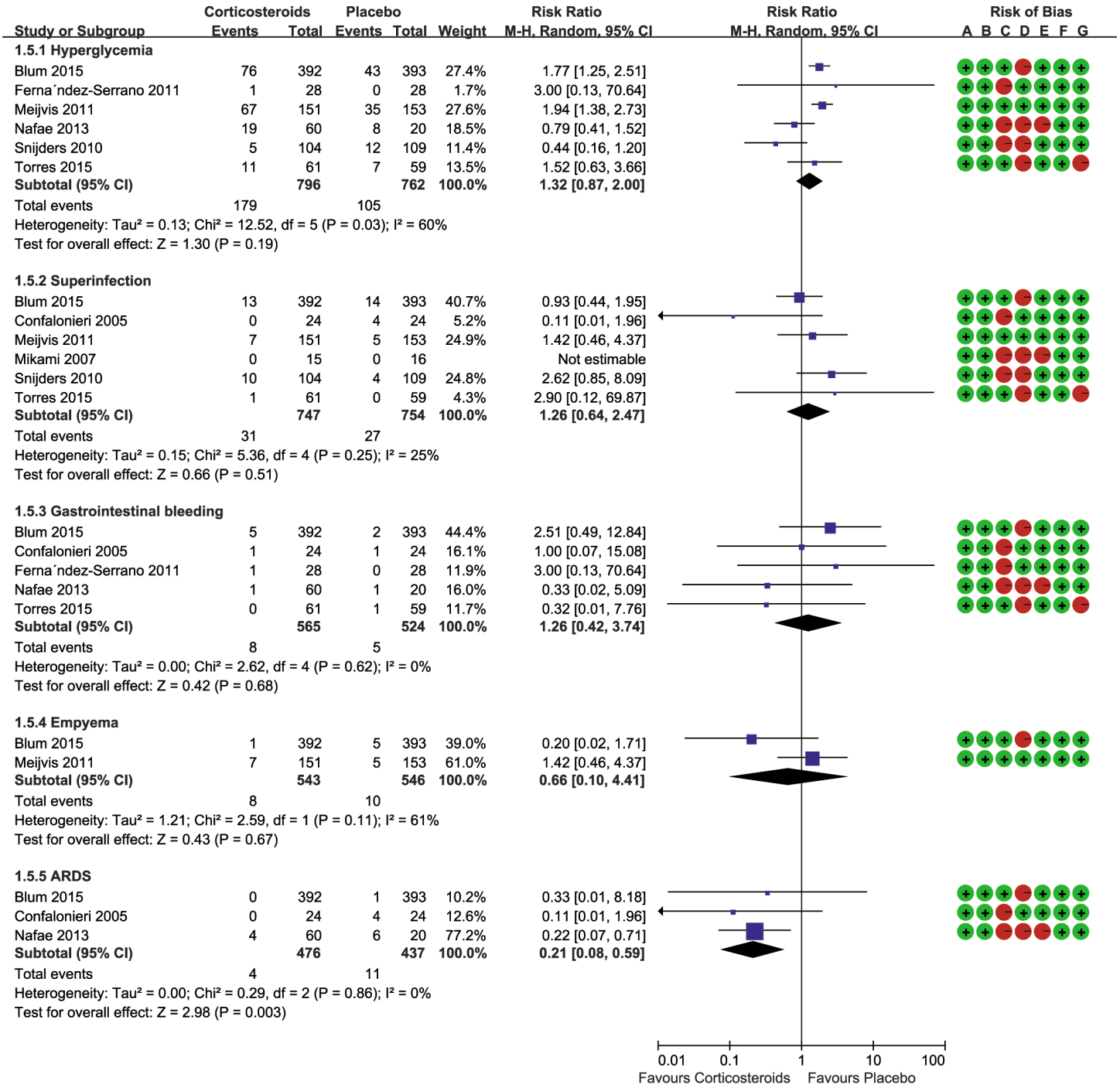
5. Wetterslev J, Thorlund K, Brok J, et al. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol.* 2009;9:86.

6. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol.* 2008;61:64-75.

e-Figure 1.



e-Figure 2.



Risk of bias legend

(**A**) Adequate description of population

(**B**) Low loss to follow-up

(**C**) Adverse events prespecified and defined

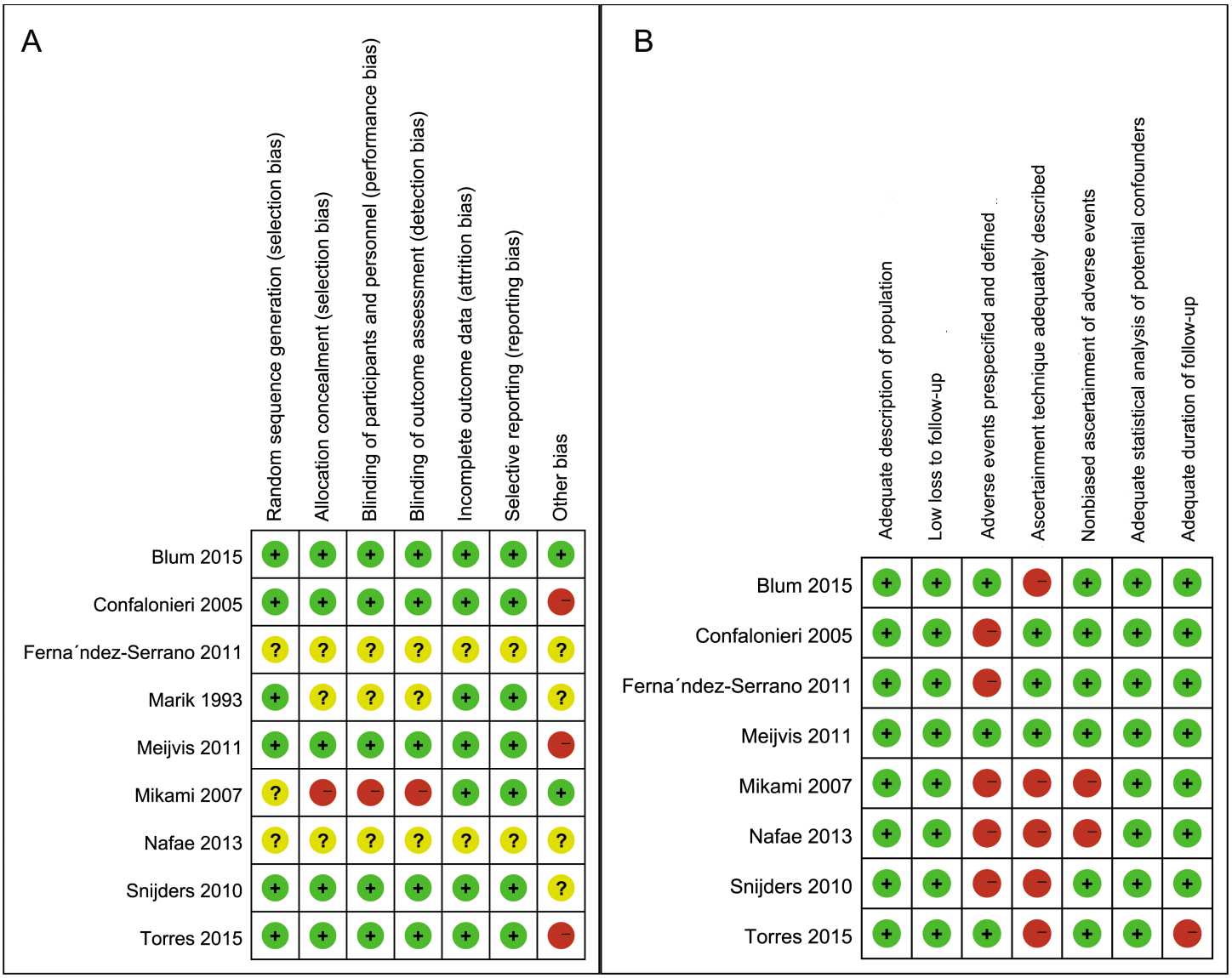
(**D**) Ascertainment technique adequately described

(**E**) Nonbiased ascertainment of adverse events

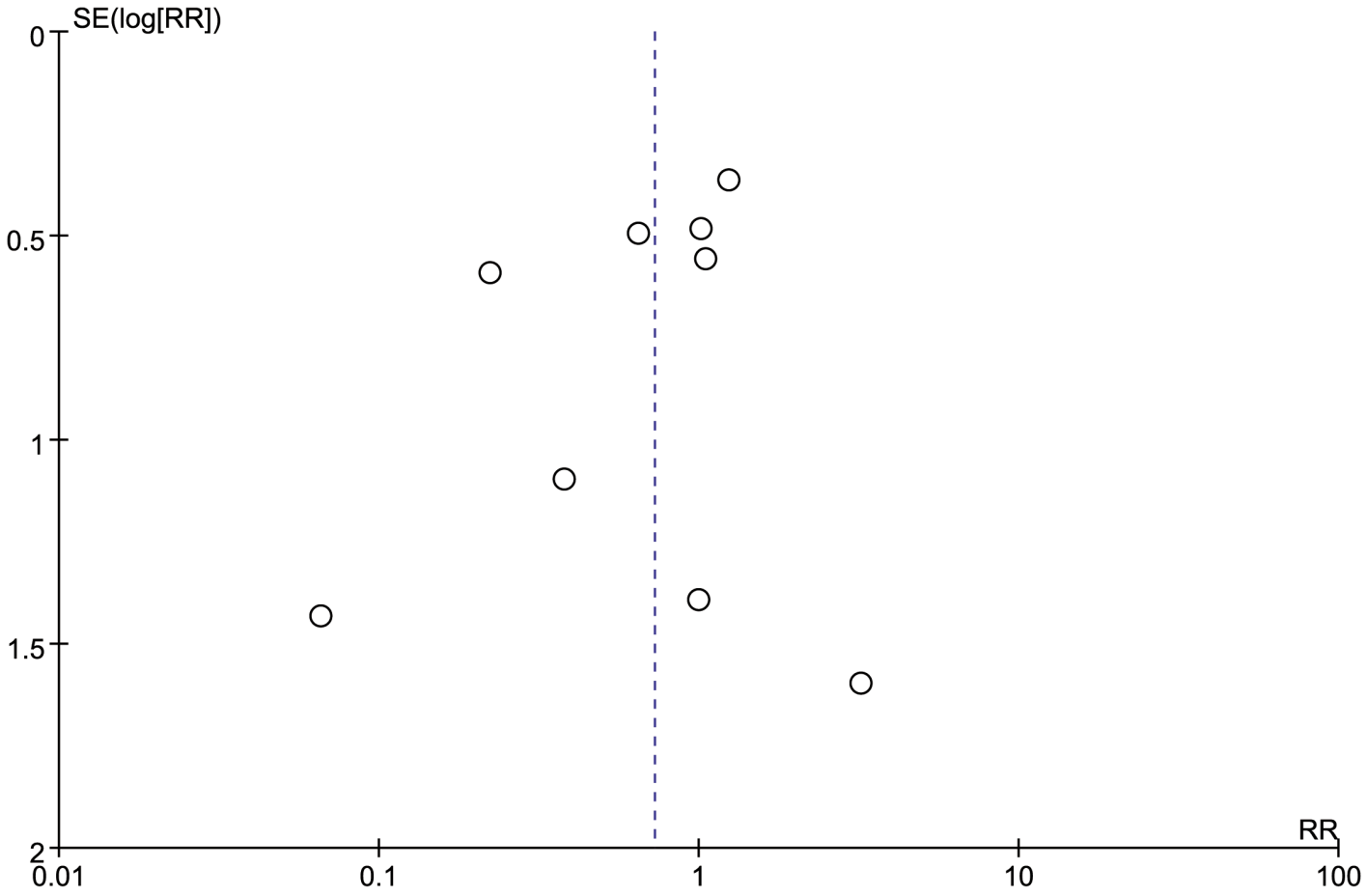
(**F**) Adequate statistical analysis of potential confounders

(**G**) Adequate duration of follow-up

e-Figure 3.



e-Figure 4.



e-Table 1. Characteristics Of the Cohort Studies.

Study	Design	No. patients (corticosteroids/control)	Patient selection	Corticosteroids	Level of CRP (corticosteroids/ control) mg/dl	Severity of illness (corticosteroids/control)
Tagami et al/2014[a]	Retrospective study	1886(943/943)	Severe CAP, requiring mechanical ventilation	Methylprednisolone 0.5-2.5 mg /kg/day (or an quivalent dose of dexamethasone, hydrocortisone, prednisolone or betamethasone) for about 7 days	NA	NA
Polverino et al/ 2012[b]	Prospective study	1592(198/1394)	Severe CAP	Methylprednisolone (or an equivalent dose of dexamethasone, hydrocortisone, prednisolone or betamethasone) for about 7 days	14 (6-25)/18 (8-27)[c]	PSI IV-V(% of total) (76/50)
Ugajin et al/2013	Prospective study	101(30/71)	Severe CAP	Methylprednisolone (prednisolone or dexamethasone) 20-60mg/d for 4-7d	12(5-23)/13(6-23)[c]	PSI V(% of total) (100/100)
Chon et al/2010	Retrospective study	97(60/37)	Severe CAP requiring mechanical ventilation	NA	20 ± 11/18 ± 13[d]	APACHE II score 27 ± 8/24 ± 8 [d]
Salluh et al/2011	Prospective study	111(61/50)	Severe CAP	Equivalent of methylprednisolone dose of 60 mg/d for about 7 days.	16 ± 13/18 ± 16[d]	APACHE II score 18 ± 8/17 ± 9 [d]
Garcia-Vidal et al/2007	Retrospective study	308(70/238)	Severe CAP	Methylprednisone 24 mg/day or prednisone o 30 mg/day for 11d	NA	PSI IV-V(% of total) (100/100)

CAP = community-acquired pneumonia, PSI = Pneumonia Severity Index score, APACHE = Acute physiology and chronic sealth evaluation simplified acute physiology score, CRP = C-reactive protein, NA = not available

[a]: We only choose propensity score-matched groups of patients without shock

[b]: We only choose the data of severe CAP patients

[c]: Data show as median (IQR).

[d] : Data show as mean ± SD

e–Table 2. Summary of Findings including GRADE quality assessment of evidence trials

Variables	No of studies	No with event/No in group(%) Corticosteroids group	Placebo group	Relative risk (95% CI)	Absolute effect	Quality of the evidence (GRADE)	Quality assessment domains
Mortality of CAP	9	43/849 (5.1%)	53/818 (6.5%)	RR 0.72 (0.43 to 1.21)	18 fewer per 1000 (from 37 fewer to 14 more)	ÅÅOO LOW	Inconsistency: not serious; indirectness: not serious; imprecision: serious; risk of bias: serious
Mortality of severe CAP	5	12/175 (6.9%)	23/172 (13.4%)	RR 0.64 (0.32 to 1.29)	48 fewer per 1000 (from 91 fewer to 39 more)	ÅÅOO LOW	Inconsistency: not serious; indirectness: not serious; imprecision: serious; risk of bias: serious
Hyperglycemia	6	179/796 (22.5%)	105/762 (13.8%)	RR 1.32 (0.87 to 2)	44 more per 1000 (from 18 fewer to 138 more)	ÅOOO VERY LOW	Inconsistency: serious; indirectness: not serious; imprecision: serious; risk of bias: serious
Superinfection	6	31/747 (4.1%)	27/754 (3.6%)	RR 1.26 (0.64 to 2.47)	9 more per 1000 (from 13 fewer to 53 more)	ÅÅOO LOW	Inconsistency: not serious; indirectness: not serious; imprecision: serious; risk of bias: serious
Gastrointestinal bleeding	5	8/565 (1.4%)	5/524 (0.95%)	RR 1.26 (0.42 to 3.74)	2 more per 1000 (from 6 fewer to 26 more)	ÅÅOO LOW	Inconsistency: not serious; indirectness: not serious; imprecision: serious; risk of bias: serious
Empyema	2	8/543 (1.5%)	10/546 (1.8%)	RR 0.66 (0.1 to 4.41)	6 fewer per 1000 (from 16 fewer to 62 more)	ÅOOO VERY LOW	Inconsistency: serious; indirectness: not serious; imprecision: serious; risk of bias: serious
ARDS	3	4/476 (0.84%)	11/437 (2.5%)	RR 0.21 (0.08 to 0.59)	20 fewer per 1000 (from 10 fewer to 23 fewer)	ÅÅOO LOW	Inconsistency: not serious; indirectness: not serious; imprecision: serious; risk of bias: serious

GRADE Working Group grades of evidence: low quality =further research is likely to have an important impact on confience in estimate of effct and is likely to change the estimate; very low quality =very uncertain about the estimate.
Quality assessment domains: inconsistency = unexplained heterogeneity of results; indirectness = diffrences in population, intervention, comparator, and outcome measures; imprecision = relatively few patients and few events resulting in wide confience intervals; reporting bias = publication bias is a systematic underestimation or over-estimation of underlying benefiial or harmful effct owing to selective publication of trial results.