SUPPLEMENTAL DIGITAL CONTENTS

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Supplemental Digital Content 1. Panel Membership and Communications

Selection of guideline leadership

Guideline leadership consisted of co-chairs (SP, DA) and co-vice-chairs (RB, AN), supported by two clinician-methodologists from the GUIDE group at McMaster University (DC, BR). Selection of the leadership for this guideline and all others is the responsibility of the Society of Critical Care Medicine (SCCM) Board of Regents (BOR). The BOR follows the rules provided in the SCCM guidelines Standard Operating Procedures Manual (SOP) which is that the BOR identifies two chairs and two co-vice chair subject matter experts for each SCCM-approved guideline. There was a due consideration for diversity, equity and inclusion in the process and particular attention is paid to assuring that expertise is evaluated via submission of the Curriculum Vitae of each candidate. The BOR reviewed declared conflicts of interest (COI) for adjudication prior to appointment using the SCCM COI system.

Selection of panelists

An interdisciplinary panel of 22 members was then identified by the appointed guidelines leadership, again following the SOP requirements followed by BOR review. The choice of panel members was based on clinical expertise in corticosteroids and critical illness with attention to diversity, equity, and inclusion in the process of panel selection. Each member of the panel completed the required COI forms before they were officially appointed to the panel. Panelists served at the discretion of the BOR with ongoing monitoring of COI and performance.

Panel communications

The full panel held regular meetings to establish the scope of the guidelines, generate a series of clinical questions of interest (PICO questions), and generate recommendations using the GRADE Methodology. Meetings were facilitated by Zoom video-conferencing hosted by SCCM with one in-person meeting held at the annual SCCM Congress in San Francisco, California (January 2023). Guidelines leadership (co-chairs, co-vice-chairs, and clinician-methodologists) held regular video conference calls via Zoom to refine processes and address barriers.

Geographic Distribution of Panel Members

Country	**Number of Panel Members**
United States	13
Canada	4
France	3
Australia	1
Jordan	1

Supplemental Digital Content 2. Conflict of Interest Management

SCCM maintains a commitment to trustworthy guidelines through a strict conflict of interest disclosure and management process. There were no disclosures directly related to the PICO questions within this guideline that required individual authors to abstain from voting on any recommendations. Disclosures are collected prior to voting by SCCM through a conflict of interest platform.

Supplemental Digital Content 3. PICO Questions

Question Development

Subsequently, the panel formulated a series of actionable questions relevant to the scope of the guideline, following the PICO (Population, Intervention, Comparison, Outcomes) format that could potentially lead to an actionable recommendation statement. For each PICO, the panel identified potential subgroup analyses of interest to be considered, subject to the availability of data during the literature review process. All PICO questions are listed in the table below.

Supplemental Digital Content 4. Outcome Prioritization

The panel identified a list of outcomes they deemed to be pertinent of the actionable PICO statements. Using the GRADE approach to outcome prioritization, each panel member independently rated each outcome on a scale of 1 to 9 (1= least important; 9 = critical to decision making). Panel members were asked to rate the importance of each of the listed outcomes **from the perspectives of patients.** Mean scores were then calculated for each outcome and categorized them based on the below 'Scoring Guide'. The final outcome ratings are displayed in the table below.

Scoring Guide

SCORES	IMPORTANCE
1-3	**Limited Importance**
4-6	**Important**
7-9	**Critically important**

Outcome Prioritization

Outcome	Mean± SD
Long-term mortality (90 day mortality, 6 month mortality)	8.714 ± 0.643
Short-term mortality (28 day, ICU mortality, hospital mortality)	8.619 ± 0.921
Long term cognitive impairment	7.952 ± 1.024
Health Related Quality of Life Measures at 6 months or longer	7.952 ± 1.244
Long term pulmonary dysfunction	7.905 ± 1.136
Return to mechanical ventilation once liberated	7.381 ± 1.161
Ventilator free days	7.333 ± 1.494
Need for ECMO	7.238 ± 1.546
Hospital length of stay	6.714 ± 1.189
ICU acquired weakness	6.714 ± 1.007
Duration of mechanical ventilation	6.619 ± 1.596
ICU length of stay	6.333 ± 1.461
Nosocomial infections	6.333 ± 1.653
Delirium	6.238 ± 1.640
Gastrointestinal bleeding	5.714 ± 1.554

Hyperglycemia	3.952 ± 1.830
Hypernatremia	3.429 ± 1.690
PaO2:FiO2 ratio	3.238 ± 2.211

n = 22 panelists

Supplemental Digital Content 5. Literature search strategy

Search Strategy for Corticosteroids in Sepsis

Published literature was identified by searching the following bibliographic databases on October 12 2022: MEDLINE (1946– October 12, 2022) with in-process records and daily updates via Ovid; Embase (1974– October 12, 2022) via Ovid; LILACS, and, the Cochrane Clinical Trials Register. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were: sepsis; and corticosteroids.

Embase <1974 to 2022 October 11>
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Bacteremia/ 89557
2 exp sepsis/ 452075
3 exp septic shock/ 90376
4 exp Systemic Inflammatory Response Syndrome/ or exp systemic inflammatory response syndrome/ 470723
5 Bacterial Infections/bl, dt, co or Bacterial Infection/bl, dt, co 71417
6 pneumonia/co, dt 55795
7 adult respiratory distress syndrome/co, dt 12551
8 Respiratory distress Syndrome/co, dt 7056
9 acute lung injury/co, dt 5852
10 community acquired infections/co, dt or Community-Acquired Infection/co, dt 6687
11 (bacter?emia$ or blood poisoning$ or py?emia$ or pyohemia$ or sepsis or sept#c?emia$ or septic* or (septic adj shock) or ((endotoxic or endo-toxic) adj shock) or (toxic adj shock)).mp. 632990
12 (SIRS or Inflammatory Response Syndrome*).mp. 37859
13 (bacteria* adj6 infect* adj6 (blood* or serum or invas* or severe or systemic)).mp. 29232
14 ARDS.mp. 47992
15 (acute adj2 (respiratory adj2 distress)).mp. 55355
16 (acute adj2 (lung adj2 injury)).mp. 47136
17 (((community-acquired or severe) adj2 pneumonia) or ((acute or adult) adj1 (respiratory adj1 distress)) or ((acute or adult) adj1 (lung adj1 injury)) or ARDS).mp. 177949
18 or/1-17959164
19 exp Adrenal Cortex Hormones/ or corticosteroid/ 1470866
20 exp Hydrocortisone/ 214777
21 Steroids/ or Steroid/ 241211
22 cortisone/ 32999

23 (corticosteroid* or cortico-steroid*or steroid* or cortison* or hydrocortison* or hydro-cortison* or methylprednisolon* or methyl-prednisolon* or betamethason* or beta-methason* or dexamethason* or dexa-methason* or glucocorticoid* or gluco-corticoid* or fludrocortison* or fludro-cortison* or mineralocorticoid* or mineralo-corticoid*).mp. 1239078
24 (Besonia or Dopomedrol or Depo-Medrol or Esametone or Firmacort or Lemod or Medesone or Medixon or Medlone or Medrate or Medrol or Medrone or Mesopren or Metastab or Methyleneprednisolone or Methylprednisolonum or Metibetasone or Metilprednisolona or Metilprednisolone or Metrisone or Metrocort or Metysolon or Moderin or Nirypan or Noretona or "predni N Tablinen" or Prednisolone or Prednol or Promacortine or Reactenol or Sieropresol or Solomet or Summicort or Suprametil or Urbason or Urbasone or Wyacort).mp. 211816
25 (Bebate or Becort or Bedifos or "Beta-methasone" or Betacorlan or Betacortril or Betafluorene or Betamamallet or Betametasona or Betametasone or Betamethasonum or Betamethazone or Betapredol or Betasolon or Betnelan or Betsolan or Celestene or Celestone or Cidoten or Corticosterone or Besacort-beta or Flubenisolone or Hormezon or Methazon or Prednisolone or Rinderon or Valisone or Visubeta).mp. 286732
26 (Aeroseb-D or Aeroseb-Dex or Anaflogistico or Aphtasolon or Auxiron or Azium or "Biso DS" or Calonat or Corsone or Cortisumman or Decacortin or Decaderm or Decadron or Decagel or Decaject or Decalix or Decameth or Decasone or Decaspray or Dectancyl or Dekacort or Deltafluorene or Dergramin or Deronil or Desadrene or Desametasone or Desamethasone or Desameton or Deseronil or Dex-ide or "Dexa Mamallet" or Dexa-Cortidelt or Dexa-Cortisyl or Dexa-Scheroson or Dexa-sine or Dexacort or Dexacortal or Dexacortin or Dexadeltone or Dexafarma or Dexalona or Desametasone or Dexameth or Dexamethazone or Dexapolcort or Dexapos or Dexaprol or Dexason or Dexasone or Dexinolon or Dexinoral or Dexone or DexPak or Dextelan or Dextenza or Dezone or Dinormon orfluormethylprednisolone or Fluormore or Fluorocort or Fortecortin or Gammacorten or Hexadecadrol or Hexadrol or Isopto-Dex or Lokalison or Loverine or Luxazone or Maxidex or Mediamethasone or Methylfluorprednisolone or Mexidex or Millicorten or Mymethasone or Ocu-trol or Oradexon or Osurdex or Ozurdex or Policort or Prednisolon or Prednisolone or SK-Dexamethasone or Spoloven or "Sunia Sol D" or Superprednol or Turbinaire or Visumetazone).mp. 213762
27 (Alforone or Florinef or Fludrocortisona or Fludrocortone or Fludrone or Fludronef or Fluodrocortisone or Fluohydrisone for Fluohydrocortisone or Fluorocortisol or Fluorocortisone).mp. 690
28 (Prednisolone or Bubbli-Pred or Co-Hydeltra or Codelcortone or Cordrol or Cortalone or Cotogesic or Cotolone or Decaprednil or Decortin or Delcortol of deltacortenol or Deltacortil or Deltahydrocortisone or Deltisilone or Derpro or "Dez-Cortidelt hostacortin" or Di-adreson or Dicortol or Donisolone or Dydeltrone or Eazolin or Erbacort or Erbasona or Estilsona or Femisolone or Hostacortin or Hydeltra or Hydeltrone or Hydrodeltalone or Hydrodeltisone or Hydroretrocortin or Hydroretrocortine or Lentosone or Metacortandralone or Meti-Derm or Meticortelone or Orapred or Paracortol or Paracotol or Precortancyl or Precortilon or Precortisyl or Predne-Dome or Prednelan or Prednicen or Predniliderm or Predniretard or Prednis or

Prednisolona or Prednisolone or Prednisolonum or Predonin or Predonine or Prelone or Prenolone or Rolisone or Scherisolon or Solone or Steran or Sterane or Sterolone or Ulacort or Ultracorten or Ultracortene).mp. 207954
29 (Prednisone or Cortisone or Dehydrocortisone or Adasone or Ancortone or Apo-Prednisone or Bicortone or Cartancyl or Colisone or Cortan or Cortidelt or Cotone or Dacorten or Dacortin or Decortancyl or Decortin or Decortisyl or Dehydrocortisone or Dekortin or Dellacort or delta cortelan or Delta E or Delta-Cortelan or Deltacortene or Deltacortisone or delta-Cortisone or Deltacortone or Deltadehydrocortisone or Delta-Dome or Deltasone or Deltison or Deltisona or Deltisone or Deltra or Diadreson or Di-Adreson or Econosone or Encorton or Encortone or Enkorton or Fernisone or Fiasone or Hostacortin or Incocortyl or In-Sone or Juvason or Lisacort or Lodotra or Lodtra or Me-Korti or Metacortandracin or Meticorten or Nisona or Nizon or Novoprednisone or Nurison or Orasone or Panafcort or Panasol or Paracort or Parmenison or Pehacort or Precort or Predeltin or Prednicen-M or Prednicorm or Prednicort or Prednicot or Prednidib or Prednilonga or Prednison or Prednisona or Prednisona or Prednisonum or Prednitone or Prednizon or Prednovister or Presone or Pronison or Rayos or Rectodelt or Retrocortine or Servisone or Sterapred or Supercortil or Ultracorten or Ultracortene or Winpred or Wojtab or Zenadrid).mp. 294892
30 or/19-29 1884668
31 18 and 30 79126
32 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. 673183
33 Randomized Controlled Trial/ 1310415
34 exp Randomized Controlled Trials as Topic/ 398406
35 "Randomized Controlled Trial (topic)"/ 236408
36 Controlled Clinical Trial/ 562366
37 exp Controlled Clinical Trials as Topic/ 412893
38 "Controlled Clinical Trial (topic)"/ 12602
39 Randomization/ 202181
40 Random Allocation/ 198321
41 Double-Blind Method/ 348093
42 Double Blind Procedure/ 199637
43 Double-Blind Studies/330581
44 Single-Blind Method/ 78017
45 Single Blind Procedure/ 47879
46 Single-Blind Studies/ 80096
47 Placebos/ 366171
48 Placebo/ 386621
49 Control Groups/ 112375
50 Control Group/ 112375
51 (random* or sham or placebo*).ti,ab,hw,kf,kw. 4142318

52 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. 606523
53 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. 3364
54 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw. 2790471
55 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. 117837
56 allocated.ti,ab,hw. 182034
57 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw. 122970
58 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. 27752
59 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw. 1363
60 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. 14939
61 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. 28592
62 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw. 151367
63 or/32-62 6057425
64 31 and 63 11771
65 Animals/ not (animals/ and humans/) 6036750
66 64 not 65 11247
67 limit 66 to dd=20180101-20221011 2338
68 67 use oemezd 591
69 limit 66 to (ed=20180101-20221011 or ez=20180101-20221011) 10123
70 69 use ppez 623
71 68 or 70 1214
72 remove duplicates from 71 1143

Cochrane Clinical Trials Registry

Search Name: Sepsis - corticosteroids
Last Saved: 12/10/2022 11:18:17

ID Search
#1 MeSH descriptor: [Bacteremia] explode all trees
#2 MeSH descriptor: [Sepsis] explode all trees
#3 MeSH descriptor: [Shock, Septic] explode all trees
#4 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees
#5 MeSH descriptor: [Bacterial Infections] explode all trees and with qualifier(s): [blood - BL, complications - CO, drug therapy - DT]
#6 MeSH descriptor: [Pneumonia] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#7 MeSH descriptor: [Community-Acquired Infections] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]
#8 MeSH descriptor: [Respiratory Distress Syndrome] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]
#9 MeSH descriptor: [Acute Lung Injury] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]
#10 (bacter?emia$ or blood poisoning$ or py?emia$ or pyohemia$ or sepsis or sept#c?emia$ or septic* or (septic adj shock) or ((endotoxic or endo-toxic) next shock) or (toxic next shock))
#11 SIRS or Inflammatory Response Syndrome*
#12 (bacteria* next6 infect* next6 (blood* or serum or invas* or severe or systemic))
#13 ((community-acquired or severe) next pneumonia)
#14 (acute) next2 (respiratory next2 distress)
#15 ards
#16 (acute) next2 (lung next2 injury)
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#19 MeSH descriptor: [Hydrocortisone] explode all trees
#20 MeSH descriptor: [Steroids] this term only
#21 corticosteroid* or cortico-steroid*or steroid* or cortison* or hydrocortison* or hydro-cortison* or methylprednisolon* or methyl-prednisolon* or betamethason* or beta-methason* or dexamethason* or dexa-methason* or glucocorticoid* or gluco-corticoid* or fludrocortison* or fludro-cortison* or mineralocorticoid* or mineralo-corticoid*
#22 Besonia or Dopomedrol or Depo-Medrol or Esametone or Firmacort or Lemod or Medesone or Medixon or Medlone or Medrate or Medrol or Medrone or Mesopren or Metastab or Methyleneprednisolone or Methylprednisolonum or Metibetasone or Metilprednisolona or Metilprednisolone or Metrisone or Metrocort or Metysolon or Moderin or Nirypan or Noretona or "predni N Tablinen" or Prednisolone or Prednol or Promacortine or Reactenol or Sieropresol or Solomet or Summicort or Suprametil or Urbason or Urbasone or Wyacort
#23 Bebate or Becort or Bedifos or "Beta-methasone" or Betacorlan or Betacortril or Betafluorene or Betamamallet or Betametasona or Betametasone or Betamethasonum or Betamethazone or Betapredol or Betasolon or Betnelan or Betsolan or Celestene or Celestone or Cidoten or Corticosterone or Besacort-beta or Flubenisolone or Hormezon or Methazon or Prednisolone or Rinderon or Valisone or Visubeta
#24 Aeroseb-D or Aeroseb-Dex or Anaflogistico or Aphtasolon or Auxiron or Azium or "Biso DS" or Calonat or Corsone or Cortisumman or Decacortin or Decaderm or Decadron or Decagel or Decaject or Decalix or Decameth or Decasone or Decaspray or Dectancyl or Dekacort or Deltafluorene or Dergramin or Deronil or Desadrene or Desametasone or Desamethasone or Desameton or Deseronil or Dex-ide or "Dexa Mamallet" or Dexa-Cortidelt or Dexa-Cortisyl or Dexa-Scheroson or Dexa-sine or Dexacort or Dexacortal or Dexacortin or

Dexadeltone or Dexafarma or Dexalona or Desametasone or Dexameth or Dexamethazone or Dexapolcort or Dexapos or Dexaprol or Dexason or Dexasone or Dexinolon or Dexinoral or Dexone or DexPak or Dextelan or Dextenza or Dezone or Dinormon orfluormethylprednisolone or Fluormore or Fluorocort or Fortecortin or Gammacorten or Hexadecadrol or Hexadrol or Isopto-Dex or Lokalison or Loverine or Luxazone or Maxidex or Mediamethasone or Methylfluorprednisolone or Mexidex or Millicorten or Mymethasone or Ocu-trol or Oradexon or Osurdex or Ozurdex or Policort or Prednisolon or Prednisolone or SK-Dexamethasone or Spoloven or "Sunia Sol D" or Superprednol or Turbinaire or Visumetazone

#25 Alforone or Florinef or Fludrocortisona or Fludrocortone or Fludrone or Fludronef or Fluodrocortisone or Fluohydrisone for Fluohydrocortisone or Fluorocortisol or Fluorocortisone

#26 Prednisolone or Bubbli-Pred or Co-Hydeltra or Codelcortone or Cordrol or Cortalone or Cotogesic or Cotolone or Decaprednil or Decortin or Delcortol of deltacortenol or Deltacortil or Deltahydrocortisone or Deltisilone or Derpro or "Dez-Cortidelt hostacortin" or Di-adreson or Dicortol or Donisolone or Dydeltrone or Eazolin or Erbacort or Erbasona or Estilsona or Femisolone or Hostacortin or Hydeltra or Hydeltrone or Hydrodeltalone or Hydrodeltisone or Hydroretrocortin or Hydroretrocortine or Lentosone or Metacortandralone or Meti-Derm or Meticortelone or Orapred or Paracortol or Paracotol or Precortancyl or Precortilon or Precortisyl or Predne-Dome or Prednelan or Prednicen or Predniliderm or Predniretard or Prednis or Prednisolona or Prednisolone or Prednisolonum or Predonin or Predonine or Prelone or Prenolone or Rolisone or Scherisolon or Solone or Steran or Sterane or Sterolone or Ulacort or Ultracorten or Ultracortene

#27 Prednisone OR Cortisone OR Dehydrocortisone OR Adasone OR Ancortone OR Apo-Prednisone OR Bicortone OR Cartancyl OR Colisone OR Cortan OR Cortidelt OR Cotone OR Dacorten OR Dacortin OR Decortancyl OR Decortin OR Decortisyl OR Dehydrocortisone OR Dekortin OR Dellacort OR delta cortelan OR Delta E OR Delta-Cortelan OR Deltacortene OR Deltacortisone OR delta-Cortisone OR Deltacortone OR Deltadehydrocortisone OR Delta-Dome OR Deltasone OR Deltison OR Deltisona OR Deltisone OR Deltra OR Diadreson OR Di-Adreson OR Econosone OR Encorton OR Encortone OR Enkorton OR Fernisone OR Fiasone OR Hostacortin OR Incocortyl OR In-Sone OR Juvason OR Lisacort OR Lodotra OR Lodtra OR Me-Korti OR Metacortandracin OR Meticorten OR Nisona OR Nizon OR Novoprednisone OR Nurison OR Orasone OR Panafcort OR Panasol OR Paracort OR Parmenison OR Pehacort OR Precort OR Predeltin OR Prednicen-M OR Prednicorm OR Prednicort OR Prednicot OR Prednidib OR Prednilonga OR Prednison OR Prednisona OR Prednisona OR Prednisonum OR Prednitone OR Prednizon OR Prednovister OR Presone OR Pronison OR Rayos OR Rectodelt OR Retrocortine OR Servisone OR Sterapred OR Supercortil OR Ultracorten OR Ultracortene OR Winpred OR Wojtab OR Zenadrid

#28 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27

#29 #17 and #28 with Publication Year from 2018 to 2022, with Cochrane Library publication date Between Jan 2018 and Oct 2022, in Trials

LILACS

"Bacteremia" or "Sepsis" or "septic" or "bacterial infection" or "pneumonia" or "respiratory distress" or "blood poisoning" or "inflammatory response" or "ards" [in field “words”]

And

"adrenal cortex hormones" or "corticosteroid" or "corticosteroids" or "hydrocortisone" or "steroids" or "steroid" or "cortisone" or "hydro-cortisone" or "methylprednisolon" or "betamethasone" or "dexamethasone" or "glucocorticoid" or "fludrocortisone" or "mineralocorticoid" [in field “words”]

And

2018 or 2019 or 2020 or 2021 or 2022 [in field “Country, year publication”]

196 citations

Search Strategy for Corticosteroids in ARDS

The following electronic databases were searched: MEDLINE 1946 to October 27, 2022), EMBASE (1974 to October 27, 2022), Centre for Disease Control (CDC) library of COVID research (November 8, 2022), CINAHL (October 27, 2022) and COCHRANE centre for trials (October 27, 2022).

MEDLINE (OVID)
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
---

1 exp Adrenal Cortex Hormones/ (419366)
2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (620132)
3 1 or 2 (791163)
4 Respiratory Distress Syndrome, Adult/ (23717)
5 Acute Lung Injury/ (7992)
6 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (48049)
7 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (18384)
8 exp Respiratory Insufficiency/ (67494)
9 ((respirat* or ventilat*) adj3 (insufficienc* or failure or depression or disturbance or dysfunction)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (81182)
10 or/4-9 (166843)
11 3 and 10 (9740)
12 randomized controlled trial.pt. (579271)
13 controlled clinical trial.pt. (95070)
14 randomi?ed.ab. (692596)

15 placebo.ab. (232634)
16 drug therapy.fs. (2540564)
17 randomly.ab. (394013)
18 trial.ab. (620821)
19 groups.ab. (2425005)
20 or/12-19 (5511256)
21 exp animals/ not humans.sh. (5058068)
22 20 not 21 (4804874)
23 11 and 22 (4573)
24 limit 23 to ed=20211104-20221027 (245)

Database: Embase <1974 to 2022 October 26>
Search Strategy:
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1 exp corticosteroid/ (1054478)
2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1068649)
3 1 or 2 (1438493)
4 adult respiratory distress syndrome/ (51511)
5 respiratory distress syndrome/ (15899)
6 exp acute lung injury/ (18356)
7 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. (99013)
8 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. (29642)
9 ((respirat* or ventilat*) adj3 (insufficienc* or failure or depression or disturbance or dysfunction)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (155185)
10 or/4-9 (263719)
11 3 and 10 (38757)
12 randomized controlled trial/ (734127)
13 Controlled clinical study/ (467520)
14 random$.ti,ab. (1850265)
15 randomization/ (95402)
16 intermethod comparison/ (289192)
17 placebo.ti,ab. (348542)
18 (compare or compared or comparison).ti. (578173)
19 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2592768)

20 (open adj label).ti,ab. (101318)
21 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (262153)
22 double blind procedure/ (200114)
23 parallel group$1.ti,ab. (30312)
24 (crossover or cross over).ti,ab. (118837)
25 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (391432)
26 (assigned or allocated).ti,ab. (461481)
27 (controlled adj7 (study or design or trial)).ti,ab. (421940)
28 (volunteer or volunteers).ti,ab. (272820)
29 human experiment/ (599686)
30 trial.ti. (373161)
31 or/12-30 (5954551)
32 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (9173)
33 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (325071)
34 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (20387)
35 (Systematic review not (trial or study)).ti. (226347)
36 (nonrandom$ not random$).ti,ab. (18182)
37 "Random field$".ti,ab. (2802)
38 (random cluster adj3 sampl$).ti,ab. (1477)
39 (review.ab. and review.pt.) not trial.ti. (1035948)
40 "we searched".ab. and (review.ti. or review.pt.) (44292)
41 "update review".ab. (125)
42 (databases adj4 searched).ab. (54537)
43 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1172026)
44 Animal experiment/ not (human experiment/ or human/) (2460426)
45 or/32-44 (4080819)
46 31 not 45 (5267395)
47 11 and 46 (4224)
48 limit 47 to dc=20211104-20221027 (665)

Cochrane Library (Wiley)
Search Name: Dipayan steroids ARDS
Date Run: 27/10/2022 22:55:59

Comment:

ID Search Hits
#1 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 15311
#2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*):ti,ab,kw (Word variations have been searched) 69108
#3 #1 or #2 71182
#4 MeSH descriptor: [Respiratory Distress Syndrome] explode all trees 2785
#5 MeSH descriptor: [Acute Lung Injury] explode all trees 587
#6 (respiratory NEXT distress) 8502
#7 acute or adult or severe 861493
#8 #6 and #7 5794
#9 ARDS 2570
#10 Acute NEXT lung* NEXT injur* 1505
#11 shock next lung* 10
#12 MeSH descriptor: [Respiratory Insufficiency] explode all trees 3132
#13 ((respirat* or ventilat*) NEXT/3 (insufficienc* or failure or depression or disturbance or dysfunction)) 12176
#14 #4 or #5 or #8 or #9 or #10 or #11 or #12 or #13 19776
#15 #3 and #14 in Trials 1390
#16 #15 with Cochrane Library publication date Between Nov 2021 and Oct 2022 97

CINAHL (Ebsco)

Thursday, October 27, 2022 4:22:05 PM				
#	**Query**	**Limiters/Expanders**	**Last Run Via**	**Results**
S29	S28	Limiters - Published Date: 20211101-20221231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	25
S28	S11 AND S27	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	418
S27	S12 OR S13 OR S14 OR S15 OR S16 OR	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases	980,617

	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL	
S26	TI (trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	171,168
S25	AB (random*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	386,168
S24	TI (randomised OR randomized)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	132,894
S23	(MH "Cluster Sample")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	5,094
S22	(MH "Pretest-Posttest Design")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	50,758
S21	(MH "Random Assignment")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	76,067
S20	(MH "Single-Blind Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	15,768

S19	(MH "Double-Blind Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	53,495
S18	AB (CLUSTER W3 RCT)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	474
S17	MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	463,363
S16	AB (CONTROL W5 GROUP)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	138,900
S15	PT (randomized controlled trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	146,618
S14	MH (placebos)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	13,473
S13	MH (sample size) AND AB (assigned OR allocated OR control)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	4,392
S12	(MH "Randomized Controlled Trials")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	133,332

S11	S3 AND S10	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2,031
S10	S4 OR S5 OR S6 OR S7 OR S8 OR S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	37,042
S9	TX ((respirat* or ventilat*) N3 (insufficienc* or failure or depression or disturbance or dysfunction))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	20,370
S8	(MH "Respiratory Failure")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	8,495
S7	TX ((acute N1 lung* N1 injur*) or (shock N1 lung*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	4,238
S6	TX (((acute or adult or severe) and (respiratory N1 distress)) or ards)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	16,897
S5	(MH "Acute Lung Injury")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,836
S4	(MH "Respiratory Distress Syndrome, Acute")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced	8,284

			Search Database - CINAHL	
S3	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	103,544
S2	TX steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	93,050
S1	(MH "Adrenal Cortex Hormones+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	40,441

WHO COVID-19 database
Nov 8, 2022
https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

searched title, abstract and subject fields for:
steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*
Yields 14000 results. Run through the RobotReviewer filter (used to be live at https://robotsearch.vortext.systems/ but now we use a desktop version, yielded 5227 records, limited to 2022, yields 1712 records

Search Strategy for Corticosteroids in CAP

MEDLINE(R) 1996 to September 01, 2022
Search Strategy:

#	Searches	Results
1	exp Pneumonia/	242993
2	pneumon*.tw.	144448
3	bronchopneumon*.tw.	1642
4	pleuropneumon*.tw.	1694
5	CAP.tw.	33871
6	HAP.tw.	5038
7	Respiratory Distress Syndrome/	18753
8	adult respiratory distress syndrome.tw.	1546
9	acute respiratory distress syndrome.tw.	15484
10	ARDS.tw.	11952
11	or/1-10	391760
12	exp Steroids/	482327
13	steroid*.tw,nm.	229299
14	exp Adrenal Cortex Hormones/	214984
15	adrenal cortex hormone*.tw,nm.	34694
16	corticosteroid*.tw,nm.	76343
17	corticoid*.tw,nm.	2328
18	glucocorticoid*.tw,nm.	87785
19	glucocorticosteroid*.tw,nm.	2201
20	pregnenedione*.tw,nm.	1130
21	pregnenolone*.tw,nm.	2852
22	hydrocortisone.tw,nm.	38720
23	hydroxypregnenolone.tw,nm.	306
24	hydroxycorticosteroid*.tw,nm.	231
25	tetrahydrocortisol.tw,nm.	242
26	cortodoxone.tw,nm.	309
27	cortisone.tw,nm.	3447

28	fludrocortisone.tw,nm.	1053
29	corticosterone.tw,nm.	19487
30	triamcinolone.tw,nm.	6772
31	prednisone.tw,nm.	28700
32	prednisolone.tw,nm.	26654
33	paramethasone.tw,nm.	16
34	methylprednisolone.tw,nm.	18158
35	dexamethasone.tw,nm.	45431
36	clobetasol.tw,nm.	1443
37	beclomethasone.tw,nm.	2241
38	betamethasone.tw,nm.	4193
39	budesonide.tw,nm.	5613
40	(efcortesol or hydrocortone or solu-cortef).tw,nm.	6
41	(betnelan or betnesol).tw,nm.	5
42	(deflazacort or calcort).tw,nm.	415
43	(medrone or solu-medrone or depo-medrone).tw,nm.	9
44	kenalog.tw,nm.	117
45	(novolizer or pulmicort or symbicort).tw,nm.	342
46	(beclometasone or aerobec or asmabec or beclazone or becodisks or becotide orclenil modulite or qvar or becloforte).tw,nm.	285
47	cortisol.tw,nm.	41259
48	or/12-47	759319
49	11 and 48	17804
50	((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.)	1197120
51	49 and 50	1773
52	limit 51 to ed=20200229-20220901	833

Embase 1974 to 2022 August 31
Search Strategy:

#	Searches	Results

1	exp pneumonia/	365350
2	pneumon*.ti,ab.	308526
3	bronchopneumon*.ti,ab.	4533
4	pleuropneumon*.ti,ab.	2936
5	cap.ti,ab.	66257
6	hap.ti,ab.	8085
7	adult respiratory distress syndrome/	50707
8	adult respiratory distress syndrome.ti,ab.	5089
9	acute respiratory distress syndrome.ti,ab.	27257
10	ards.ti,ab.	27592
11	or/1-10	601636
12	exp steroid/	1686012
13	steroid*.ti,ab.	357451
14	exp corticosteroid/	1043905
15	adrenal cortex hormone*.ti,ab.	135
16	corticosteroid*.ti,ab.	173153
17	corticoid*.ti,ab.	7281
18	glucocorticoid*.ti,ab.	99473
19	glucocorticosteroid*.ti,ab.	5142
20	pregnane derivative/	2062
21	pregnenedione*.ti,ab.	4
22	pregnenolone*.ti,ab.	5929
23	hydrocortisone.ti,ab.	20390
24	hydroxypregnenolone.ti,ab.	745
25	hydroxycorticosteroid*.ti,ab.	747
26	tetrahydrocortisol.ti,ab.	452
27	cortodoxone.ti,ab.	8
28	cortodoxone/	2163
29	cortisone.ti,ab.	8452
30	fludrocortisone.ti,ab.	2160
31	corticosterone.ti,ab.	31809

32	triamcinolone.ti,ab.	10700
33	prednisone.ti,ab.	54760
34	prednisolone.ti,ab.	43330
35	paramethasone.ti,ab.	63
36	methylprednisolone.ti,ab.	30300
37	dexamethasone.ti,ab.	87851
38	clobetasol.ti,ab.	2103
39	beclomethasone.ti,ab.	4025
40	betamethasone.ti,ab.	7368
41	budesonide.ti,ab.	9858
42	(efcortesol or hydrocortone or 'solu cortef').ti,ab.	39
43	(betnelan or betnesol).ti,ab.	35
44	(deflazacort or calcort).ti,ab.	851
45	(medrone or 'solu medrone' or 'depo medrone').ti,ab.	34
46	kenalog.ti,ab.	361
47	(novolizer or pulmicort or symbicort).ti,ab.	667
48	((beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil) and (modulite or qvar or becloforte)).ti,ab.	39
49	cortisol.ti,ab.	83681
50	or/12-49	1852847
51	11 and 50	76899
52	exp randomized controlled trial/ or exp single blind procedure/ or exp double blind procedure/ or exp crossover procedure/	804613
53	(random* or placebo* or factorial* or crossover* or 'cross-over' or 'cross over' or assign* or allocat* or volunteer* or ((singl* or doubl*) adj2 (blind* or mask*))).ab,ti.	2613555
54	52 or 53	2721847
55	51 and 54	6391
56	limit 55 to dc=20200229-20220831	1588

ClinicalTrials.gov

18 Studies found for: (Corticosteroids OR steroids) | Community-acquired Pneumonia

Supplemental Digital Content 6. Systematic Review and Data Synthesis

Study Selection

We screened all citations in duplicate (DC, KD, TP) in two stages. First, we screened titles and abstracts, and then for any citation selected in this first stage, we screened the full texts. We included, published full articles or abstracts with any randomized control trials that presented original data that addressed the Population, Intervention, and Comparison for each PICO. We captured reasons for exclusion during full text review. A third reviewer (BR) adjudicated disagreements, when necessary. We also contacted experts in the field and reviewed references of included studies to ensure we did not miss any additional studies.

Data Collection Process and Data Items

Three reviewers (DC, TP, KD) abstracted data independently and in duplicate using a pre-specified standardized data abstraction form. A fourth reviewer (BR) adjudicated disagreements. We collected data on trial characteristics, demographic data, intervention and control procedures, and outcomes of interest. In the case of missing data, we contacted the study authors.

Risk of Bias Assessment in Individual Studies

We assessed risk of bias independently and in duplicate using the Cochrane Risk of Bias 2.0 tool for RCTs. We used the tool to assess for risk of bias (ROB) in the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We rated each domain as "low", "some concerns" or "high". We determined overall ROB for each trial based on the highest risk attributed to any one domain. We assessed certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach(6). In keeping with GRADE methods, we use terminology consistent with the overall certainty of evidence. This includes stronger language for high certainty evidence, and less certain language ('probably' or 'may') for moderate or low certainty evidence.

Summary Measures and Synthesis of Results

We used the DerSimonnian-Laird random effects model with inverse-variance weighting to generate pooled treatment effects across studies. We assessed heterogeneity between trials using a combination of the Chi^2 test, the I^2 statistic, and visual inspection of the forest plots. We present results of dichotomous outcomes using relative risk (RR) and continuous outcomes as mean difference (MD), both with 95% confidence intervals (CIs). We have also provided absolute differences with 95% CIs which we used for GRADE ratings. If medians and interquartile ranges (IQR) were reported instead of mean and standard deviation (SD), we assumed normality in data distribution and converted IQR to SDs by dividing the IQR by 1.35(87).

Supplemental Digital Content 7. GRADE Methodology

1. Certainty in the evidence. We used well-established GRADE approaches to determine overall certainty in the evidence separately for each outcome. One of the clinician-methodologists then generated an Evidence Profile using the GDT software (www.GRADEPRO.com). In the GRADE approach, randomized controlled trials are initially considered to yield 'high' certainty evidence, which may then be downgraded if there are concerns around one or more of the following domains: (1) risk of bias, (2) inconsistency, (3) indirectness of the evidence, (4) imprecision, and (5) 'other' factors, which includes publication bias, presence of a dose-response relationship, magnitude of the effect, assessment of the effect of plausible residual confounding or bias. Non-randomized studies are initially considered to yield 'low' certainty evidence, which may then be upgraded or further downgraded based on the assessment of the same 5 domains. The certainty of the evidence for each outcome was then categorized as 'high', 'moderate', 'low', or 'very low':

Certainty Level	Description
⨁⨁⨁⨁ High	We are very confident that the true effect lies close to that of the estimate of the effect.
⨁⨁⨁◯ Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of that effect, but there is a possibility that it is substantially different.
⨁⨁◯◯ Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⨁◯◯◯ Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

2. Evidence-to-Decision Framework

For each PICO question, panel members held one or more web-based meetings via Zoom video conferencing platform, to review the Evidence Profile, discuss the evidence and various factors that may influence decision-making, and to generate a recommendation. The GRADE Evidence-to-Decision (EtD) framework was used to help organize panel discussions during deliberation meetings. The EtD incorporates panel judgment across 12 domains:

Domain	Question
Priority of the Problem	Is the problem a priority?
Desirable effects	How substantial are the desirable effects?
Undesirable effects	How substantial are the undesirable effects?
Certainty of evidence	What is the overall certainty of the evidence of effects?
Values	Is there important uncertainty or variability in how much people value the main outcome?
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?
Resources required	How large are the resource requirements (costs)?
Certainty of evidence of	What is the certainty of the evidence of resource requirements (costs)?

required resources	
Cost effectiveness	Does cost-effectiveness of the intervention favor the intervention or the comparison?
Equity	What would be the impact on health equity?
Acceptability	Is the intervention acceptable to key stakeholders?
Feasibility	Is the intervention feasible to implement?

3. Recommendation Generation

After reviewing the Evidence Profile and discussing each consideration in the EtD for a PICO question, the panel deliberated and decided on a recommendation direction (for, against, neutral) and strength (strong vs. conditional). By convention, strong recommendations are phrased as "We recommend…" and conditional recommendations as "We suggest…". The description of recommendation strengths and their implications for patients, clinicians, and policy makers are shown in **Table 1**.

Supplemental Digital Content 8. Final Voting Process

After all draft recommendations were generated, all panel members, except the clinician-methodologists, were electronically polled to indicate their agreement with each recommendation. The poll for each recommendation consisted of the PICO question, the draft recommendation statement, and a Rationale drafted by guideline leadership. Panelists were asked to select from three options: 'Agree', 'Disagree', or 'Abstain'. An opportunity was provided to provide comments to explain their selection for each recommendation and these were reviewed and where appropriate, addressed by panel leadership. Panel members with conflicts of interest for a particular question were asked to Abstain from voting on the associated recommendation. Based on SCCM requirements, consensus was defined as 80% agreement among at least 75% of panel members, excluding those who abstained.

Voting Results

Recommendation	Response Rate (%)	Yes (%)	No (%)	Abstain (%)
1. We **suggest** administering corticosteroids to patients with septic shock.	100%	90%	0%	10%
2. We **recommend against** administration of high dose/short duration corticosteroids (>400mg/day hydrocortisone equivalent for less than 3 days) for septic shock.	100%	95%	0%	5%
3. We **suggest** administering corticosteroids to hospitalized patients with acute respiratory distress syndrome.	100%	100%	0%	0%
4. We **recommend** corticosteroids for patients hospitalized with severe bacterial community acquired pneumonia.	100%	100%	0%	0%
5. We make **no recommendation** for corticosteroids for patients hospitalized with less severe bacterial community acquired pneumonia.	100%	100%	0%	0%

Voting panel members n=20

9. Evidence profiles and forest plots

A. Sepsis/Septic Shock
B. Acute Respiratory Distress Syndrome
C. Community Acquired Pneumonia

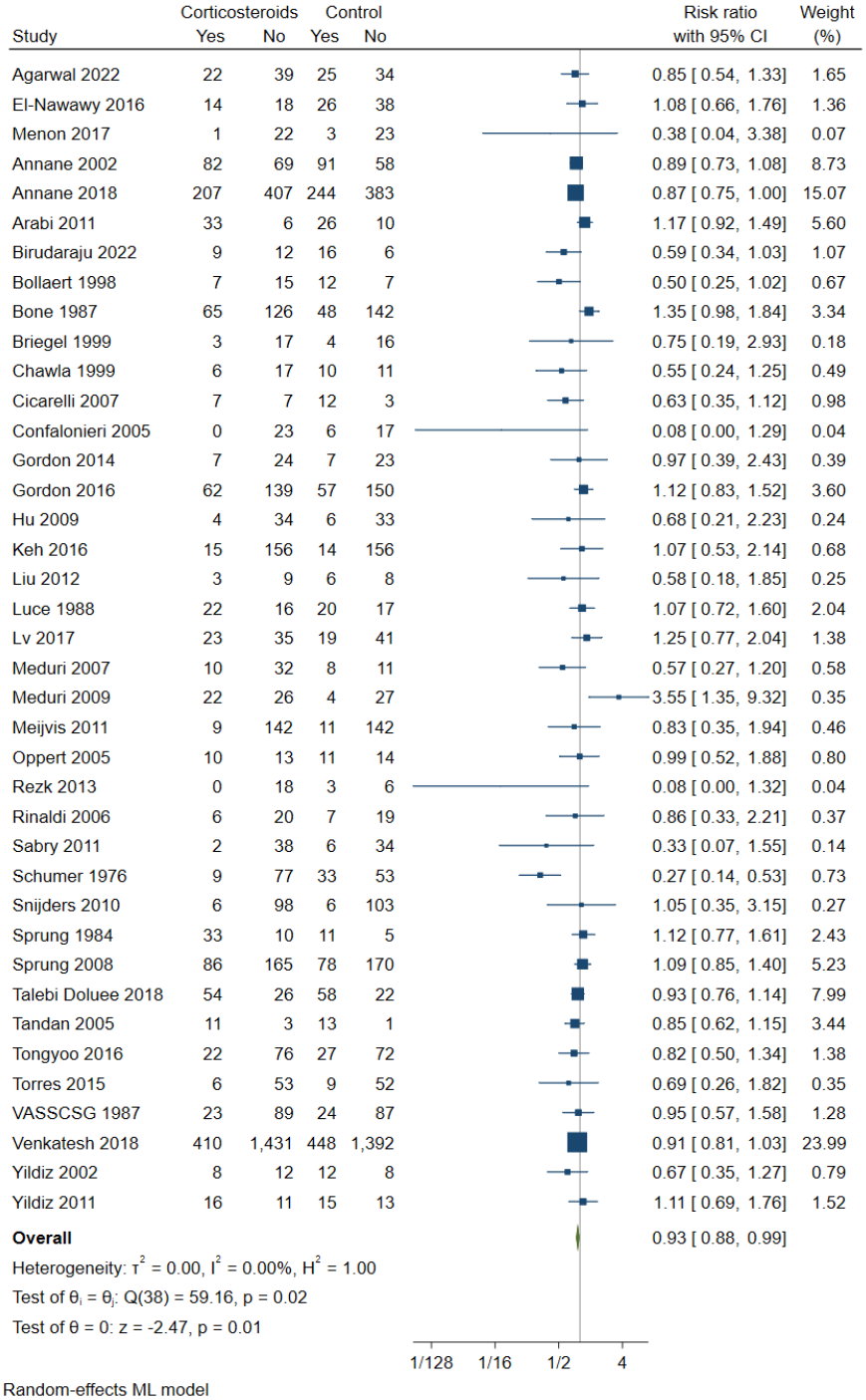
Supplemental Digital Content 9A

Question: Should corticosteroids be administered to hospitalized patients with sepsis?

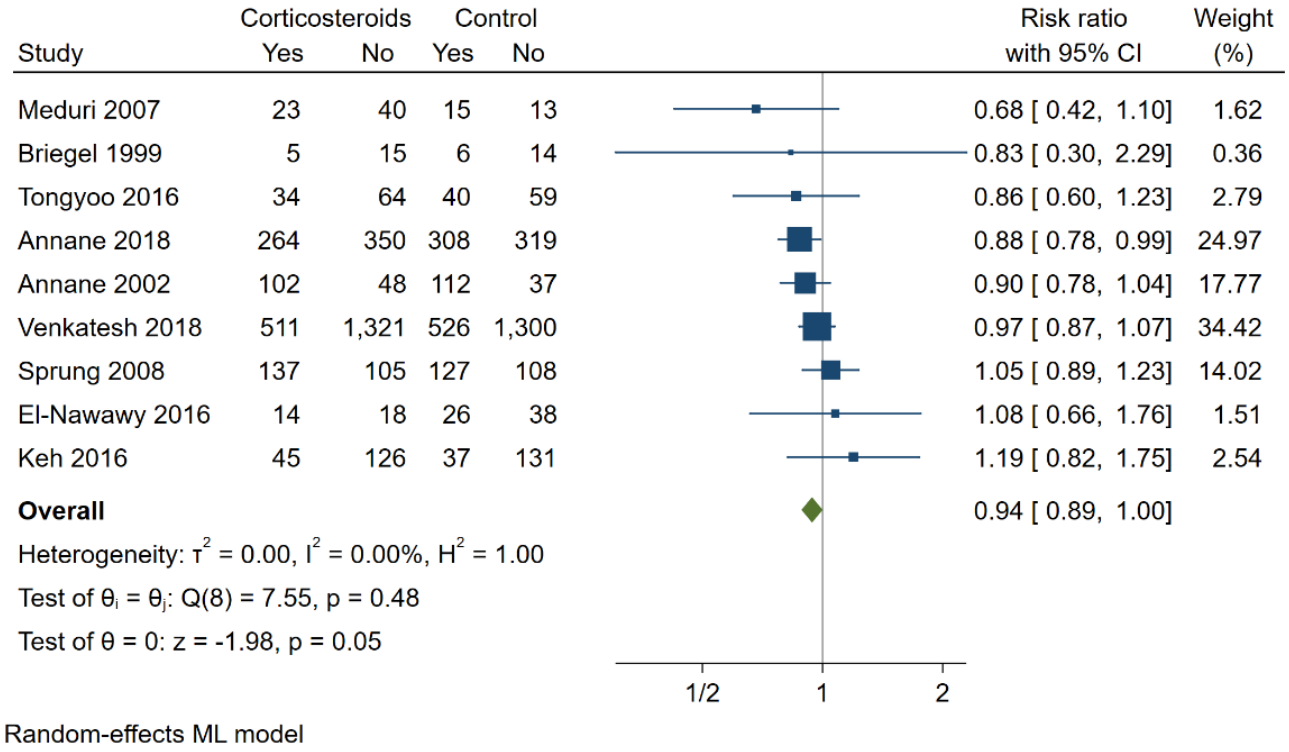
<u>Forest Plots</u>

Sepsis and Septic Shock

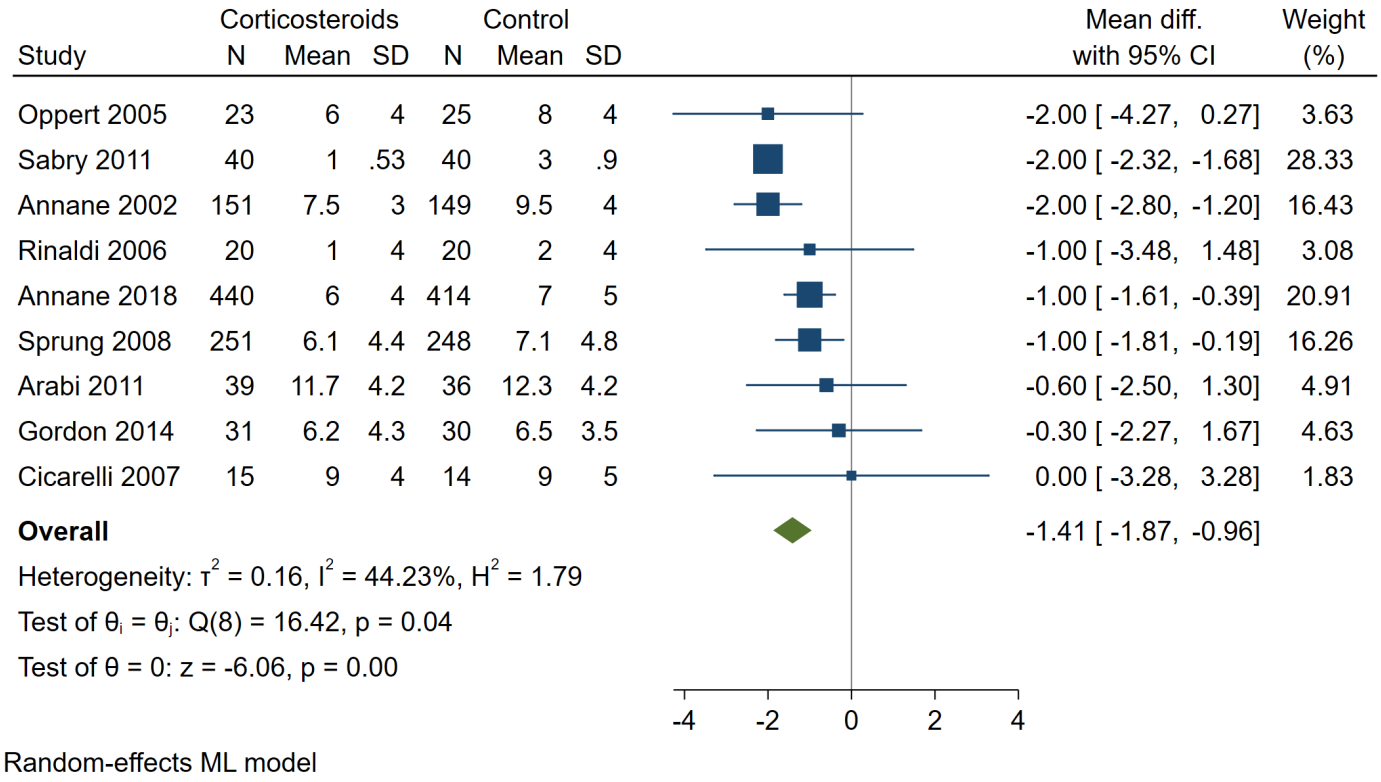
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. ICU/Short term mortality



Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Long term mortality

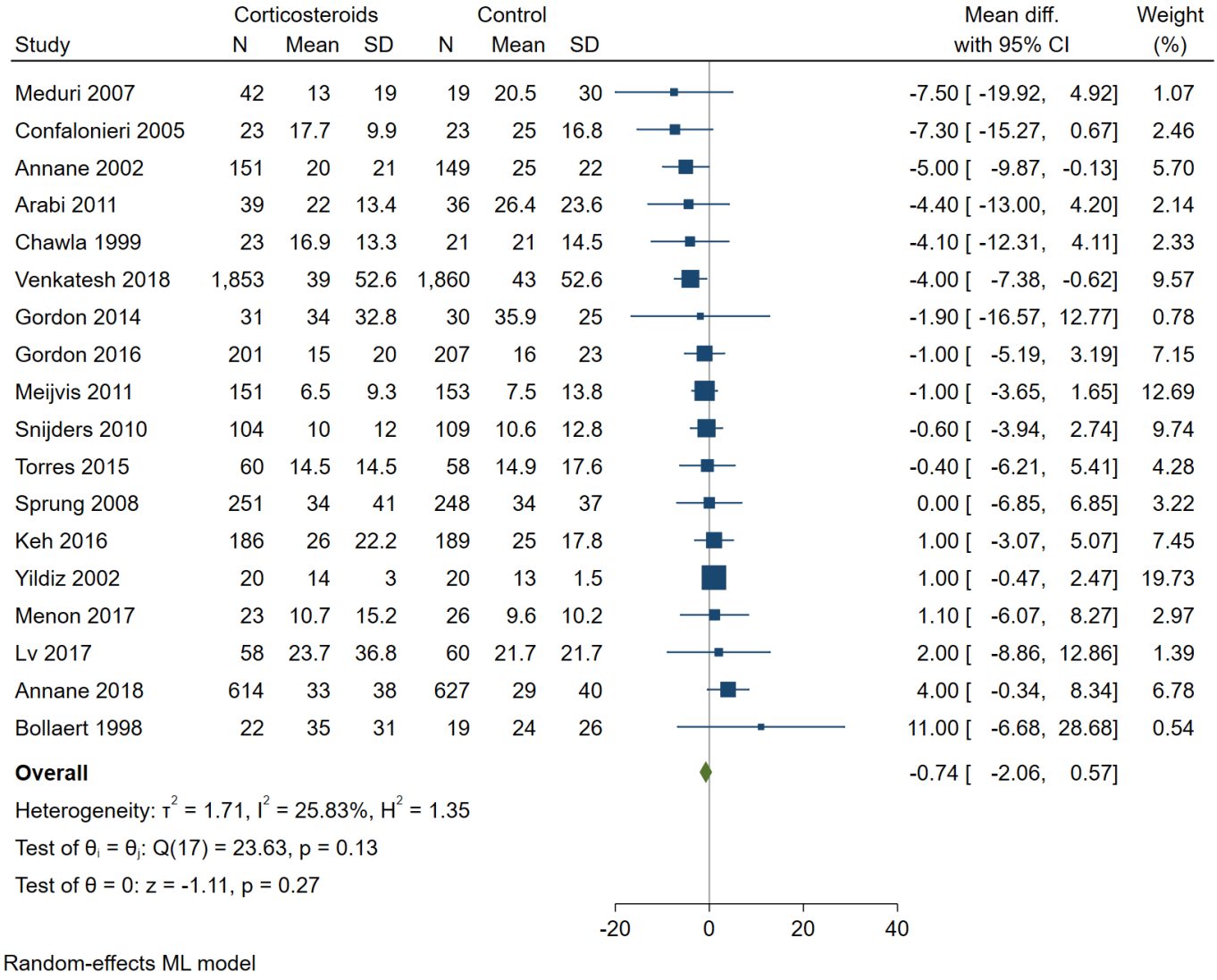


Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Change in qSOFA.

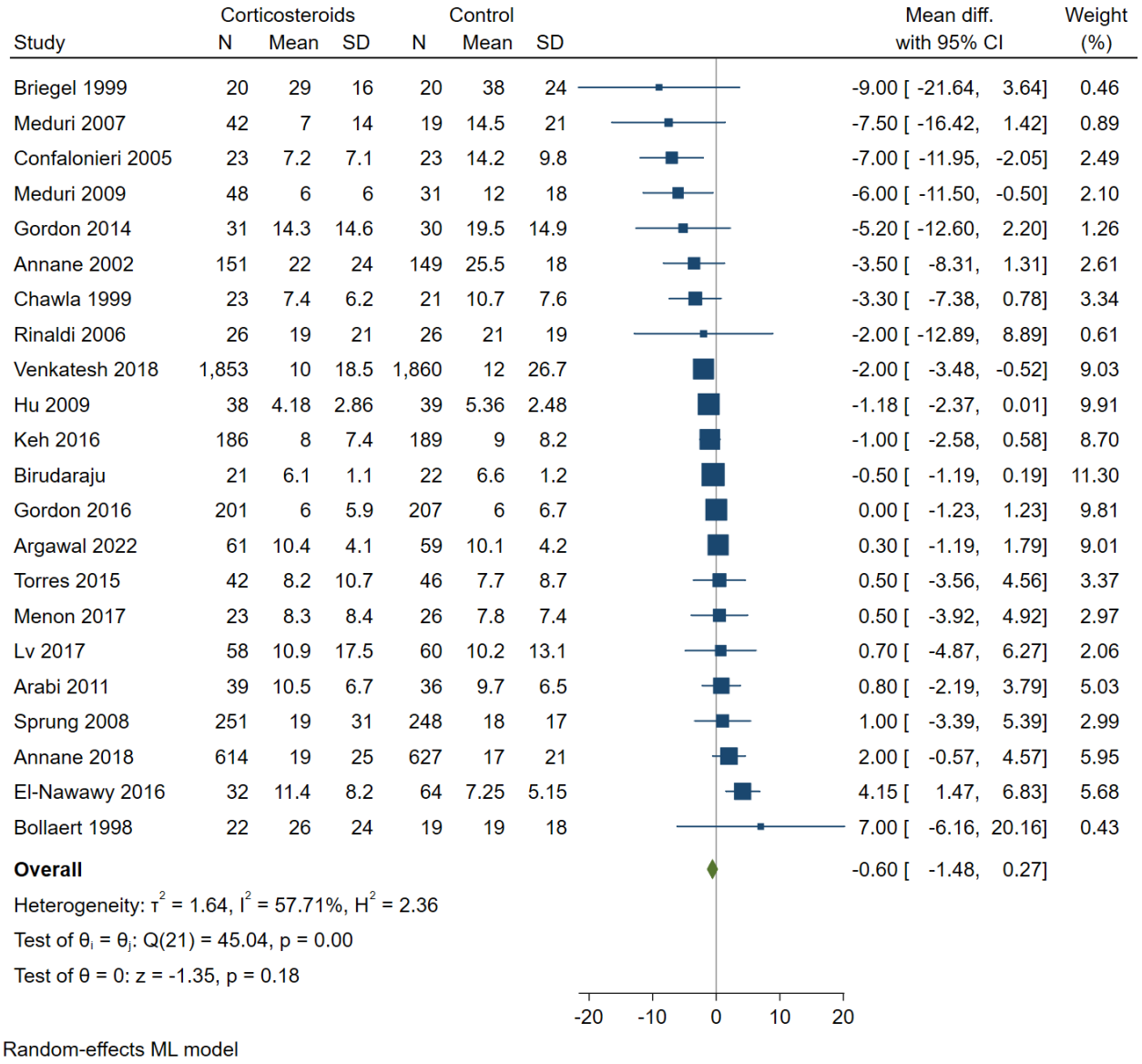


Random-effects ML model

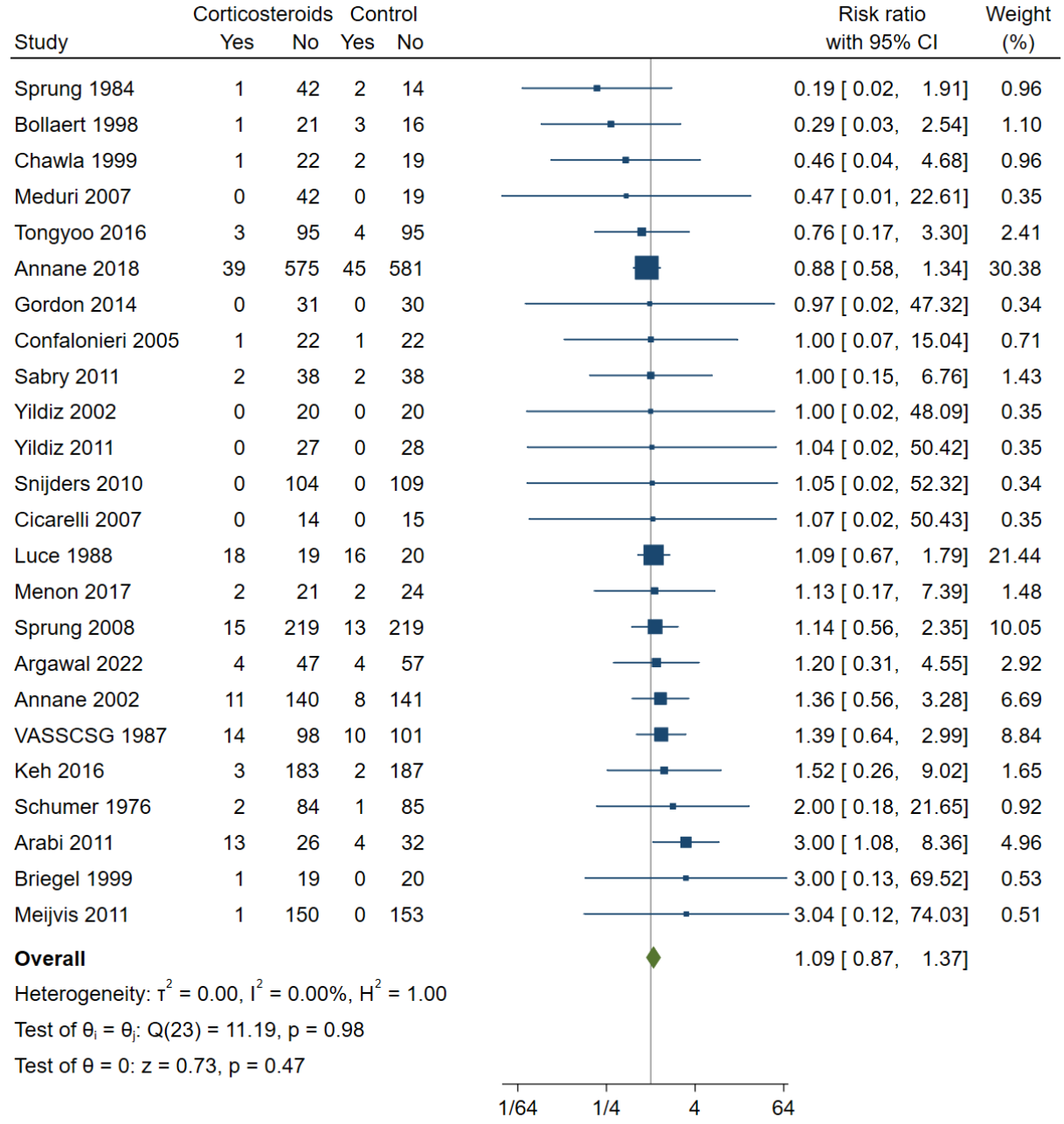
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Duration of hospitalization



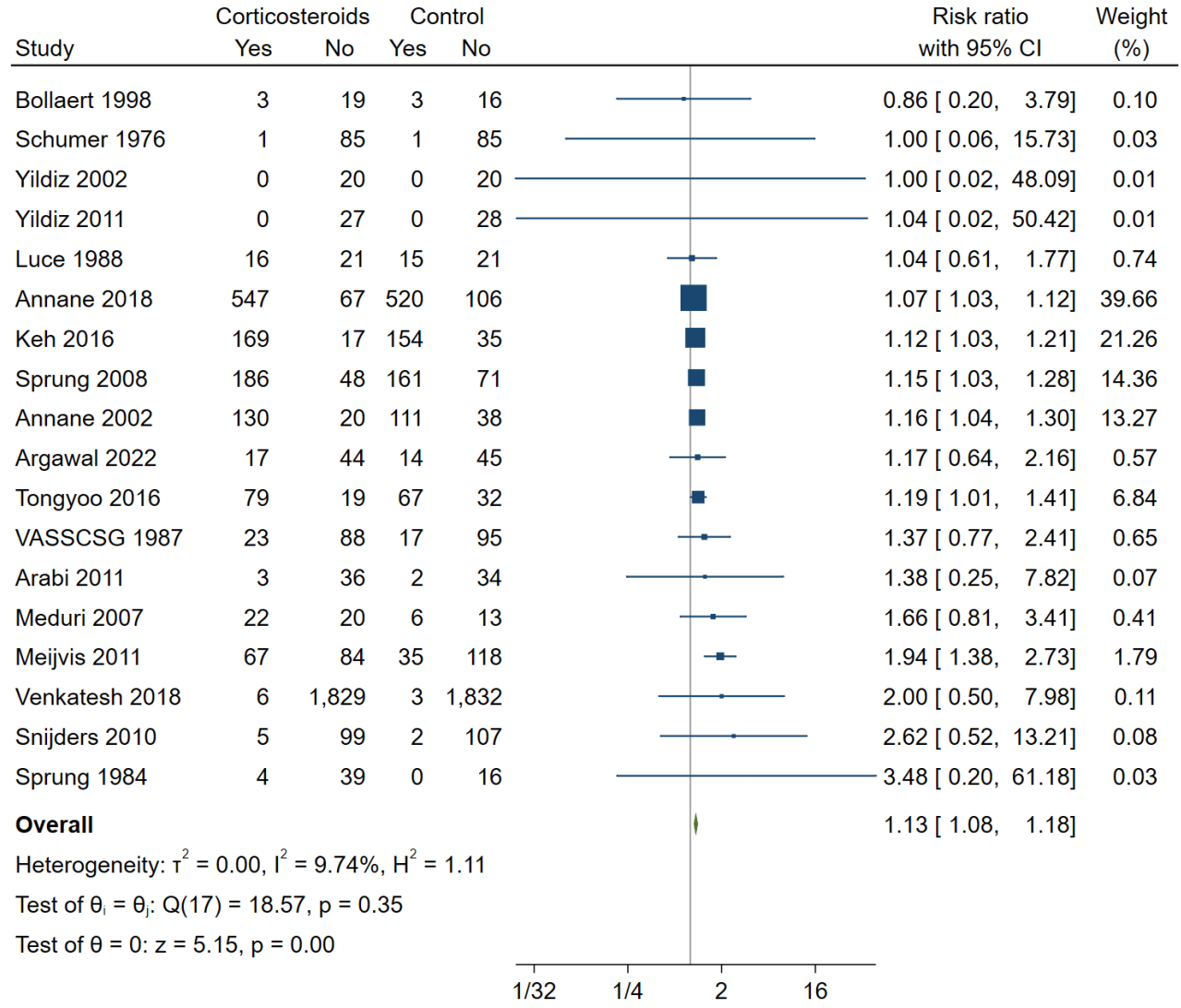
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Duration of ICU stay



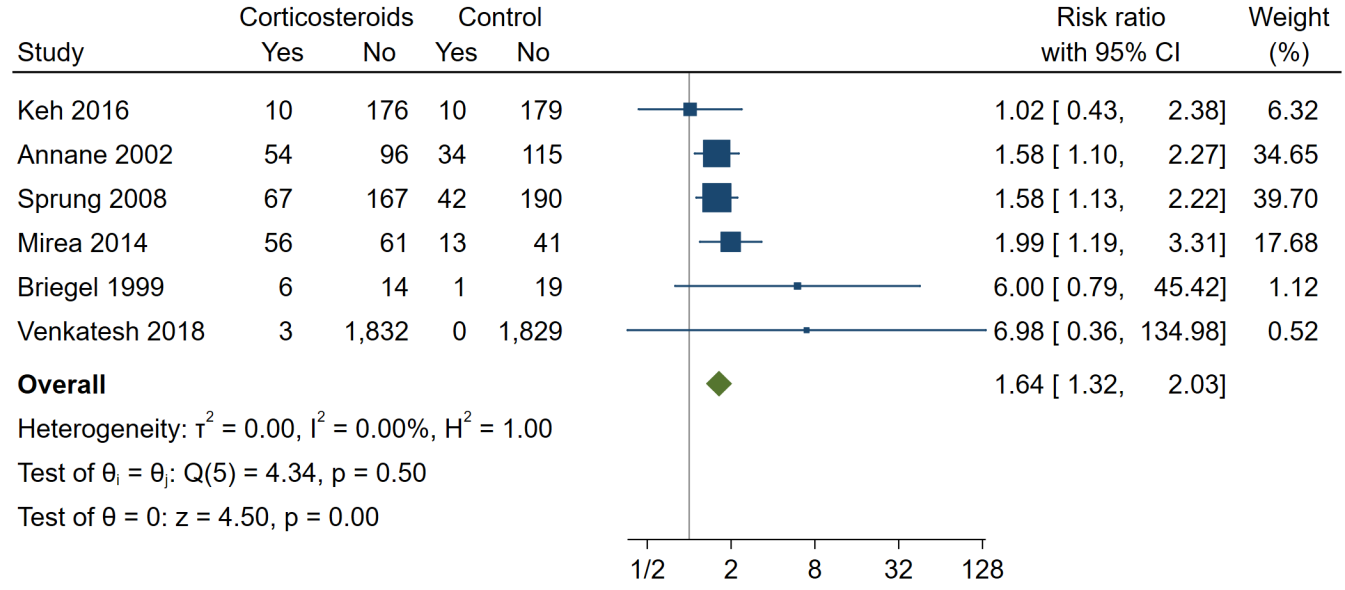
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. GI Bleed



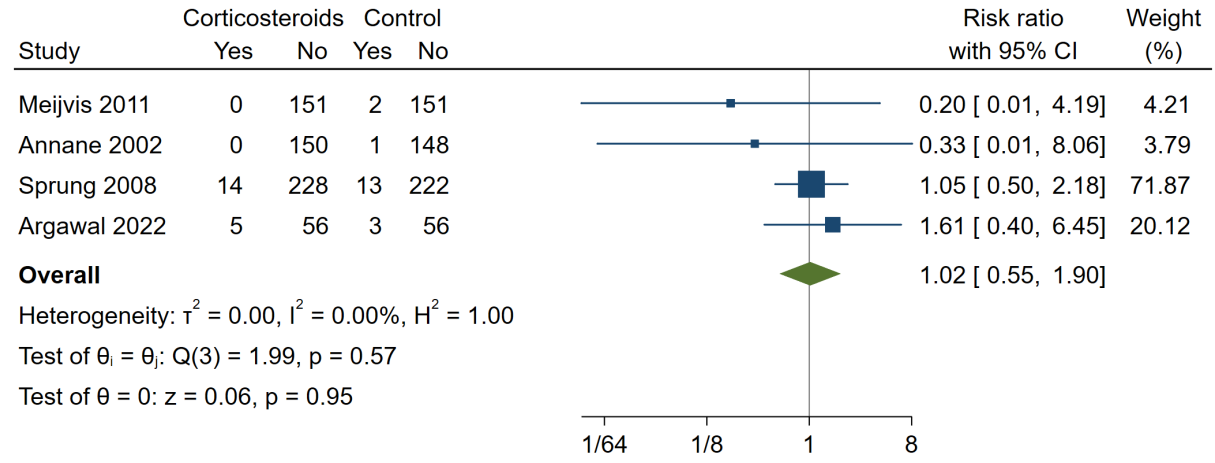
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Hyperglycemia



Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Hypernatremia

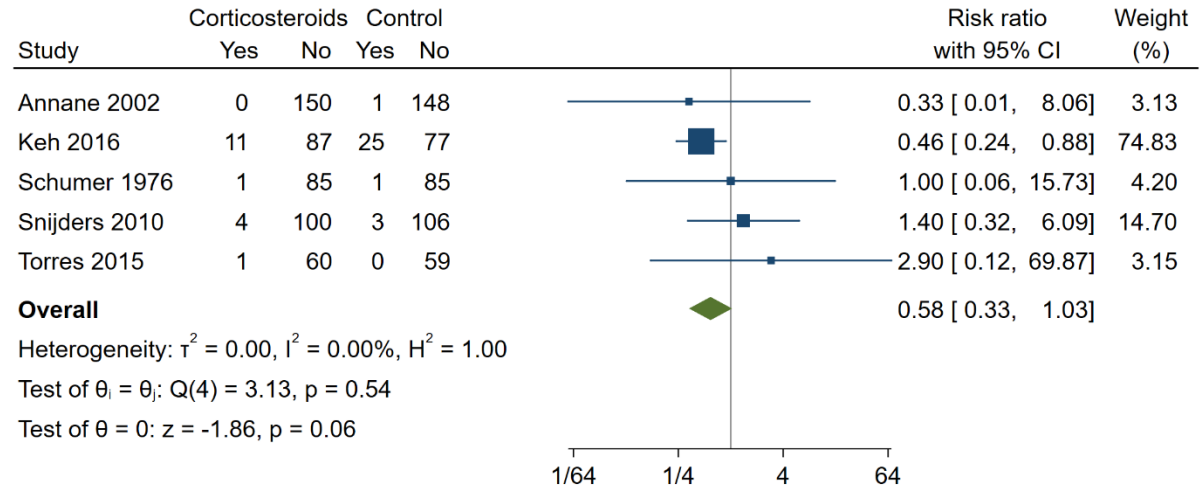


Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Myocardial Infarction



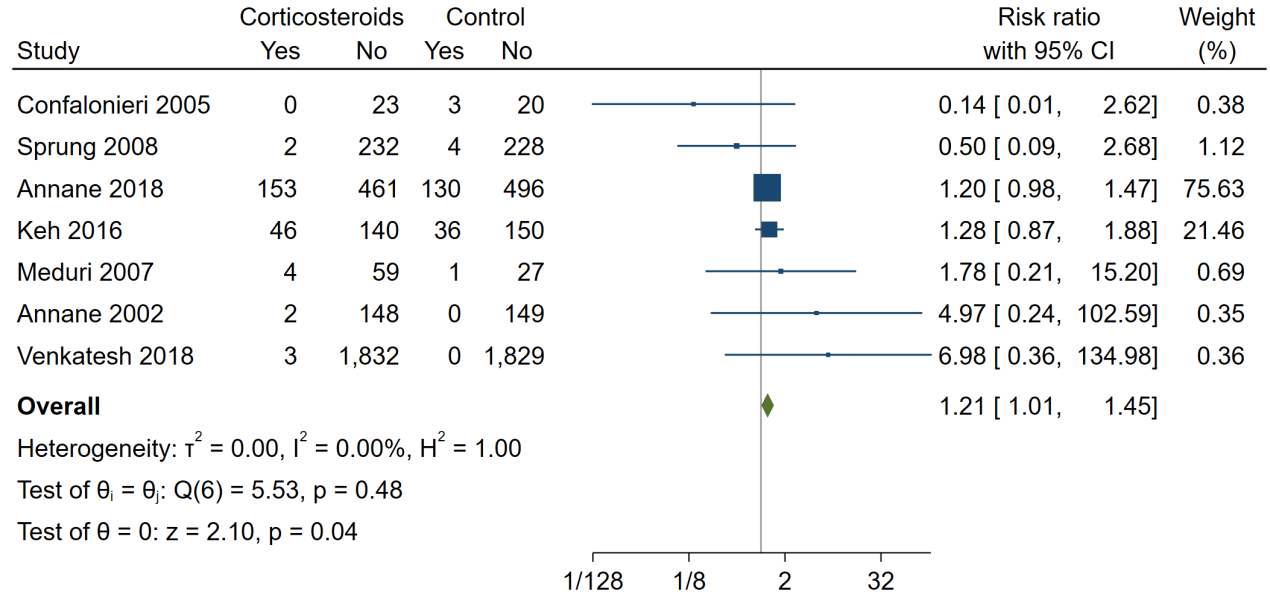
Random-effects ML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Neuropsychiatric effects



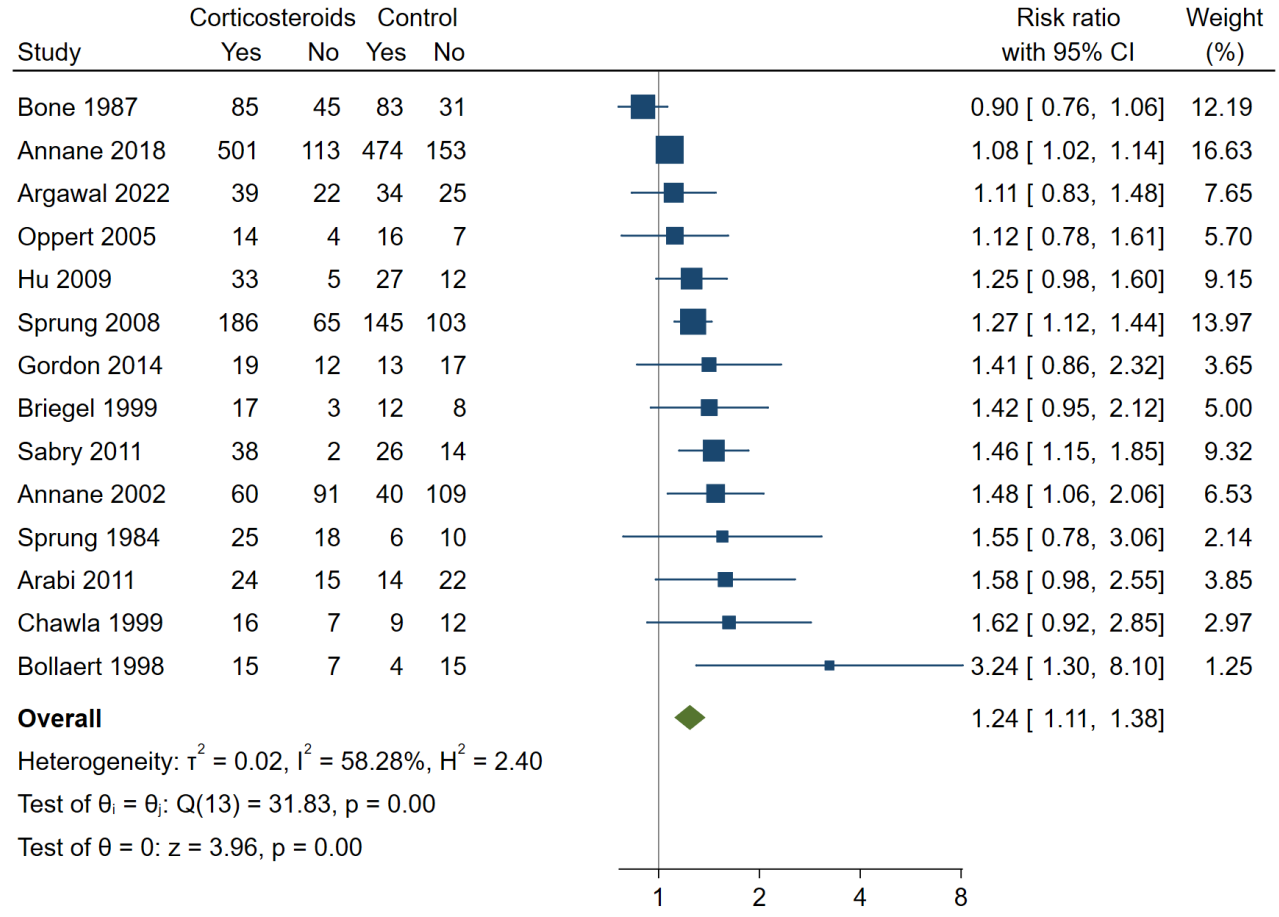
Random-effects ML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Neuromuscular weakness



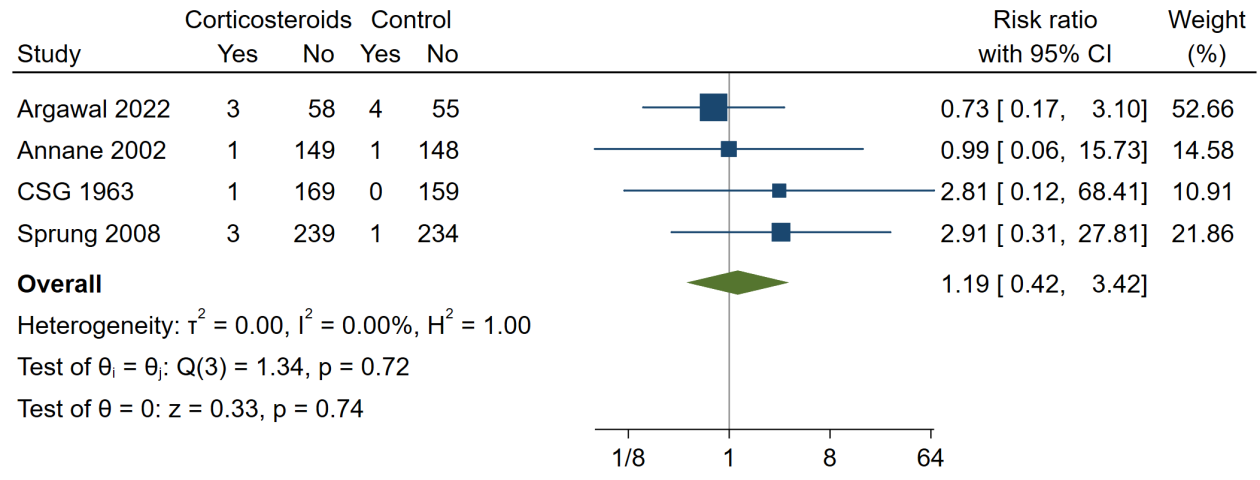
Random-effects ML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Shock reversal



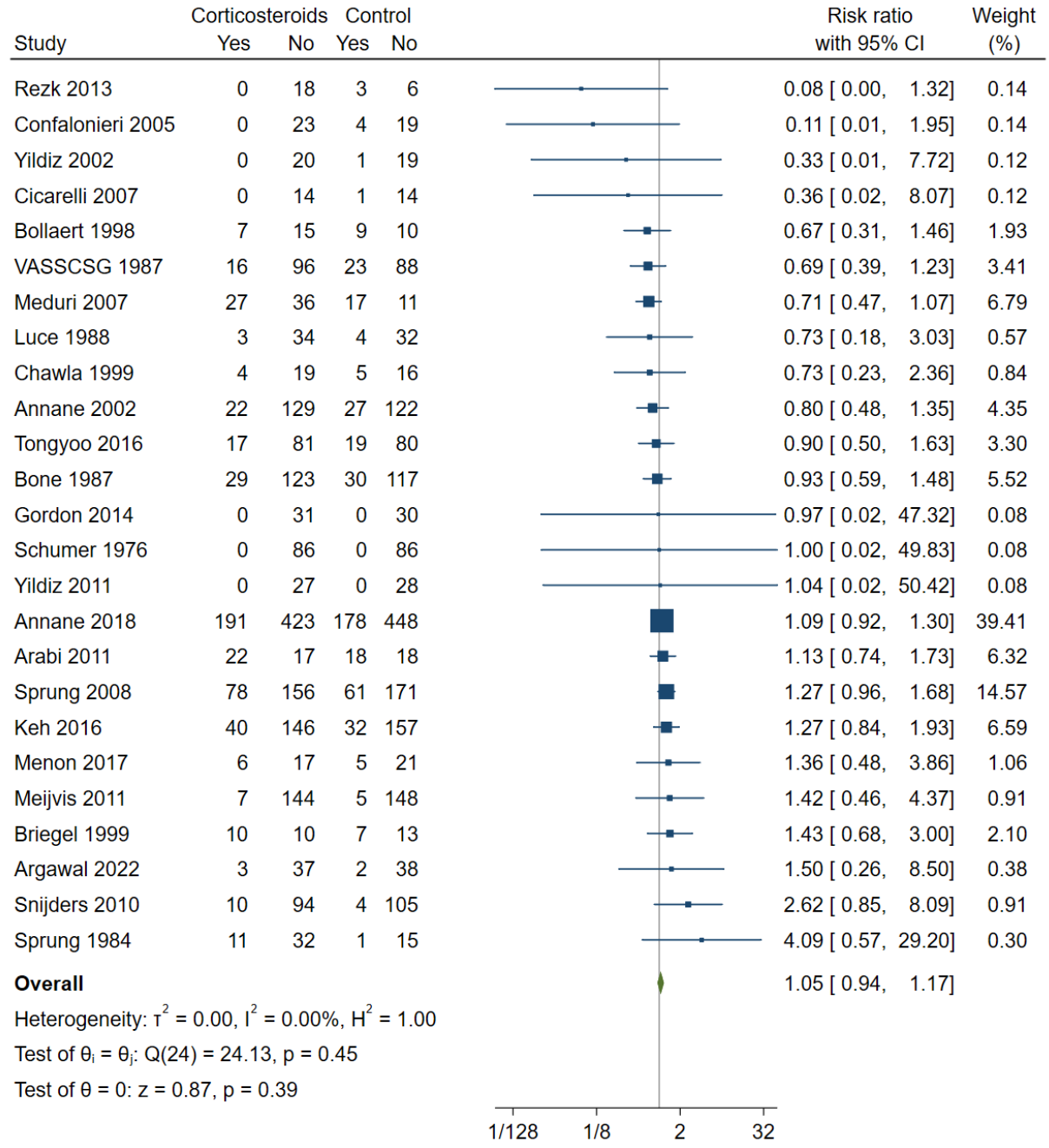
Random-effects ML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Stroke



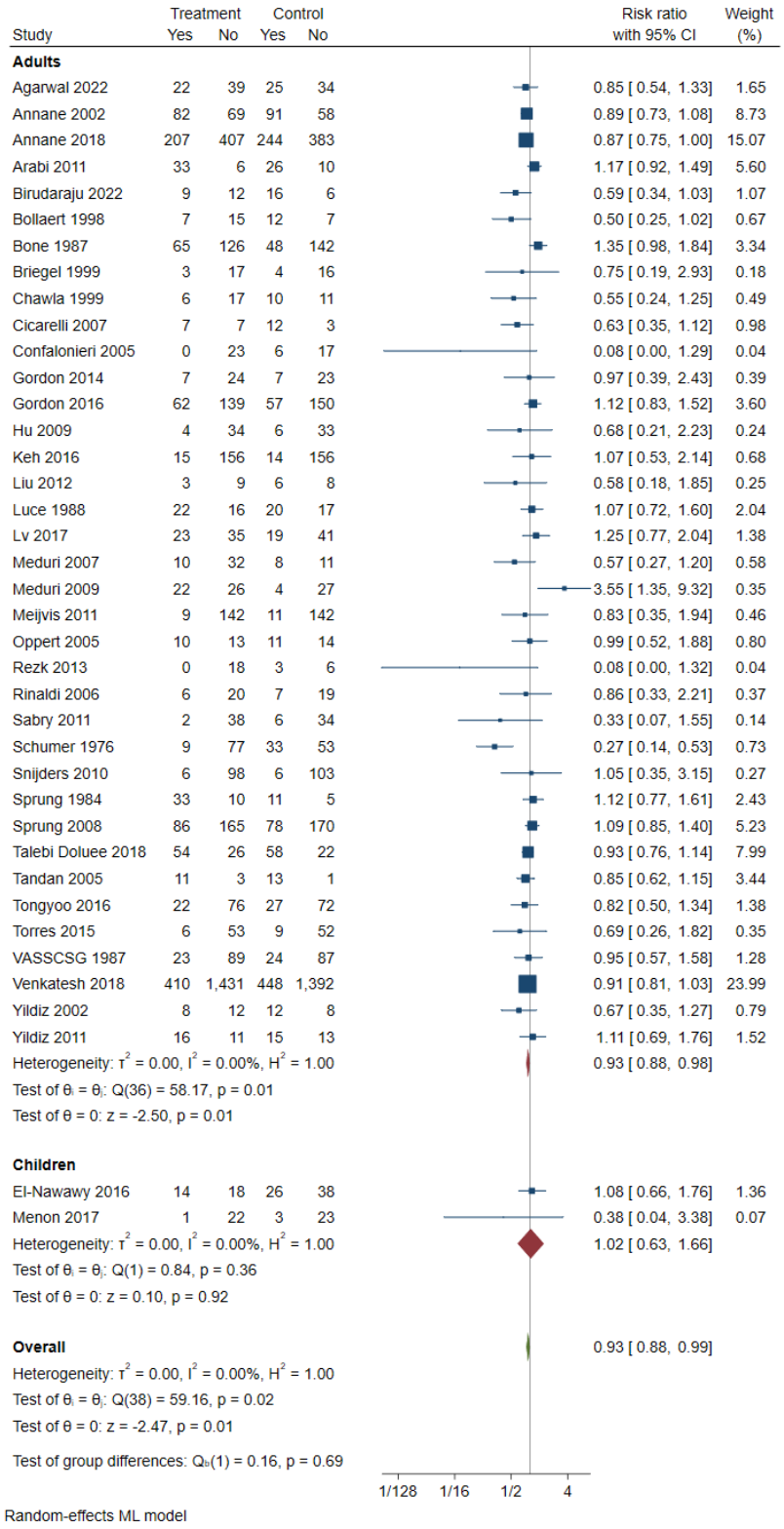
Random-effects ML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Superinfection

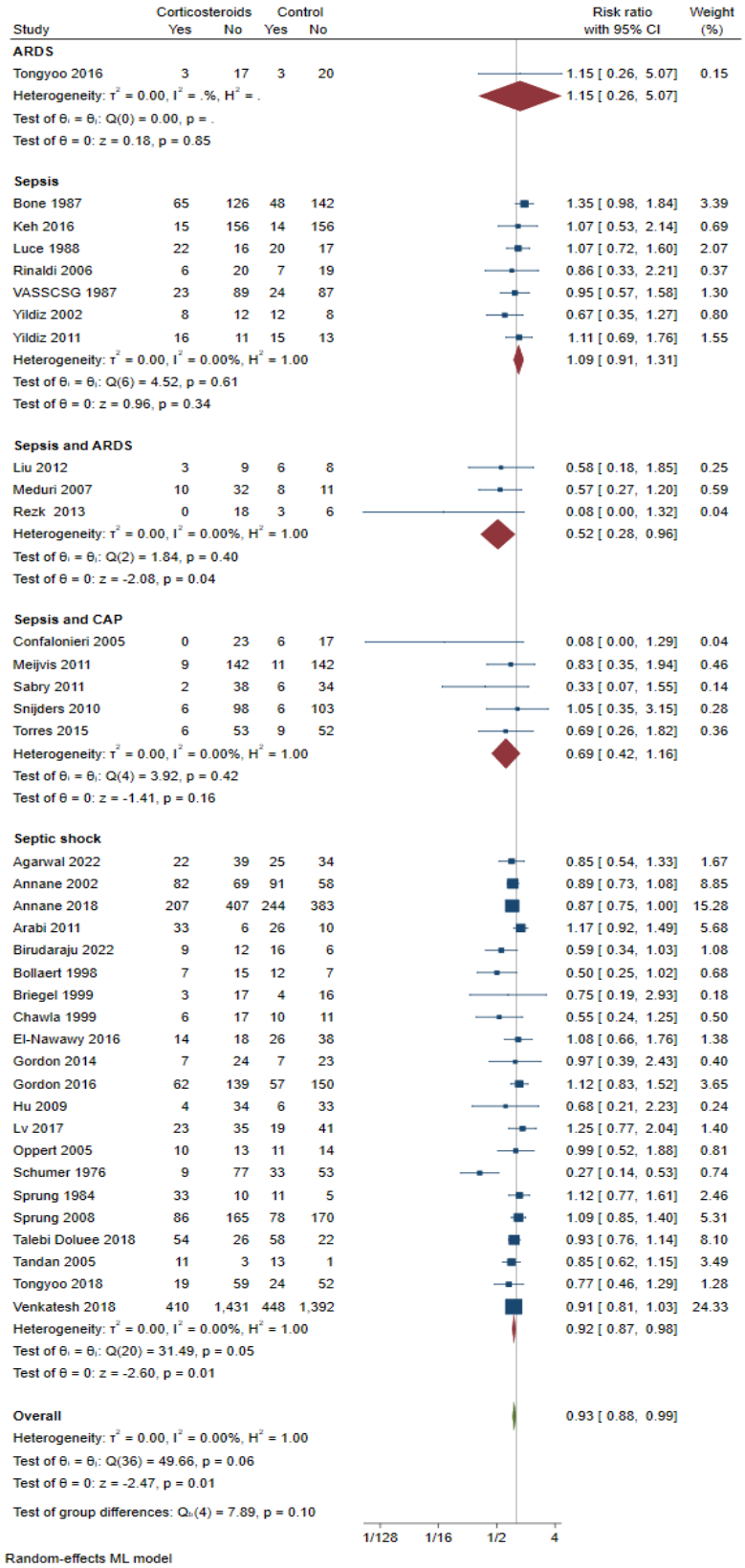


Mortality Subgroup Analysis

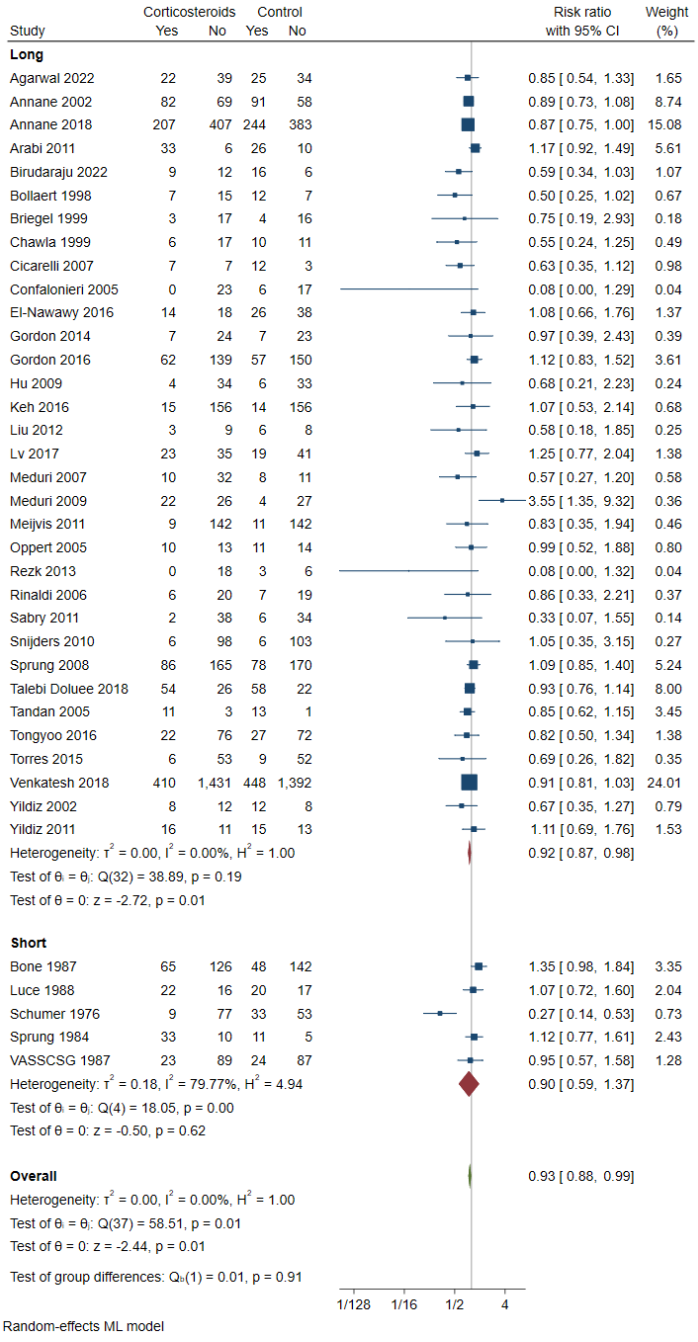
Forest plot: Children vs Adult Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality



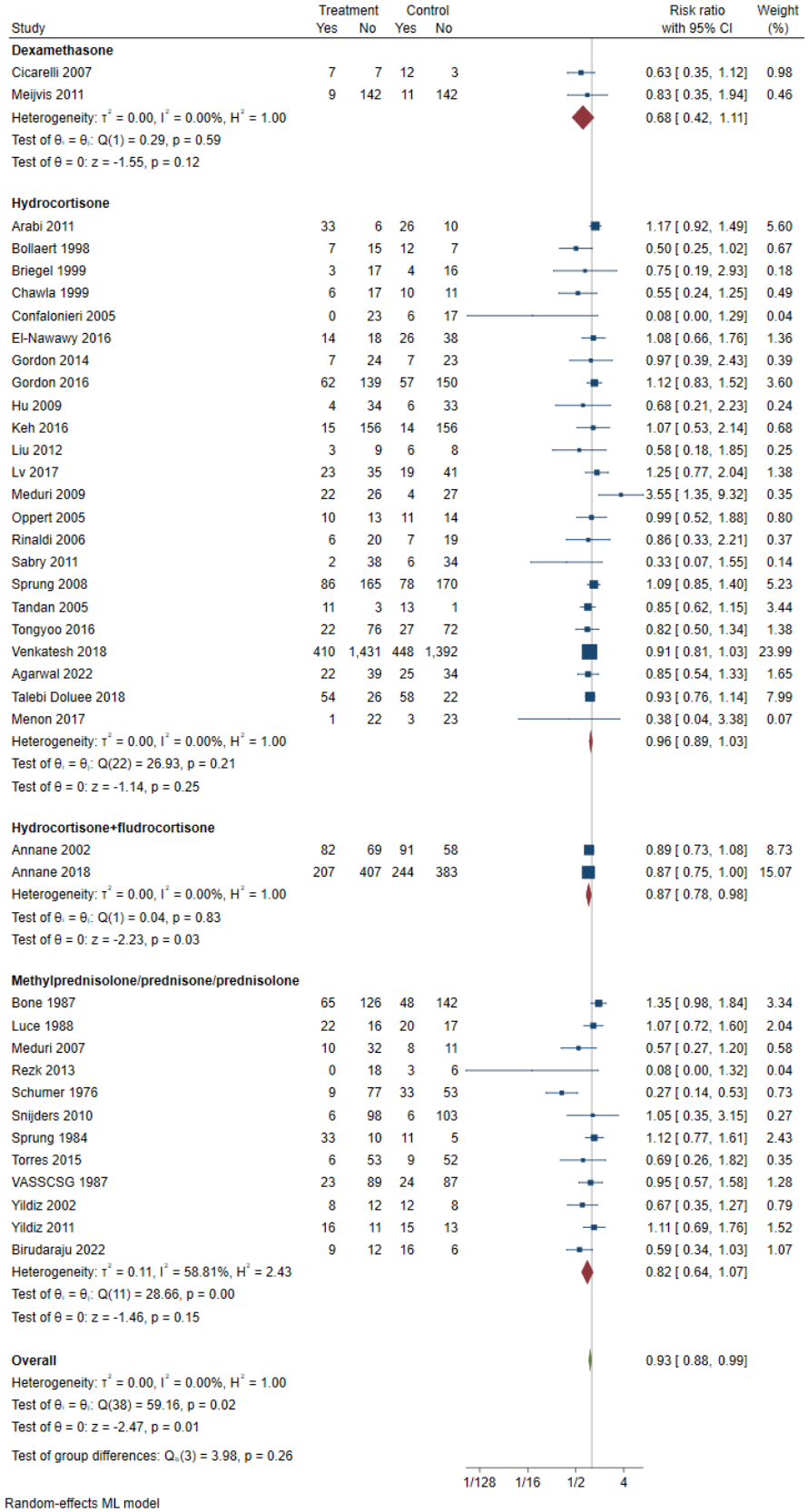
Forest plot: Disease State Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality



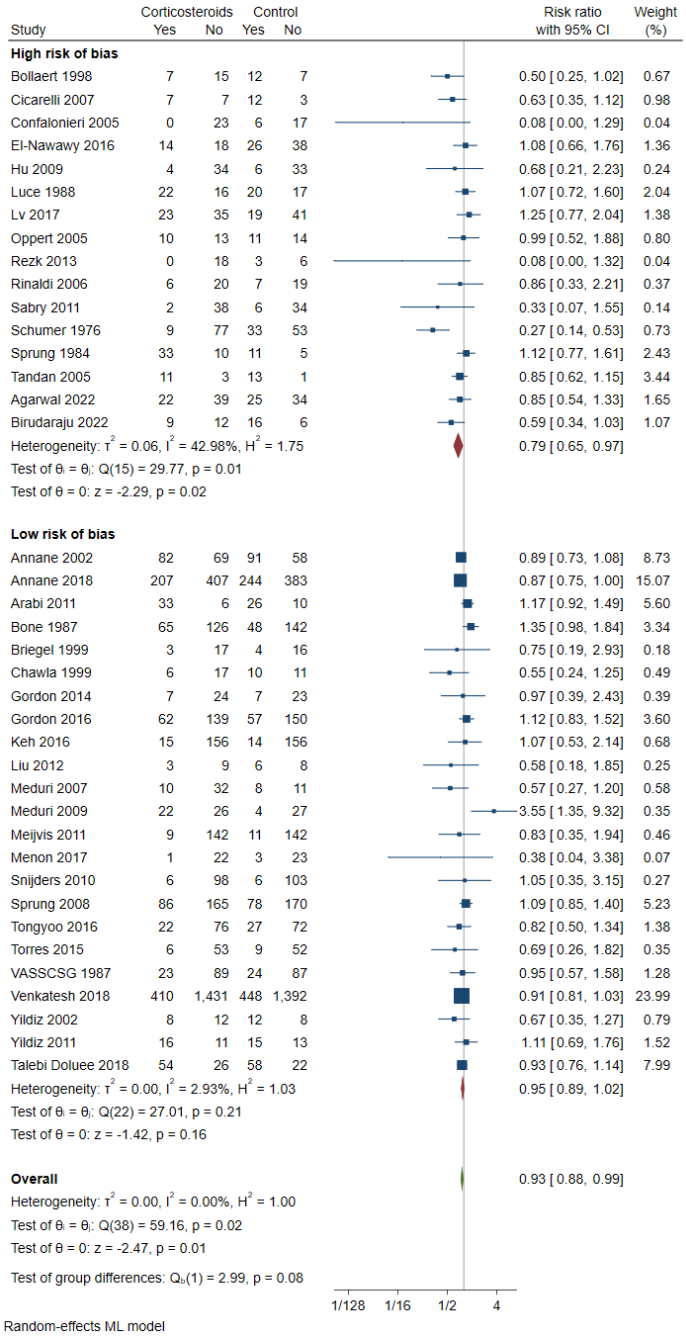
Forest plot: Long (>3 days) vs Short (3 days or less) Corticosteroid Duration Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality



Forest plot: Corticosteroids Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality

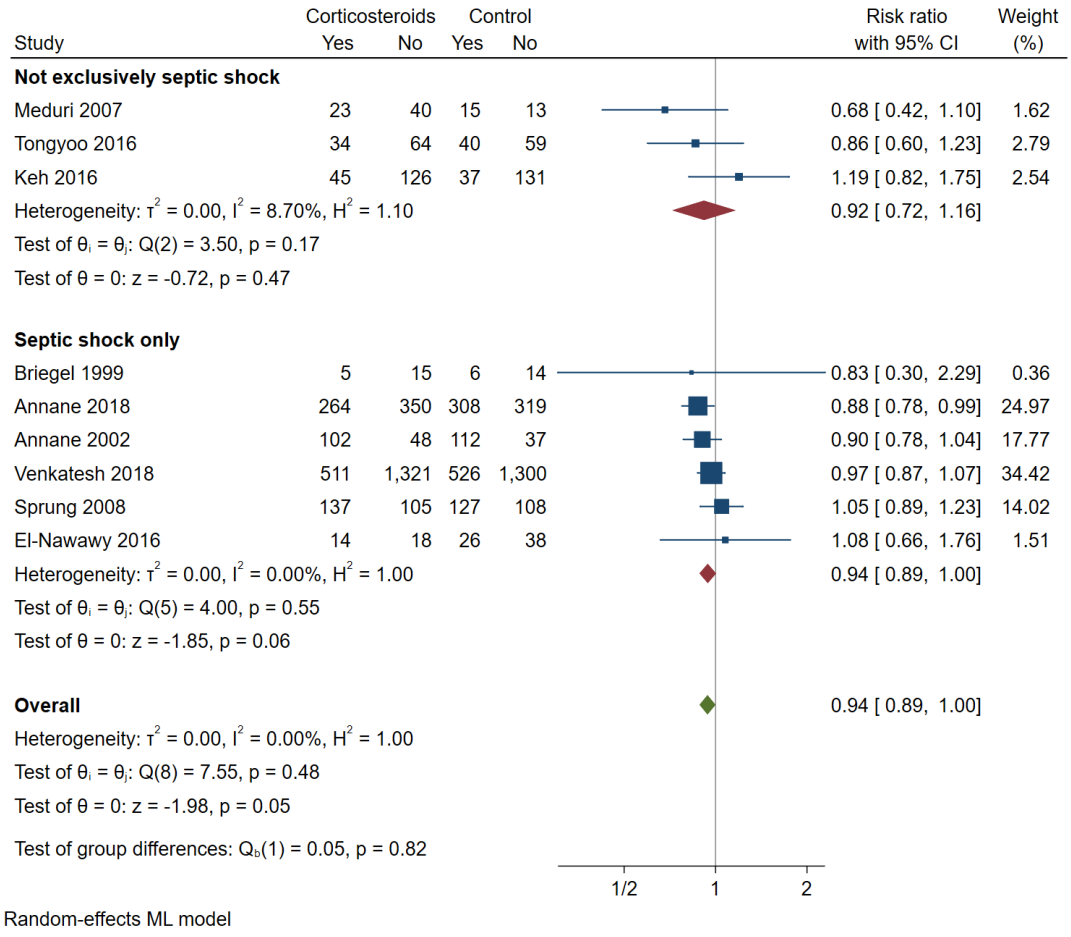


Forest plot: Risk of Bias Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality

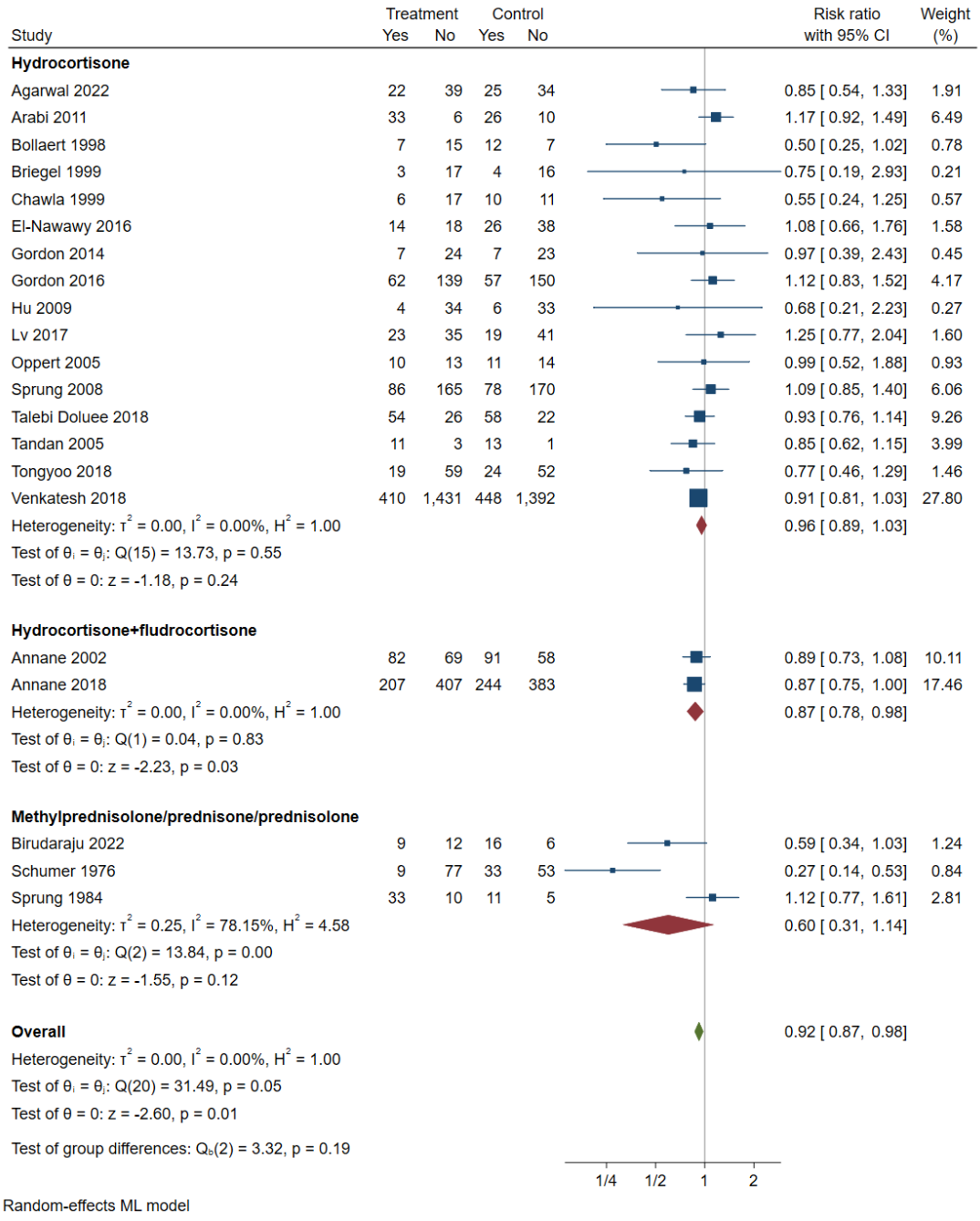


Forest plot: Septic Shock vs Not Exclusively Septic Shock Subgroup. Corticosteroids versus placebo or no corticosteroids. Long term mortality

Sepsis/Septic Shock Vs. Septic Shock Only Long-Term Mortality

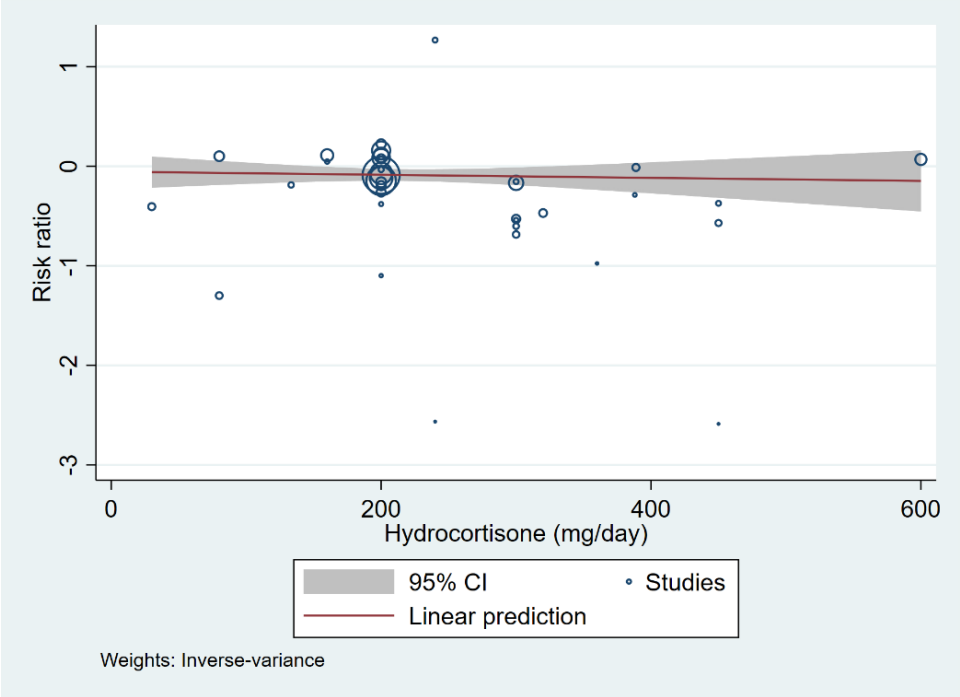


Forest plot: Corticosteroid Molecule Subgroup in Patients with Only Septic Shock. Corticosteroids versus placebo or no corticosteroids. 28 Day Mortality

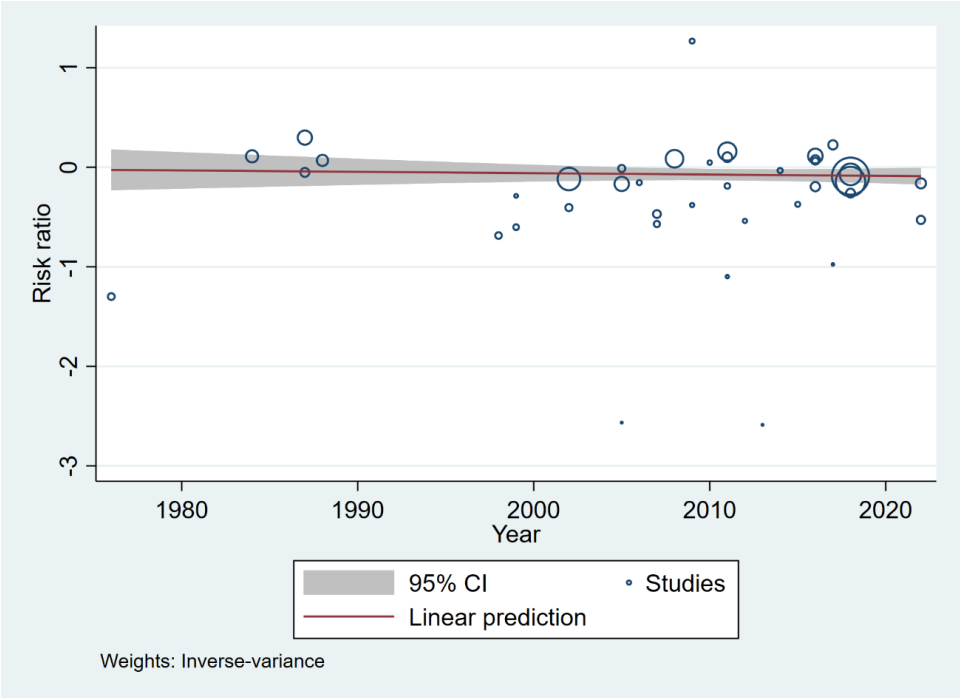


Meta-regression

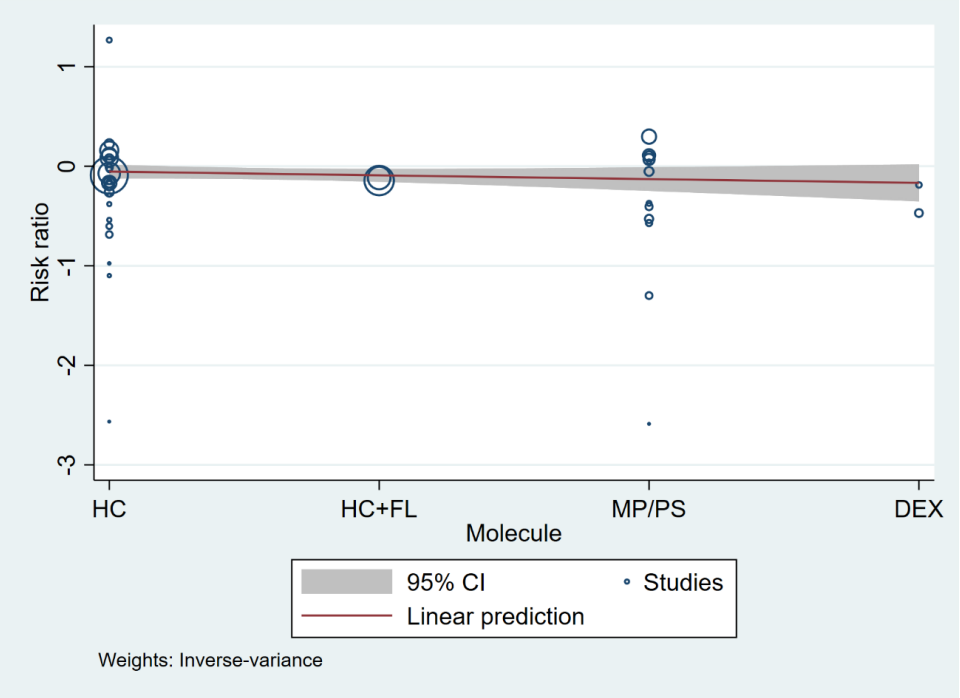
Mortality meta-regression in all patients with sepsis and septic shock based on hydrocortisone equivalent dose per day



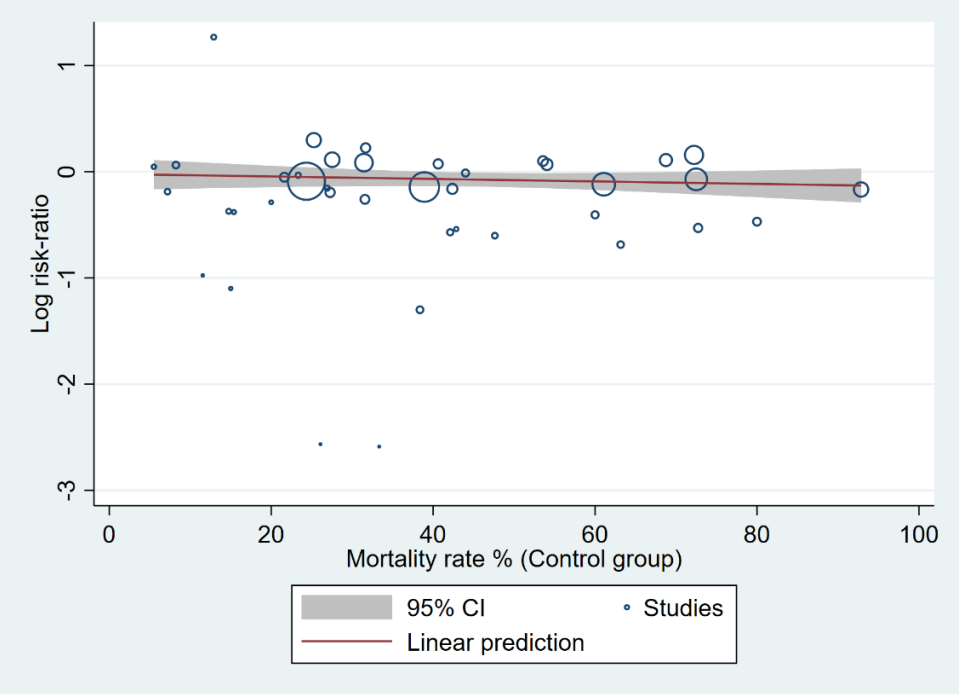
Mortality meta-regression in all patients with sepsis and septic shock based on study year



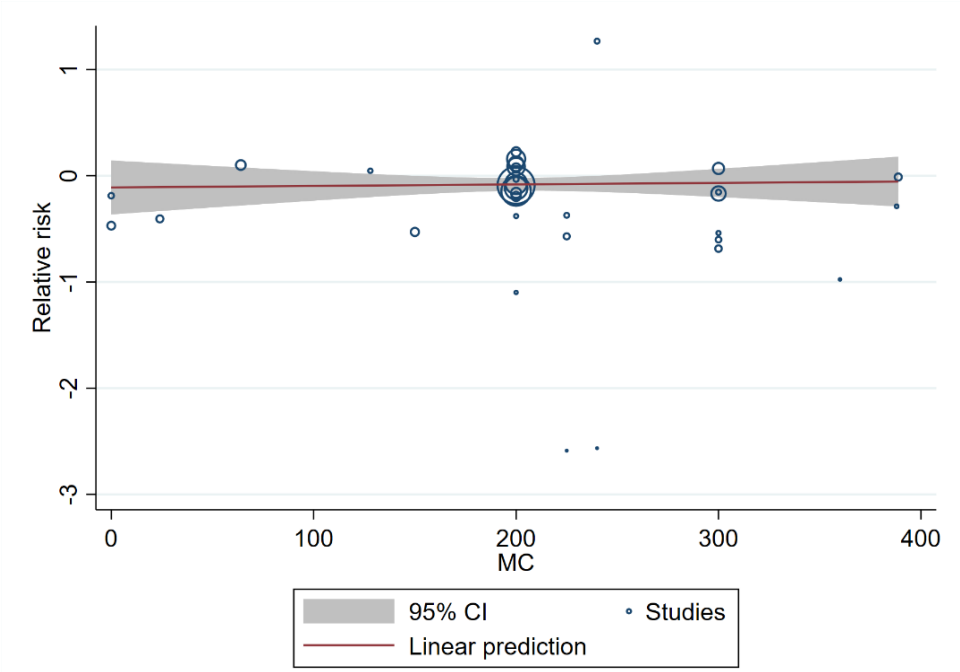
Mortality meta-regression in all patients with sepsis and septic shock based on molecule



Mortality meta-regression in all patients with sepsis and septic shock based on baseline mortality risk

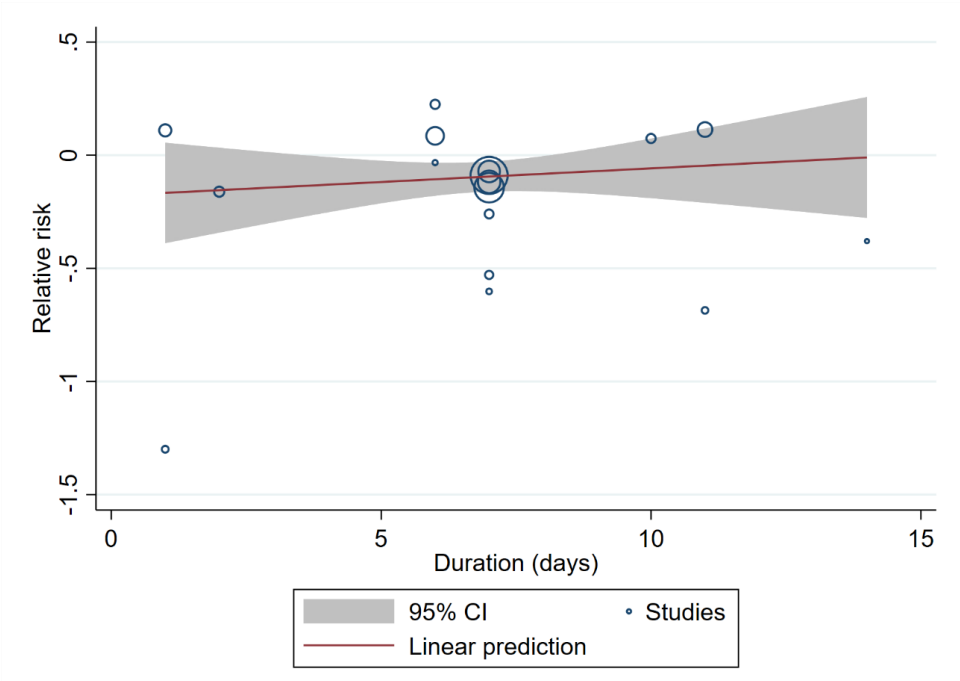


Mortality meta-regression in all patients with sepsis and septic shock based on mineralocorticoid potency.

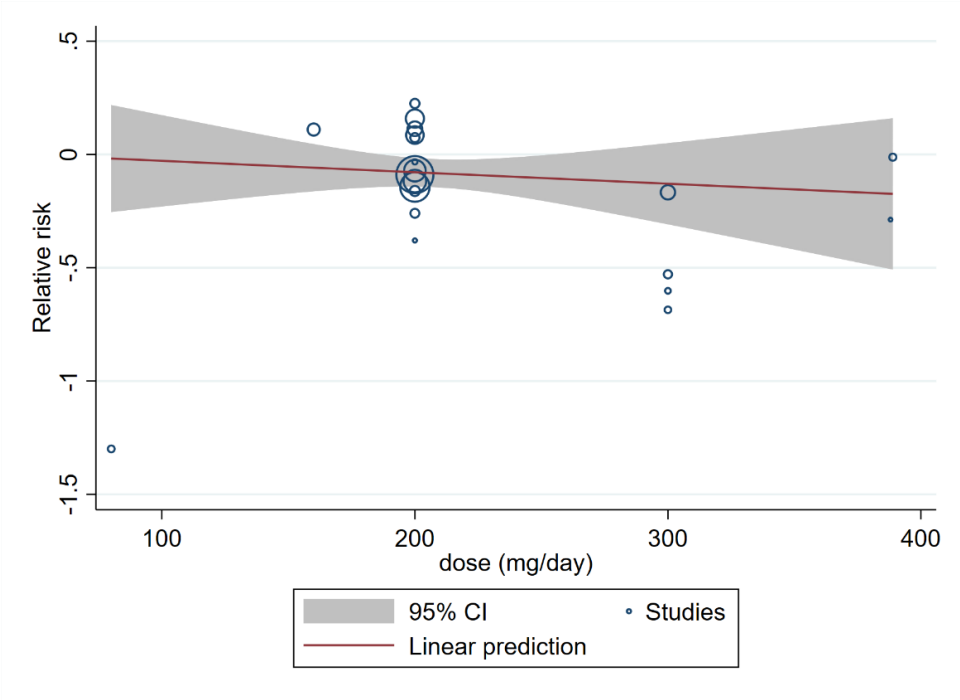


For similar doses of corticosteroids, we used the following mineralocorticoid activity: dexamethasone (0), prednisolone/prednisone (0.8), cortisone (0.8), hydrocortisone (1), and fludrocortisone (125) (16). For trials that included fludrocortisone, we used the fludrocortisone activity only for analysis.

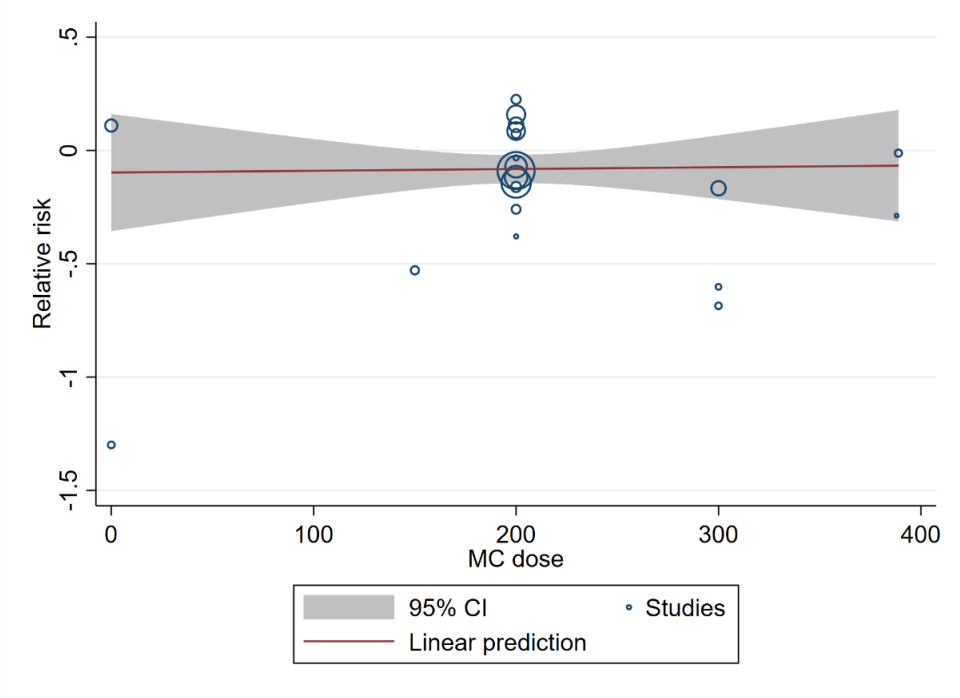
Mortality meta-regression in only patients with septic shock based on duration of corticosteroid



Mortality meta-regression in only patients with septic shock based on hydrocortisone equivalent dose per day



Mortality meta-regression in only patients with septic shock based on mineralocorticoid potency



Study Characteristics

Study	Number of Randomized Patients	Population	Interventions	Primary Outcome
Annane 2002	Multicentre (19 sites) France N= 300	Adults with vasopressor and ventilator dependent septic shock	HC 50mg IV q6h, FC 50ug PO q24h x 7 days	28 day mortality
Annane 2018 (APROCCHSS)	Multicentre (34 sites) France N=1241 Originally a 2x2 factorial design with APC (terminated)	Adult patients with vasopressor dependent septic shock	HC 50mg IV q6h, FC 50ug PO q24h x 7 days	90 day mortality
Arabi 2011	One centre Saudi Arabia N = 75	Adult patients with liver cirrhosis and septic shock	HC 50mg IV q6h until resolution, then tapered every 2 days	28 day mortality
Argawal 2022	One centre India N = 120	Geriatric paitents (age>60) with septic shock	HC 200mg IV divided in 4 doses	28 day mortality
Birudaraju 2022	One centre USA N = 43	Adult paitents with severe sepsis or septic shock	MP 20mg q8hours for 7 days	Not mentioned
Bollaert 1998	Multicentre (2 sites) France N = 41	Adult patients with vasopressor dependent septic shock	HC 100mg IV q8h x 5 days, then tapered off over 6 days	Shock reversal
Bone 1987	Multicentre (19 sites) USA N = 382	Adults with sepsis or septic shock	MP 30mg/kg 20min IV q6h x 1 day	14 day mortality
Branco 2014	One centre Brazil N =56	Children with volume refractory septic shock	HC 6mg/kg/day x 7 days or until vasoactive treatment stopped	Not mentioned
Briegel 1999	One centre Germany N = 40	Adult patients with vasopressor dependent septic shock	HC 100mg IV, then 0.18 mg/kg/h continuous infusion until shock reversal, then tapered off	Shock reversal
Chawla 1999	One centre USA N = 44	Adult patients with vasopressor dependent septic shock	HC 100mg IV q8h x 3 days, then tapered off over 4 days	Shock reversal
Cicarelli 2007	One centre Brazil N = 29	Adult patients with vasopressor dependent septic shock	DM 0.2mg/kg IV every 36h x 3	28 day mortality

Confalonieri 2005	Multicentre (6 sites) Italy N = 46	Adults with severe community-acquired pneumonia	HC 200mg bol IV, then 10mg/h continuous infusion x 7 days, then tapered off over 4 days	Improvement in multiple organ dysfunction syndrome (MODS) score
CSG 1963	Multicentre (5 sites) USA N = 329	Adults (n = 194) and children (n = 135) with vasopressor-dependent septic shock	HC 300mg IV for 1 day, then HC 250mg for 1 day, then HC 200mg po on day 3, then tapered off 50mg over 3 days	Hospital mortality
deGraaf 2014	Multicentre (3 sites) UK N = 29	Children with severe septic shock	HC 25mg/m2 q6h x 2 days	Not mentioned
El-Nawawy 2016	One centre Africa N = 96	Children with septic shock.	HC 50mg/m2/24h via continuous infusion x 5 days with weaning over next 5 days	Not mentioned
Gordon 2014	Multicentre (4 sites) UK N = 61	Adults with septic shock on a maximal dose of vasopressin of up to 0.06 U/min	HC 50mg IV q6h x 5 days, then bd x 3 days, then od x 3 days	Difference in plasma vasopressin concentration between treatment groups
Gordon 2016 (VANISH)	Multicentre (18 sites) UK N = 421	Adult patients who had sepsis and who required vasopressors despite adequate IV fluid resuscitation and initial vasopressors	HC 50mg IV bolus q6h for 5 days, q12h for 3 days then q24h for 3 days	Kidney Failure free days at 28 days
Hu 2009	One centre China N = 77	Adults with septic shock	HC 50mg IV q6h x 7 days, then HC 50mg q8h x 3 days, then HC 50mg q12h x 2 days, then HC 50mg q24h x 2 days	Time to Shock reversal
Keh 2016 (HYPRESS)	Multicentre (34 sites) Germany N = 353	Patients with evidence of infection, SIRS and evidence of organ dysfunction present for not longer than 48 hours. Septic shock excluded.	HC 50mg bolus then continuous infusion 200mg/d for 1st 5 days, then 100mg on day 6/7, then 50mg on days 8/9 then 25mg on days 10/11	Septic Shock at 14 days
Liu 2012	One centre China N = 26	Adults with ARDS and sepsis	HC 100mg IV q8h x 7 days	Not mentioned
Luce 1988	One centre USA N= 75	Adults with sepsis and septic shock	MP 30mg/kg IV q6h x 1 days,	Incidence of ARDS
Lv 2017	One centre China N=118	Adults with septic shock	HC 200mg IV infusion daily for 6 days then tapered, tapered sooner if off vasopressors	28 day mortality

Meduri 2007	Multicentre (5 sites) USA N = 91 2:1 randomization	Adults with early ARDS	MP 1mg/kg loading dose IV, then 1mg/kg/d continuous infusion x 14 days, then 0.5mg/kg/d x 7 days, then 0.25mg/kg/d x 4 days, then 0.125mg/kg/d x 3 days.	Improvement in Lung Injury Score (LIS) at day 7
Meduri 2009	Single Centre USA N=79	Adults with sepsis with or without shock	Hydrocortisone 300 mg IV bolus followed by 10 mg/h infusion	28 day mortality
Meijvis 2011	Multicentre (2 sites) The Netherlands N = 304	Adults with confirmed community-acquired pneumonia who presented to emergency departments	DM 5mg IV q24h x 4 days	Length of hospital stay
Menon 2017	Multicentre (7 sites) Canada N = 57 (8 post randomization exclusions)	Children between >38 weeks to 17 years old, who had received vasoactive med for between 1-6 hours. Excluded if other source of shock than sepsis.	Initial bolus hydrocortisone 2mg/kg followed by 1mg/kg q6h until met stability criteria for at least 12h. Dosing was then reduced to 1mg/kg q8h until all vasoactive meds were off x 12h.	Feasibility
Mirea 2014	One Centre Romania N =171	Vasopressor dependent septic shock	1- HC 200mg/d divided in 4 doses x 7 days 2- HC 200mg/d continuous infusion x 7 days	Adverse events
Oppert 2005	One centre Germany N = 40	Adult patients with vasopressor dependent septic shock	HC 50mg bolus IV, then 0.18 mg/kg/h continuous infusion up to cessation of vasopressor for ≥ 1 hour, reduced to a dose of 0.02 mg/kg/h for 24 hours, then reduced by 0.02 mg/kg/h every day	Shock resolution
Rezk 2013	One centre Egypt N = 27 2:1 randomization	Adults with ARDS and hospital- or community-acquired pneumonia	MP 1mg/kg, followed by 1mg/kg/d IV x 14 days, then 0.5mg/kg/d x 7 days, then 0.25mg/kg/d x 4 days, then 0.125mg/kg/d x 3 days.	Not mentioned
Rinaldi 2006	One centre Italy N = 40	Adults with sepsis and not receiving vasopressor support	HC 300mg continuous IV per day x 6 days, then tapered off	Not mentioned
Sabry 2011	Multicentre (3 sites) Egypt N = 80	Adults admitted to ICU with community-acquired pneumonia and sepsis	HC 200mg IV, then 12.5 mg/h x 7 days	Improvement in PaO2:FiO2

Schumer 1976	One centre USA N = 172 Three study arms	Adults with septic shock with positive blood culture	1-DM 3mg/kg IV x1 2-MP 30mg/kg IV x1 3- placebo	Hospital mortality
Slusher 1996	Multicentre (2 sites) USA, Kenya and Nigeria N = 72	African children with sepsis or septic shock	DM 0.2mg/kg q8h x 2 days	Hospital mortality
Snijders 2010	One centre The Netherlands N = 213	Adults with severe community acquired pneumonia	PS 40mg IV od x 7 days	Treatment failure at day 30
Sprung 1984	Multicentre (2 sites) USA N = 59 Three groups	Adult patients with vasopressor dependent septic shock	1- DM 6mg/kg IV 2- MP 30mg/kg IV 3- placebo	Hospital mortality
Sprung 2008 (CORTICUS)	Multicentre (52 sites) Europe and Israel N = 499	Adults with septic shock	HC 50mg q6h x 5 days, then 50mg bd x 3 days, then 50mg od x 3 days	28 day mortality
Talebi Doluee 2018	One centre Iran N = 160	Adult patients with septic shock who did not respond to vasopressor therapy for over 60 minutes	HC 50mg IV q6h x 7 days	Not mentioned
Tandan 2005	One centre India N = 28	Adults with septic shock and adrenal insufficiency	HC (dose and duration not stated)	28 day mortality
Tongyoo 2018	One centre Thailand N = 154	Patients with severe sepsis or septic shock receiving IMV were eligible if, within 12 h of study entry, they met the diagnostic criteria for ALI-ARDS	HC IV bolus 50mg q6h x 7 days	Survive with no organ support at 28 day
Tongyoo 2016	One centre Thailand N = 206	Patients with severe sepsis or septic shock receiving IMV were eligible if, within 12 h of study entry, they met the diagnostic criteria for ALI-ARDS	HC IV bolus 50mg q6h x 7 days	28 day mortality
Torres 2015	Multicentre (3 sites) Spain N = 61	Adults with both severe CAP and high inflammatory response	MP 0.5mg/kg/12h IV x 5 days	Treatment Failure
Valoor 2009	One centre India N = 38	Children with septic shock unresponsive to fluid therapy alone	HC 5mg/kg/d IV in 4 divided doses, then HC 2.5mg/kg/d x 7days	Time to shock reversal

VASSCSG 1987	Multicentre (10 sites) USA N = 223	Adults with sepsis or septic shock	MP 30mg/kg IV, then 5 mg/kg/h constant infusion x 9 hours	14 day mortality
Venkatesh 2017 (ADRENAL)	Multicentre (45 sites) International N=3800	Adults with septic shock (SIRS + suspicion of infection) and requiring vasopressors for >4 hours	Hydrocortisone 200 mg/day continuous infusion for 7 days, until ICU discharge, or death	90 day mortality
Yildiz 2002	One centre Turkey N = 40	Adults with sepsis, severe sepsis and septic shock	PS IV bolus q12h (5mg at 6:00 and 2.5mg at 18:00) x 10 days	28 day mortality
Yildiz 2011	One centre Turkey N = 55	Adults with sepsis or septic shock	PS IV bolus q8h (10mg IV at 6:00, 5mg at 14:00 and 5mg at 22:00) x 10 days	28 day mortality

HC = hydrocortisone, FC = fludrocortisone, Methylprednisolone = MP, Dexamethasone = DM, Prednisolone = PS, IV = intravenous, ug = micrograms, SIRS = systemic inflammatory response syndrome, IMV = invasive mechanical ventilation, CAP = community acquired pneumonia, ALI = acute lung injury, ARDS = acute respiratory distress syndrome, ICU = intensive care unit.

GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)		
Long term Mortality (assessed 60-365 days)												
9	randomised trials	not serious	Serious[a]	not serious	Serious[b]	none	1135/3222 (35.2%)	1197/3216 (37.2%)	**RR 0.95** (0.89 to 1.00)	**19 fewer per 1,000** (from 41 fewer to 0 fewer)	⊕⊕◯◯ Low	CRITICAL
Short-term Mortality (assessed 14-30 days)												
40	randomised trials	not serious	Serious[c]	not serious	not serious	Possible publication bias	1354/4944 (27.4%)	1460/4919 (29.7%)	**RR 0.93** (0.88 to 0.98)	**21 fewer per 1,000** (from 36 fewer to 6 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Shock Reversal at 7 days (assessed with: stable BP off vasopressors x 24 hours)												
13	randomised trials	not serious	not serious	not serious	not serious	none	1072/1481 (72.4%)	903/1441 (62.7%)	**RR 1.24** (1.11 to 1.38)	**150 more per 1,000** (from 69 more to 238 more)	⊕⊕⊕⊕ High	CRITICAL
Organ Dysfunction at Day 7 (assessed with: Total SOFA score at D7)												
9	randomised trials	not serious	not serious	not serious	not serious	none	1010	976	-	MD **1.41 points lower** (1.87 lower to 0.96 lower)	⊕⊕⊕⊕ High	CRITICAL
ICU Length of Stay (assessed with: days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)		
22	randomised trials	not serious	serious[a]	not serious	Serious[b]	none	3805	3821	-	MD **0.6 days fewer** (1.48 fewer to 0.27 more)	⨁⨁◯◯ Low	CRITICAL
Hospital Length of Stay (assessed with: days)												
18	randomised trials	not serious	Serious[a]	not serious	Serious[b]	none	3852	3854	-	MD **0.74 days fewer** (2.06 fewer to 0.57 more)	⨁⨁◯◯ Low	CRITICAL
Neuromuscular Weakness												
7	randomised trials	not serious	not serious	serious[d]	Serious[a]	none	210/3105 (6.8%)	174/3073 (5.7%)	**RR 1.21** (1.01 to 1.45)	**12 more per 1,000** (from 1 more to 25 more)	⨁⨁◯◯ Low	CRITICAL
GI Bleeding												
24	randomised trials	not serious	not serious	serious[d]	very serious[e]	none	132/2191 (6.0%)	119/2164 (5.5%)	**RR 1.09** (0.87 to 1.37)	**5 more per 1,000** (from 7 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Neuropsychiatric Effects												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	not serious	not serious	Serious[d]	serious[a]	none	17/499 (3.4%)	30/505 (5.9%)	**RR 0.58** (0.33 to 1.03)	**25 fewer per 1,000** (from 40 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL
Hypernatremia												
5	randomised trials	not serious	not serious	Serious[d]	not serious	none	142/2392 (5.9%)	100/2473 (4.0%)	**RR 1.64** (1.32 to 2.03)	**26 more per 1,000** (from 13 more to 42 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Superinfection												
25	randomised trials	not serious	not serious	Serious[d]	very serious[c]	none	503/2331 (21.6%)	456/2268 (20.1%)	**RR 1.05** (0.94 to 1.17)	**10 more per 1,000** (from 12 fewer to 34 more)	⨁◯◯◯ Very low	CRITICAL
Stroke												
4	randomised trials	not serious	not serious	Serious[d]	very serious[c]	none	8/623 (1.3%)	6/602 (1.0%)	**RR 1.19** (0.42 to 3.42)	**2 more per 1,000** (from 6 fewer to 24 more)	⨁◯◯◯ Very low	CRITICAL
Myocardial Infarction												
4	randomised trials	not serious	not serious	Serious[d]	very serious[c]	none	19/604 (3.1%)	19/596 (3.2%)	**RR 1.02** (0.55 to 1.90)	**1 more per 1,000** (from 14 fewer to 29 more)	⨁◯◯◯ Very low	CRITICAL
Hyperglycemia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)		
18	randomised trials	not serious	not serious	Serious[d]	not serious	none	1278/3860 (33.1%)	1111/3823 (29.1%)	**RR 1.13** (1.08 to 1.18)	**38 more per 1,000** (from 23 more to 52 more)	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a=significant inconsistency in the effect of some trials, with a high I^2

b=Crosses the MID by at least one

c=there are concerns about inconsistency but not enough to rate down by one level, similarly, there are concerns for possible publication bias but not enough to rate down by one. Therefore based on the combination of our concerns, we have rated this down by one.

d=Variable definitions, unclear if this is all of the same outcome collected

e=crosses the MID in both directions

Summary of Judgements: Corticosteroid Administration in Septic Shock

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of Recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	✓	○

ROB Assessments

AUTHOR	OVERALL BIAS	1) BIAS ARISING FROM THE RANDOMIZATION PROCESS	2) BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTION	3) BIAS DUE TO MISSING OUTCOME DATA	4) BIAS IN MEASUREMENT OF THE OUTCOME	5) BIAS IN SELECTION OF THE REPORTED RESULTS
MOHAMMED	High	Low	Probably High	Low	Low	Low
BIRUDARAJU	High	Probably High	Low	Low	Low	Probably Low
CHANG	High	Probably High	Probably High	Low	Low	Low
WANI	High	Probably High	High	Low	Low	Probably High
ARGAWAL	High	Probably Low	Probably High	Low	Probably Low	Probably High
SEVRANSKY	High	Probably Low	Low	Probably High	Low	Low
LV 2017	Low	High	Low	Low	Low	Low
LYU	Low	Low	Low	Low	Low	Low
MOSKOWITZ	Low	Low	Low	Low	Low	Low
TONGYOO	Low	Low	Low	Low	Low	Probably Low
ANNANE 2002	Low	Low	Low	Low	Low	Low
ANNANE 2018	Low	Low	Low	Low	Low	Low
ARABI 2011	Low	Low	Low	Probably Low	Low	Probably Low
BOLLAERT 1998	Low	Low	Low	Low	Low	Low
BONE 1987	Low	Low	Low	Low	Low	Probably Low
CHAWLA 1999	Low	Low	Low	Low	Low	Probably High
CONFALONIERI 2005	Low	Low	Low	Low	Low	High
EL-NAWAWY 2016	Low	Low	Low	Probably High	Low	Probably High
GORDON 2014	Low	Low	Probably Low	Probably Low	Low	Low
GORDON 2016	Low	Low	Low	Low	Low	Low
KEH 2016	Low	Low	Low	Low	Low	Low
LUCE 1988	Low	Low	Low	Probably High	Low	Probably Low
MEDURI 2007	Low	Low	Probably Low	Low	Low	Probably Low
MEIJVIS 2011	Low	Low	Low	Low	Low	Low

MENON 2017	Low	Low	Low	Low	Low	Low
SNIJDERS 2010	Low	Low	Probably Low	Low	Low	Low
SPRUNG 2008	Low	Low	Low	Low	Low	Low
TANDAN 2005	Low	Low	Low	Probably High	Low	Probably High
TONGYOO 2016	Low	Low	Low	Low	Low	Low
TORRES 2015	Low	Low	Low	Low	Low	Low
VENKATESH 2017	Low	Low	Low	Low	Low	Low
BALAKRISHNAN 2018	Low	Probably Low	Low	Low	Probably Low	Low
TALEBI DOLUEE	Low	Probably Low	Low	Low	Low	Probably Low
LIU 2012	Low	Probably Low	Probably Low	Probably Low	Low	Probably Low
VALOOR 2009	Low	Probably Low	High	Low	Low	Low
CICARELLI 2007	Probably High	Low	Low	Probably Low	Probably High	Probably Low
MIREA 2014	Probably High	Probably High	Probably High	Probably High	Probably High	High
REZK 2003	Probably High	Probably High	High	Low	Probably High	Probably High
SLUSHER 1996	Probably High	Probably High	Probably Low	Low	Probably High	Low
SPRUNG 1984	Probably High	Probably High	High	Low	Probably High	Low
SCHUMER 1976	Probably Low	High	Probably Low	Low	Probably Low	Low
BRIEGEL 1999	Probably Low	Low	Low	Low	Probably Low	Probably Low
RIANLDI 2006	Probably Low	Probably High	High	Low	Probably Low	Low
SABRY 2011	Probably Low	Probably High	Probably Low	Low	Probably Low	Low
BRANCO 2014	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High

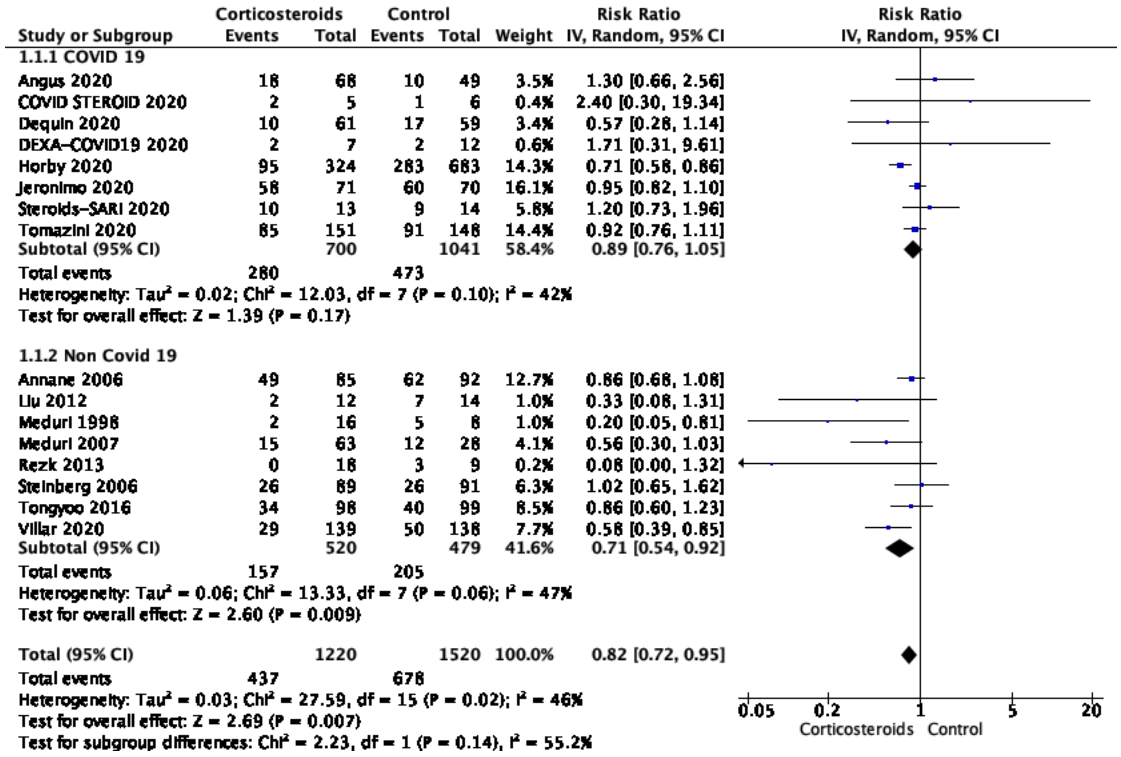
CSG 1963	Probably Low	Probably Low	Probably Low	Low	Probably Low	Probably High
DEGRAAF 2014	Probably Low	Probably Low	Probably High	Probably High	Probably Low	Probably Low
HU 2009	Probably Low	Probably Low	Probably High	Low	Probably Low	Probably Low
OPPERT 2005	Probably Low	Probably Low	Probably Low	Probably High	Probably Low	Probably Low
VASSCSG 1987	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low
YILDIZ 2002	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low
YILDIZ 2011	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low

Supplemental Digital Content 9B

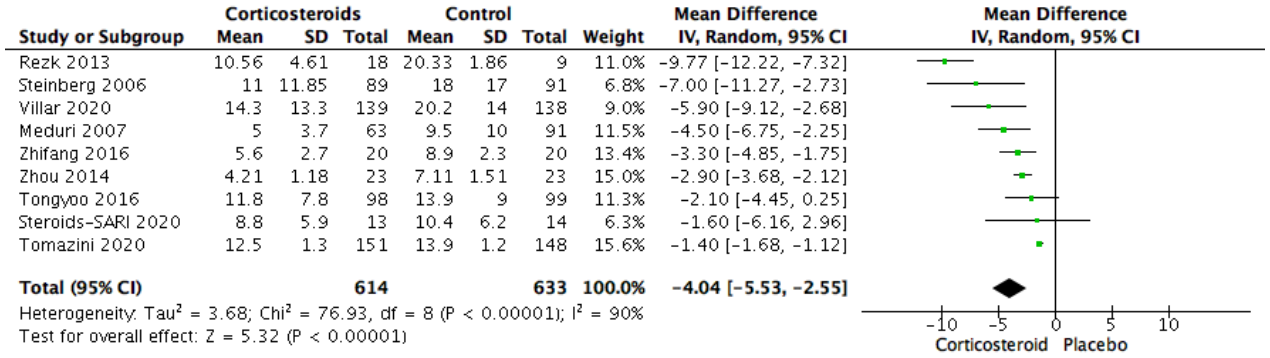
Question: Should corticosteroids be administered to hospitalized patients with ARDS?

Forest Plots

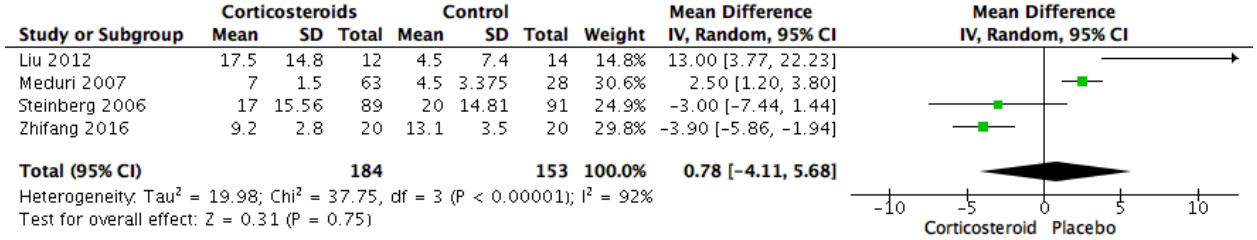
Forest plot: Corticosteroids versus placebo or no corticosteroids in patients with ARDS. Grouped by COVID-19 Status. 28 day Mortality.
Df = degrees of freedom



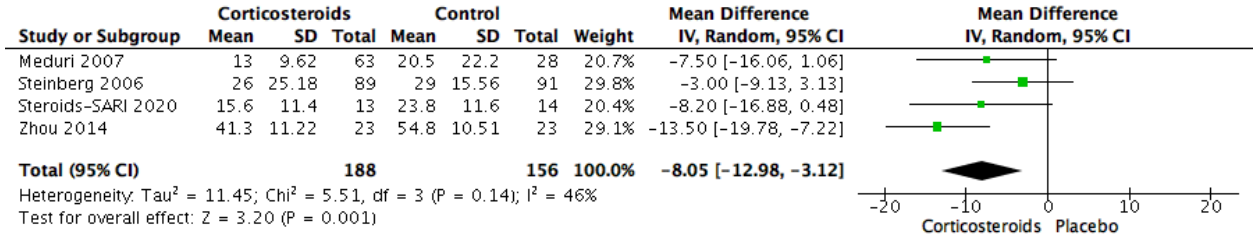
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Duration of mechanical ventilation. Df = degrees of freedom



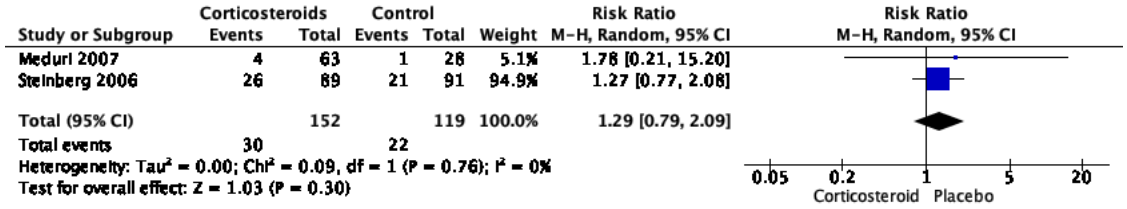
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). ICU length of stay. Df = degrees of freedom



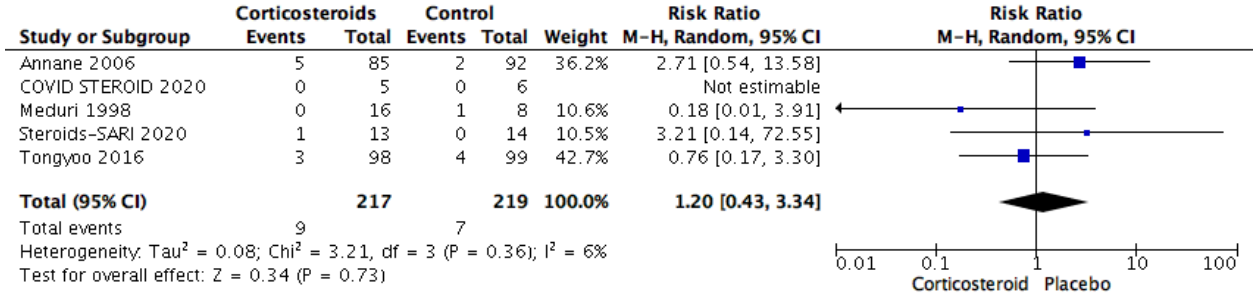
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Hospital length of stay. Df = degrees of freedom



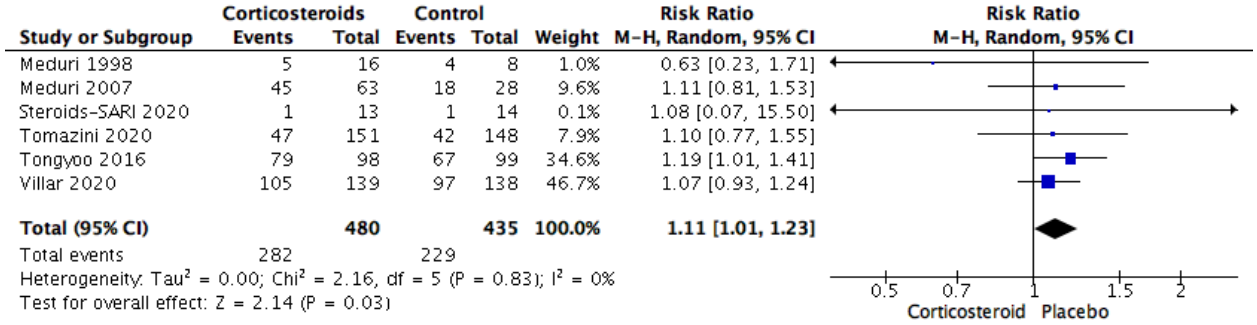
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of neuromuscular weakness. Df = degrees of freedom



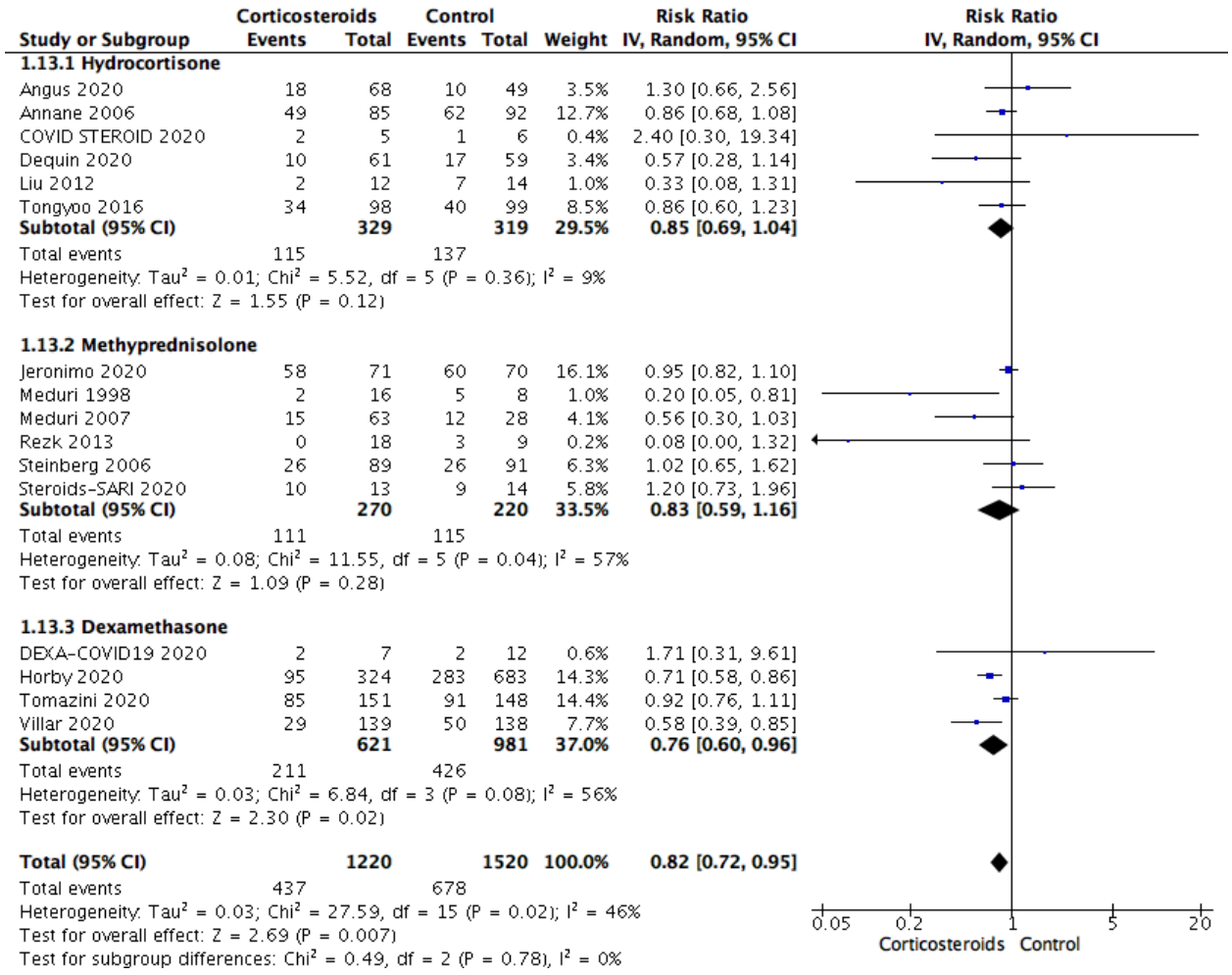
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of gastrointestinal bleeding. Df = degrees of freedom



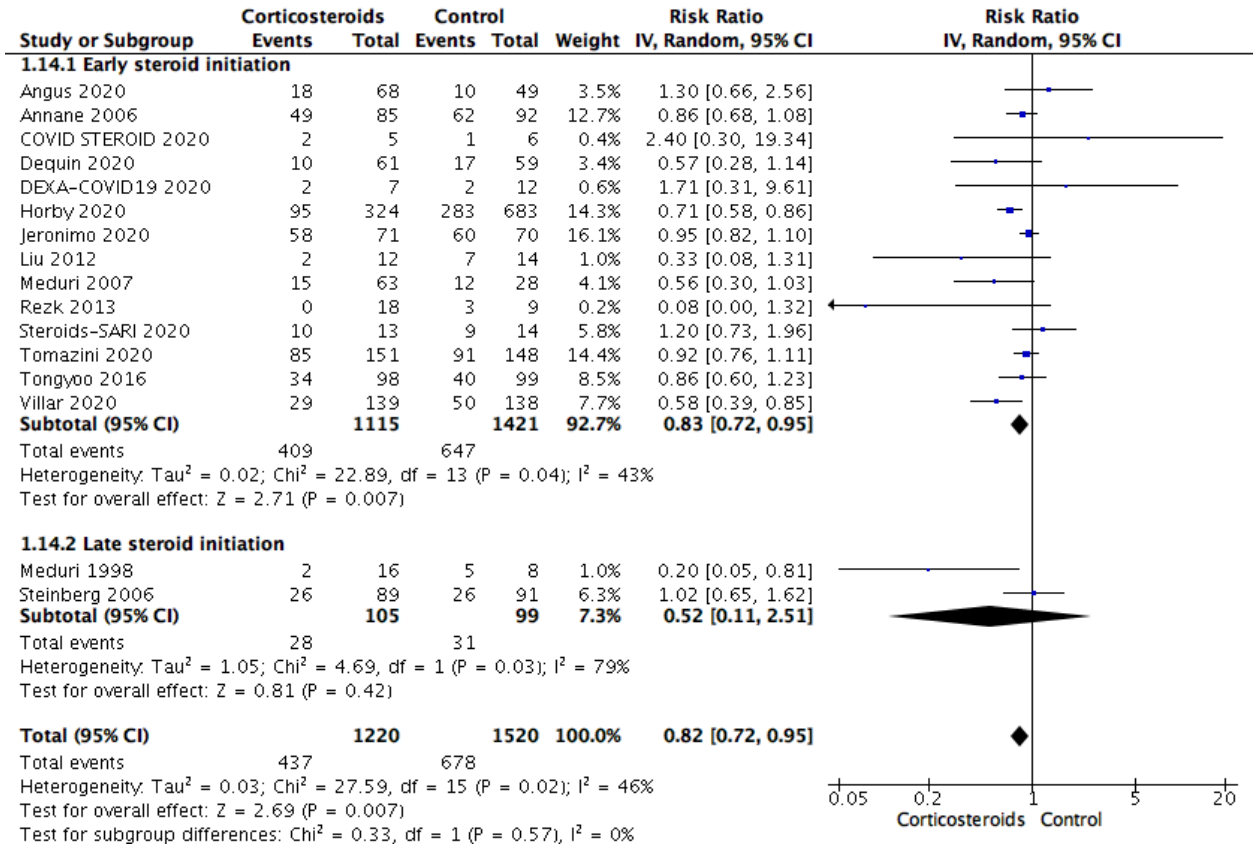
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of hyperglycemia. Df = degrees of freedom



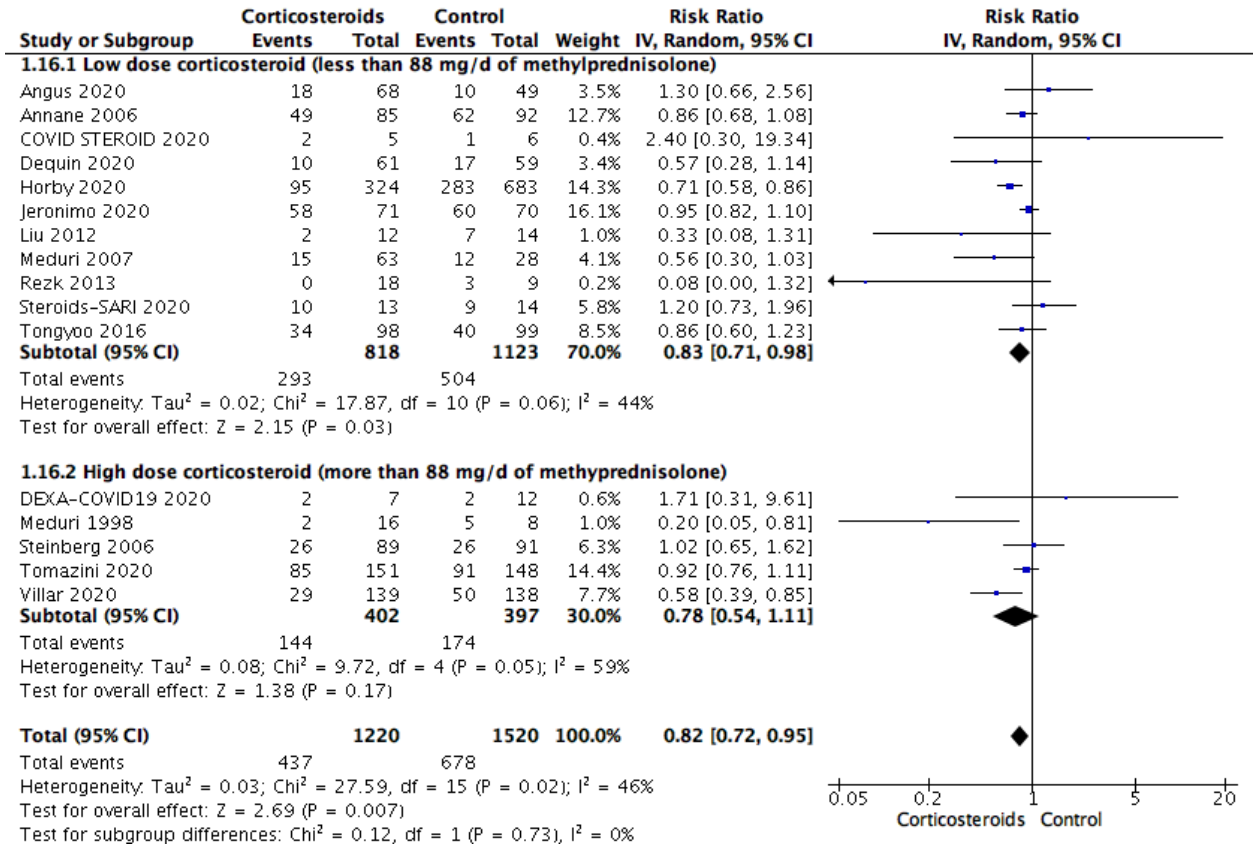
Forest plot: Effect of corticosteroids on mortality. Studies are grouped by steroid subtype. Df = degrees of freedom.



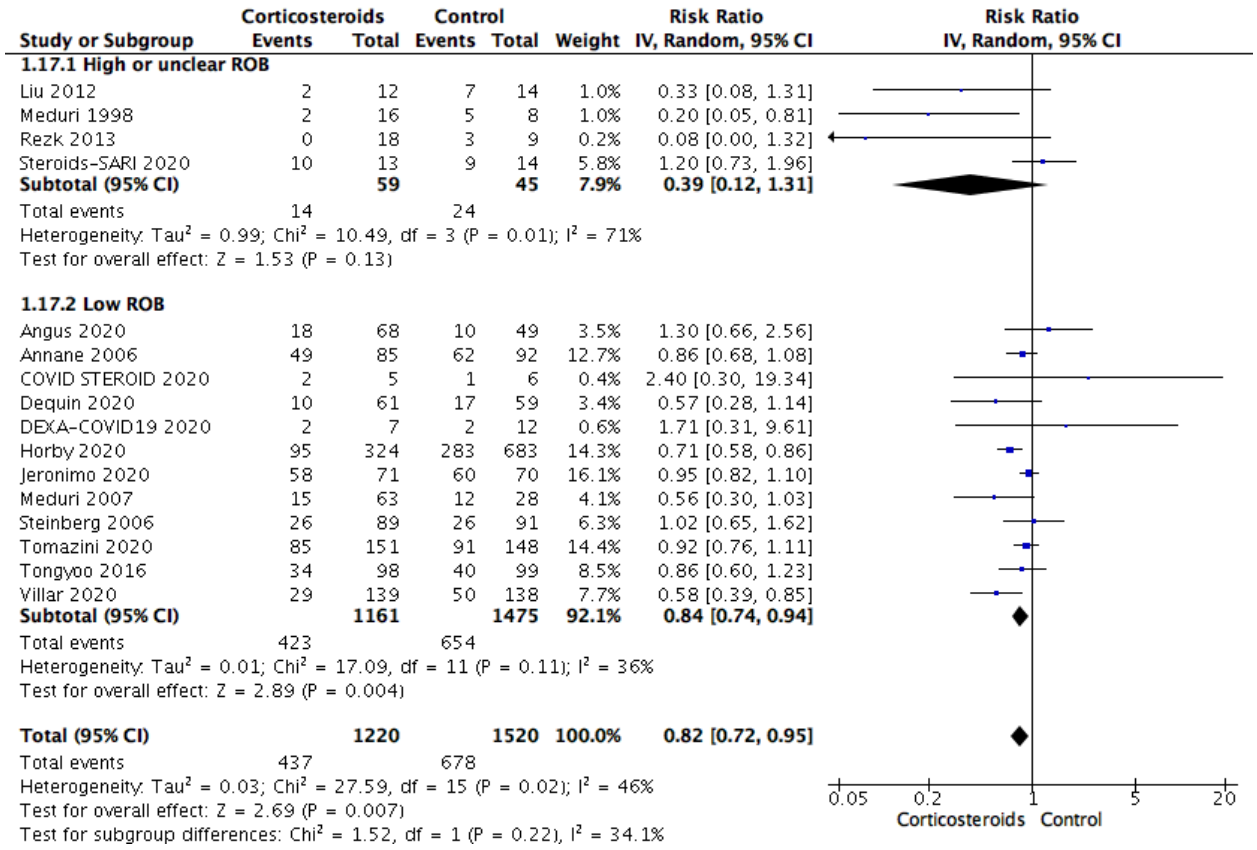
Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by steroid initiation time. Df = degrees of freedom.



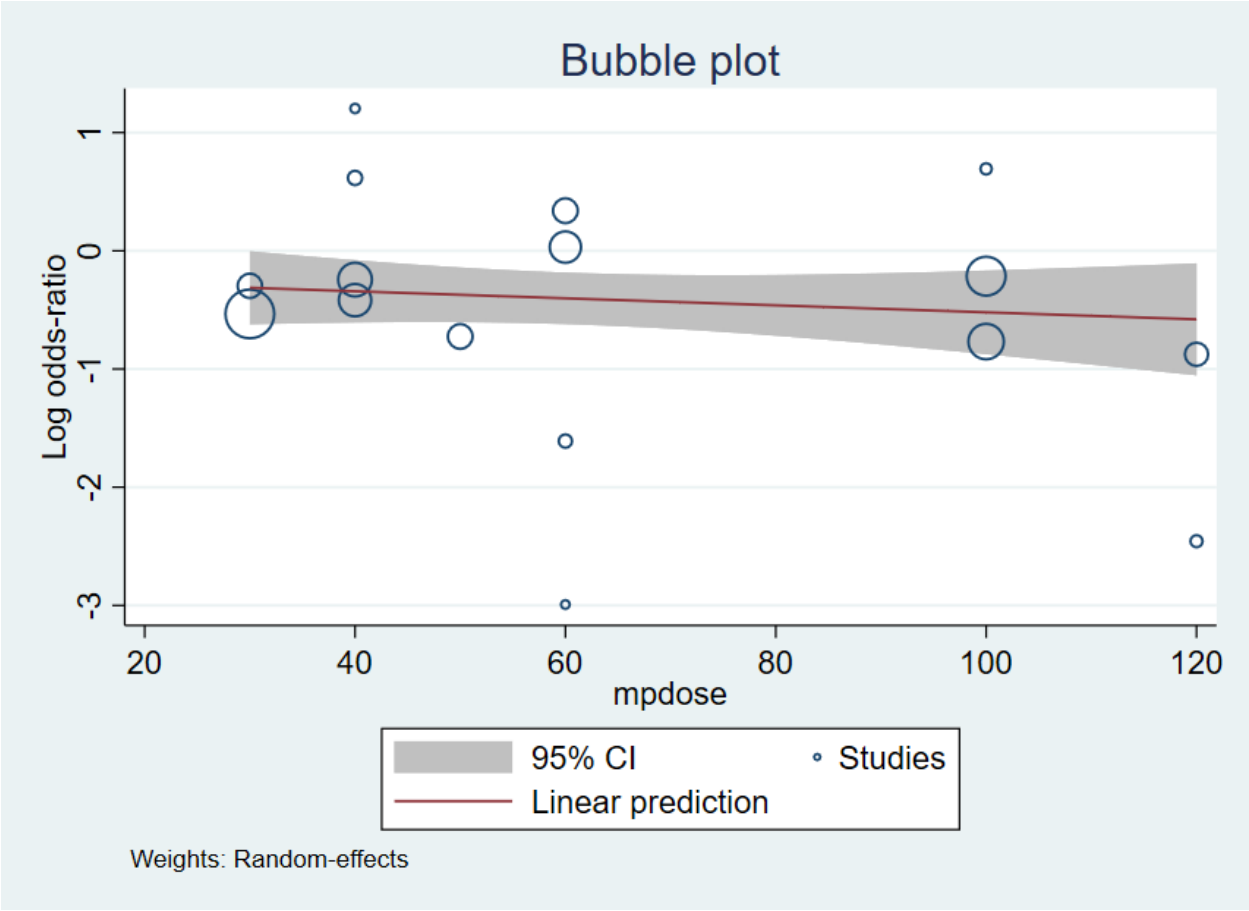
Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by steroid dosage. Df = degrees of freedom.



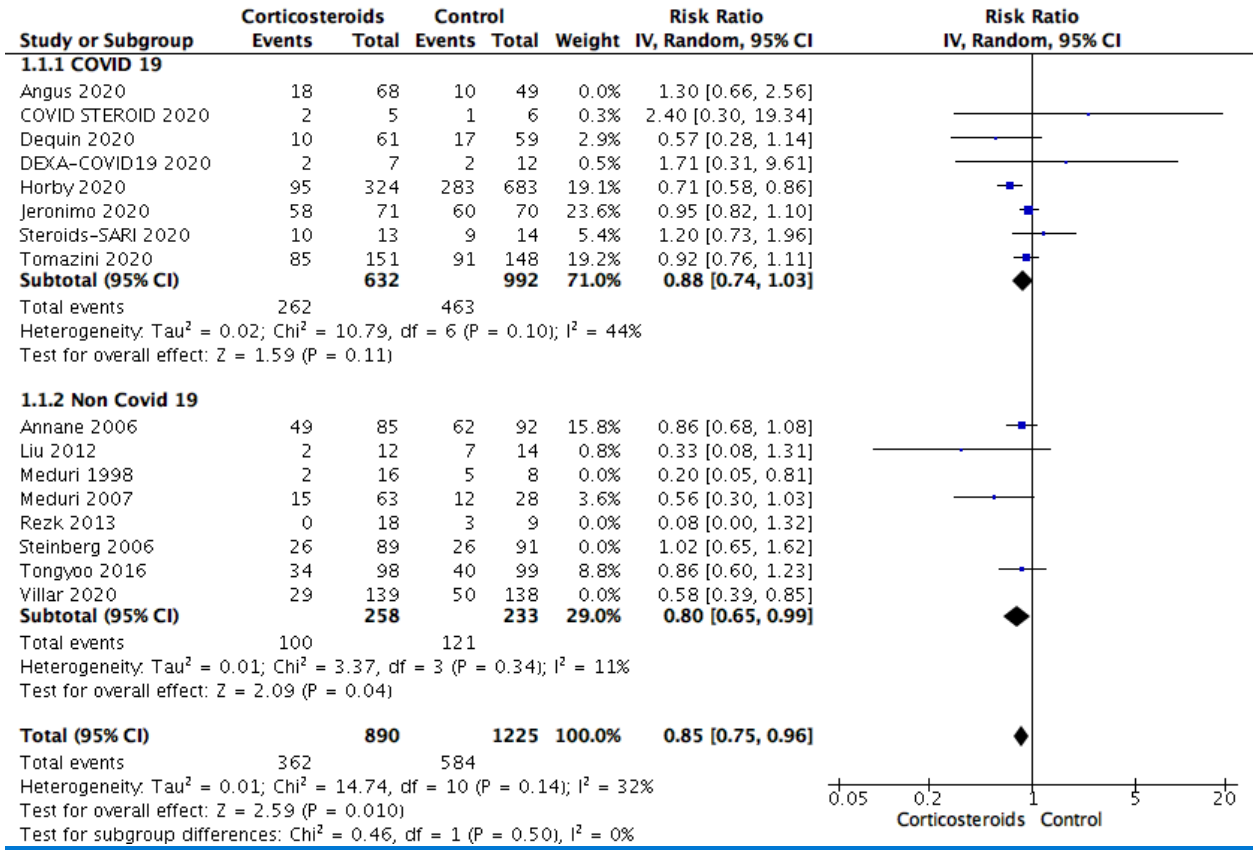
Forest plot: Effect of corticosteroids on mortality. Studies are grouped by ROB. Df = degrees of freedom.



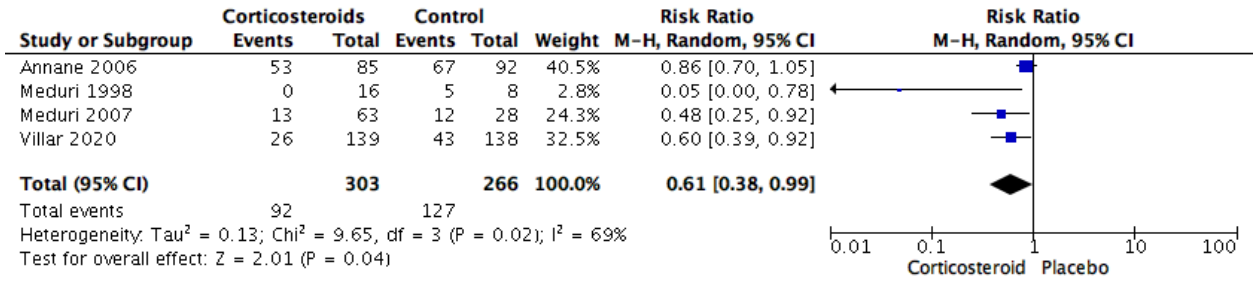
Metaregression for mortality based on average daily steroid dose. CI = confidence interval



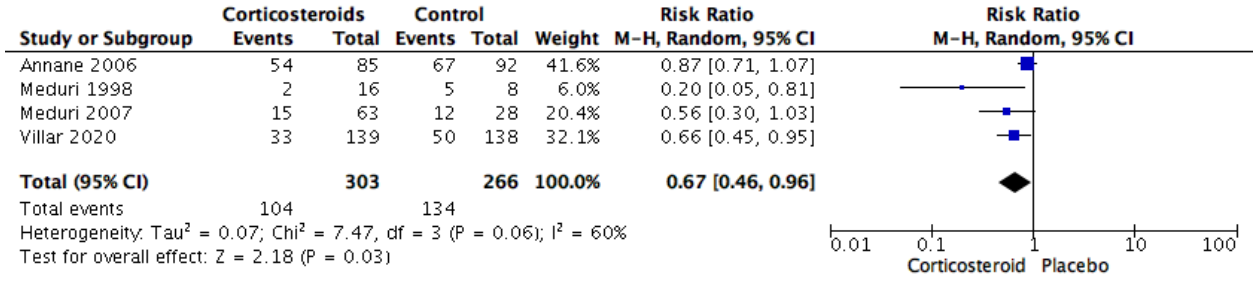
Forest plot: Effect of corticosteroids on mortality. Studies are grouped by COVID status and a sensitivity analysis removing studies that do not report 28 day mortality is done. Df = degrees of freedom.



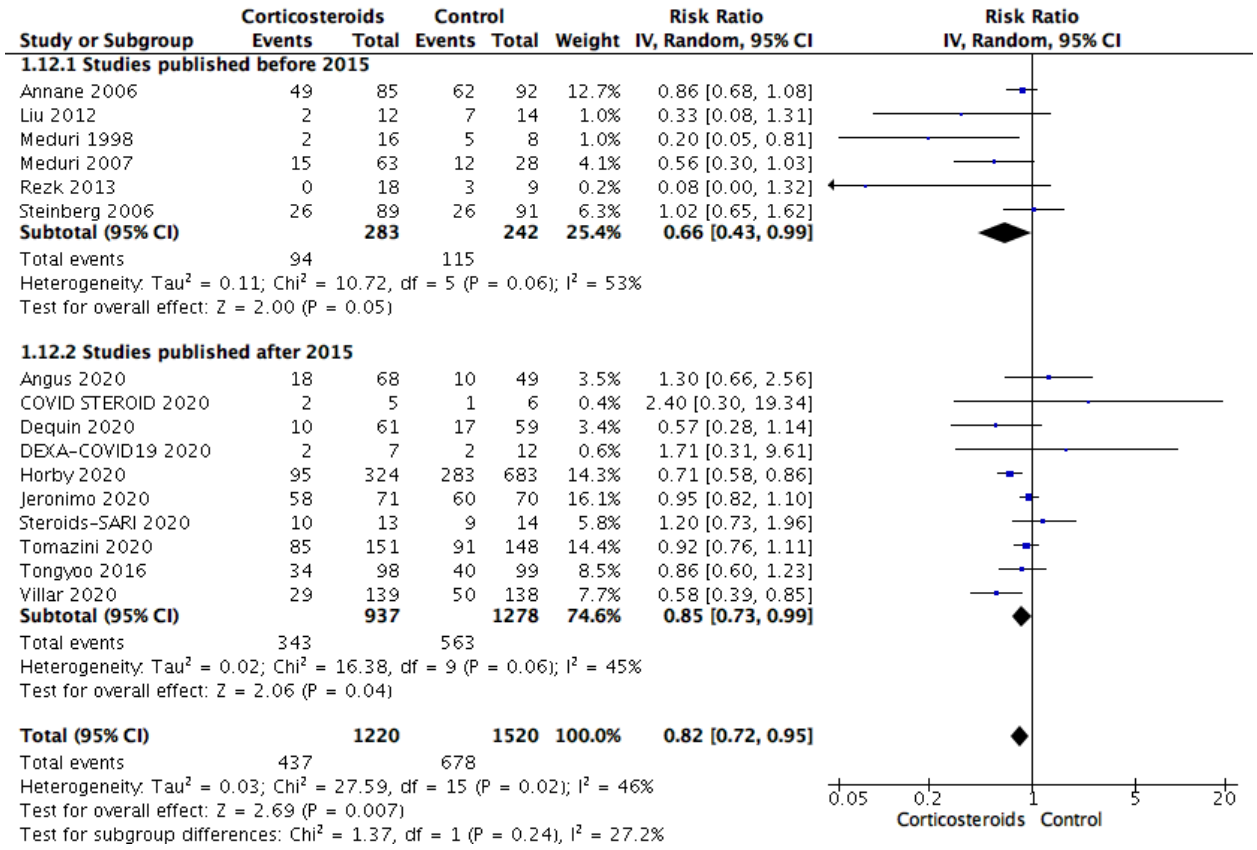
Forest Plot: ICU mortality. Df = degrees of freedom



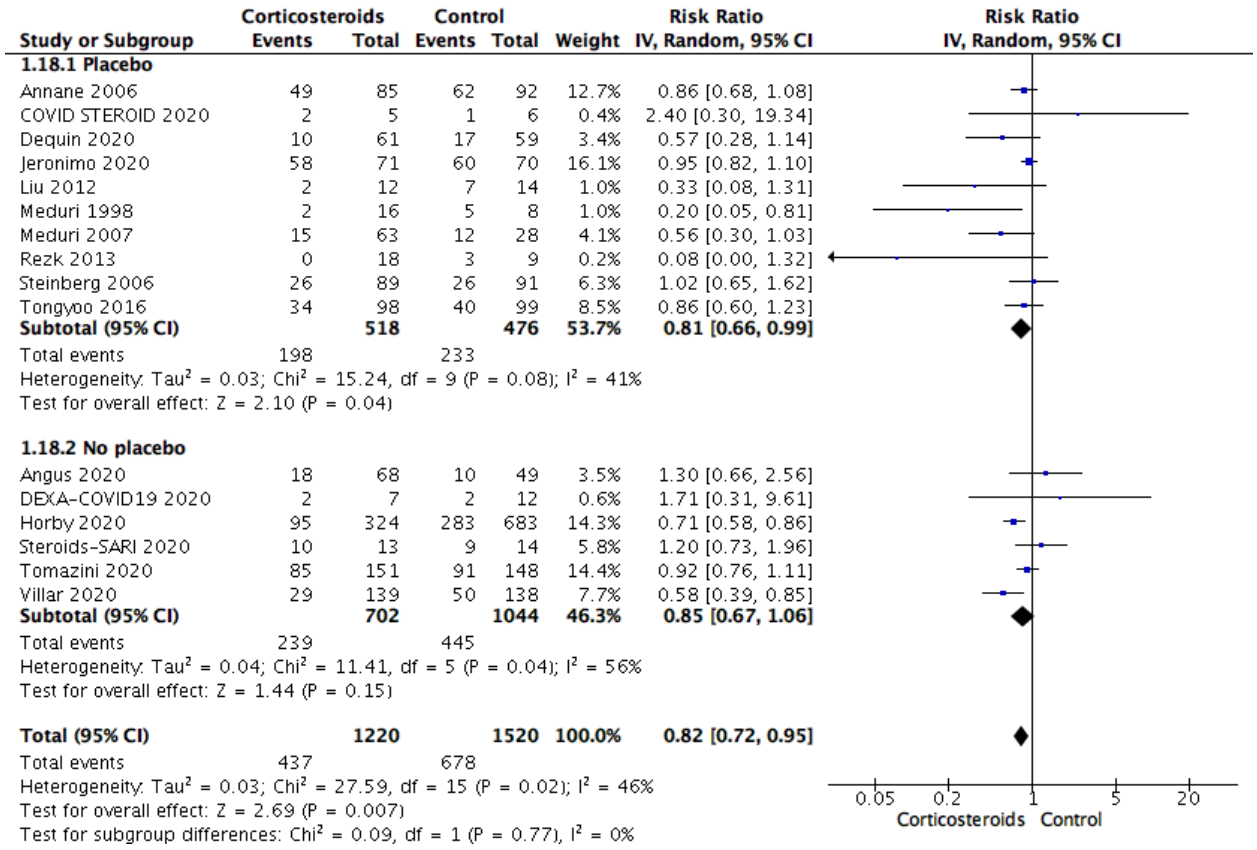
Forest Plot: Hospital mortality. Df = degrees of freedom



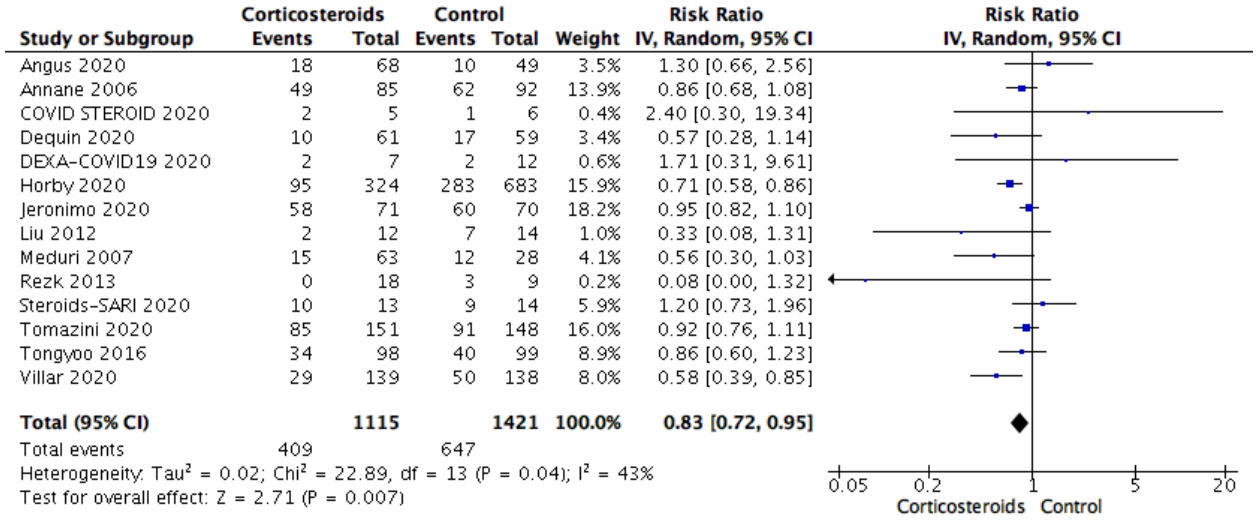
Forest plot: Effect of corticosteroids on mortality. Studies are grouped by publication date. Df = degrees of freedom



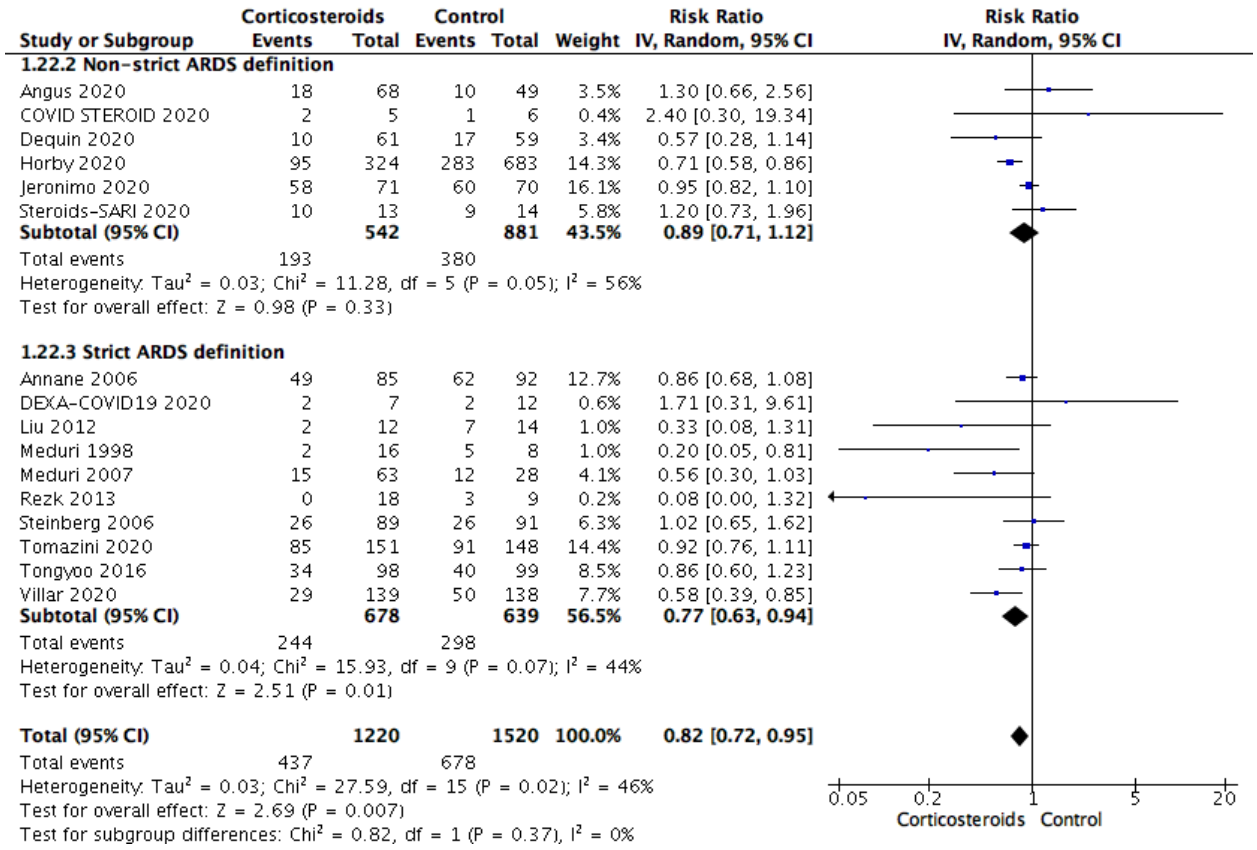
Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by presence of placebo. Df = degrees of freedom



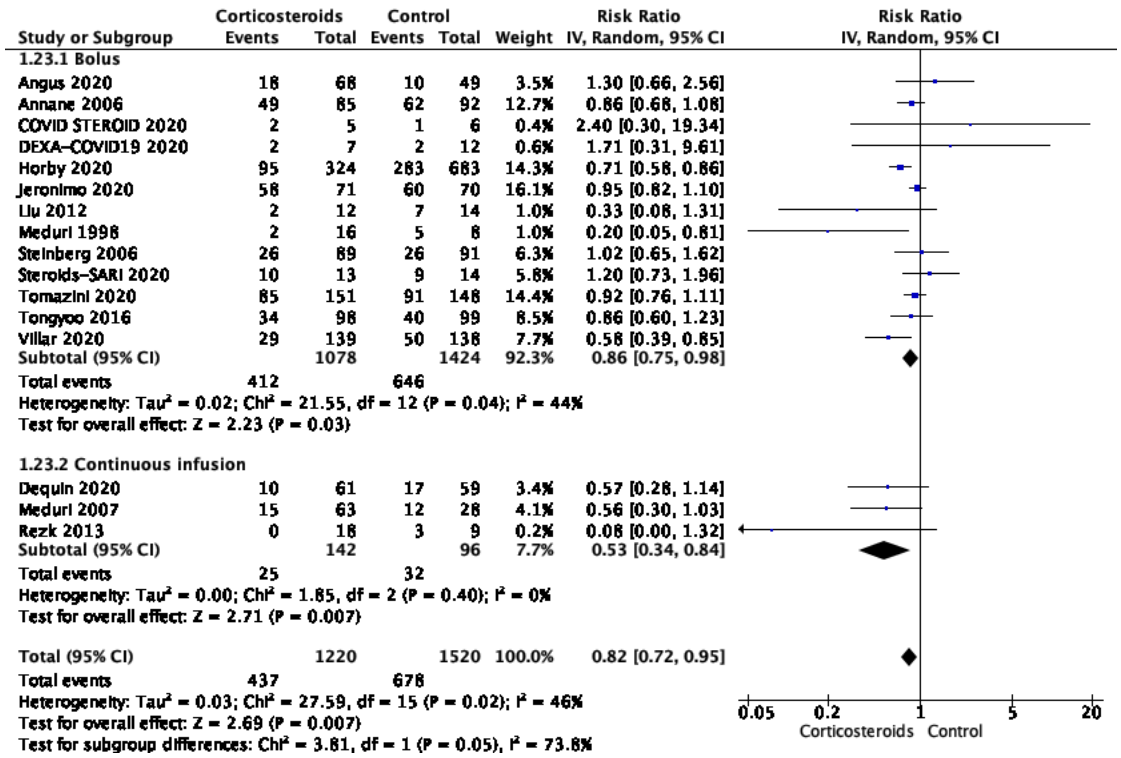
Forest Plot: Effect of corticosteroids on mortality with sensitivity analysis removing studies that initiated corticosteroids late . Df = degrees of freedom.



Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by ARDS definition. Df = degrees of freedom



Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by bolus vs infusion dosing of corticosteroids. Df = degrees of freedom



Study Characteristics

Author, date, single vs multi-center, location	Total number of patients (n)	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Steinberg, 2006; multi-center; USA	180	Adult patients* (intubated and receiving mechanical ventilation; 7 to 28 days after onset of ARDS, on day of study entry PaO2/FiO2 had to be < 200 mmHg **Age (mean, SD), Gender (Female):* Placebo: 49.2, 16.5; Methyl prednisone: 49.0, 19.0; 82/180	Trauma 23/180 Sepsis36/180 Multiple transfusions 2/180 Aspiration 30/180 Pneumonia 68/180 other 20/180	Methylprednisolone sodium succinate diluted in 50 mL of 5% dextrose in water; single IV dose of 2 mg/kg of PBW; followed by 0.5 mg/kg of PBW every 6 hours for 14 days; then dose of 0.5 mg/kg of PBW every 12 hours for 7 days, then tapering of dose	Primary Outcome: Overall mortality at 60 days post enrollment Secondary Outcomes: Ventilator-free days; early mortality; length of ICU stay; length of hospital stay; days of mechanical ventilation; neuromuscular weakness; superinfection
Meduri, 2007; multi-center; USA	91	Adult patients* receiving mechanical ventilation; meeting criteria for ARDS according to AECC (Bernard 1994); within 72 hours **Age (mean, SD), Gender (Female):* Placebo: 53.2, 15.3, Methyl prednisone: 50.1, 15.3, 44/91	Pneumonia 38/91 Aspiration of gastric content 18/91 Sepsis 15/91 other 20/91	Methylprednisolone; loading dose of 1 mg/kg, followed by infusion of 1 mg/kg/day from day 1 to day 14; 0.5 mg/kg/day on days 15 to day 21; 0.25 mg/kg/day on days 22 to day 25; then 0.125 mg/kg/day from day 26 to day 28	Primary Outcomes: 1-point reduction in LIS score or successful extubation by day 7 Secondary Outcomes: Early mortality; ICU mortality; hospital mortality; length of ICU stay; length of hospital stay; days of mechanical ventilation; hyperglycemia; neuromuscular weakness; infection
Liu, 2012; single center; China	26	Adults 18 to 80 years of age*; fulfils criteria of ARDS according to the AECC (Bernard 1994); ARDS diagnosis within 3 days of admission; fulfils CIRCI diagnosis according to Society of Critical Care Medicine of PLAs Guidelines 2006 **Age (mean, SD), Gender (Female):* Placebo: 55.9, 15.3, Corticosteroids: 69.8, 14.9; 7/26	Pneumonia 11/26 Trauma 2/26 other organs infection 7/26 severe pancreatitis 3/26 other 3/26	Stress dose glucocorticoid; hydrocortisone 100 mg IV 3 times a day for 7 days	Primary Outcome: Overall mortality day 28 Secondary Outcomes: Length of ICU stay
Rezk, 2013; single center; Kuwait	27	Patients* receiving mechanical ventilation; meeting ARDS criteria (AECC, Bernard 1994); within 48 hours	Trauma 8/27 hospital acquired pneumonia 11/27	Methylprednisolone; loading dose of 1 mg/kg followed by infusion of 1 mg/kg/day on days 1 to 14, 0.5 mg/kg/day	Primary Outcome: Mortality at day 14

		Age (mean, SD), Gender (Female): Placebo: 50.44, 13.99, Corticosteroids 42.67, 13.95; 4/27	community acquired pneumonia 8/27	from day 15 to day 21, 0.25 mg/kg/day from day 22 to day 25, 0.125 mg/kg/day from day 26 to day 28	Secondary Outcomes: Days of mechanical ventilation
Tongyoo, 2016; single center; Thailand	104	Patients* 18 years or older; with severe sepsis or septic shock; mechanical ventilation; within 12 hours of study entry; meeting criteria for ARDS (AECC definition, Bernard 1994) *Age (mean, SD), Gender (Female):* Placebo: 64.3, 16.0; Corticosteroids 64.5, 17.3; 92/197	NR	Hydrocortisone; IV bolus, 50 mg in 10 mL of normal saline, every 6 hours for 7 days	Primary Outcome: Overall mortality at day 28 Secondary Outcomes: Survival without organ support on day 28; days of mechanical ventilation until day 28; mortality at day 60; hyperglycemia; GI bleed; infection
Villar, 2020; multi-center; Spain	277	Patients* aged 18 years or older; intubated and mechanically ventilated; had acute onset of ARDS, as defined by the American- European Consensus Conference criteria for ARDS,11 or by the Berlin criteria as moderate-to-severe ARDS,12 which includes having an initiating clinical condition (eg, pneumonia, aspiration, inhalation injury, sepsis, trauma, or acute pancreatitis) within 1 week of the known clinical insult, or new or worsening respiratory symptoms; bilateral pulmonary infiltrates on chest imaging (x-ray or CT scan); absence of left atrial hypertension, pulmonary capillary wedge pressure of less than 18 mm Hg, or no clinical signs of left heart failure; and hypoxemia, as defined by a ratio between partial pressure of oxygen in arterial blood and fraction	Pneumonia 96/197 Urinary tract infection 37/197 Skin and soft tissue infection 27/197 Intra-abdominal infection 22/197 Hemoculture-positive 56/197	Dexamethasone plus conventional treatment; Patients in the dexamethasone group received an intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. Treatment with dexamethasone was maintained for a maximum of 10 days after randomization or until extubation (if occurring before day 10).	Primary Outcomes: Number of ventilator-free days at 28 days, number of days alive and free of mechanical ventilation until day 28 post randomization Secondary Outcomes: All-cause mortality at 60 days; ICU mortality; Hospital mortality; serious hyperglycemia; superinfection

		of inspired oxygen (PaO2/FiO2) of 200 mm Hg or less on positive end-expiratory pressure (PEEP) of 5 cm H2O or more, regardless of FiO2. **Age (mean, SD), Gender (Female):* Placebo: 58, 15; Dexamethasone 56, 14; 86/277			
Meduri, 1998; multi-center; USA	24	Patients* 18 years or older; meeting ARDS criteria (AECC definition, Bernard 1994); 7 days of mechanical ventilation with an LIS of 2.5 or greater and less than a 1-point reduction from day 1 of ARDS**;** no evidence of untreated infection **Age (mean, SD), Gender (Female):* Control 51, 6.6; Methylprednisolone 47, 3.9; 15/24	Pneumonia 147/277 Sepsis 67/277 Aspiration 33/277 Trauma 21/277 others 9/277	Methylprednisolone; loading dose 2 mg/kg for first 14 days, then 1 mg/kg for day 15 - 21, then 0.5 mg/kg for day 22 - 28, 0.25 mg/kg for day 28 - 30 then 0.125 mg/kg for day 31 and 32. If patient extubated before day 14, then therapy advanced directly to day 15	Primary Outcomes: Improvement in LIS (> 1 point) at 10 days of treatment, ICU survival Secondary Outcomes: Hospital mortality; days of mechanical ventilation; hyperglycemia; GI bleeds; superinfection
Annane, 2006; multi-center; France	177	Selected Septic shock Patients (subgroup of septic shock trial)* with septic-shock associated ARDS (AECC definition, Bernard 1994) **Age (mean, SD), Gender (Female):* Placebo: 59, 18; Steroids: 61, 16; 56/177	Pneumonia 11/24; Aspiration 3/24; Blasto 1/24; Sepsis 5/24; Postoperative 2/24; Drug reaction 2/24	Hydrocortisone 50 mg IV q6h or fludrocortisone 50 ug daily for 7 days	Primary Outcome: Overall mortality on day 28 Secondary Outcomes: ICU mortality; hospital mortality; gastrointestinal bleeding; superinfection
Zhou, 2014; single center; China	46	Patients* with Severe ARDS (AECC definition, Bernard 1994); SBP 90 mmHg and above; Oxygenation index less than 250 mmHg; Multi-lobe lung lesions; Caused by severe CAP **Age (mean, SD), Gender (Female):* 50.2, 2.3; 16/46	NR	Methylprednisolone; 120 mg IV daily for 7 days	Primary Outcomes: Length of hospital stay; Days of mechanical ventilation
Zhifang, 2016; single center; China	40	Patients* with ARDS diagnosis based on the Europa League in 1994 (AECC definition, Bernard 1994); **Age (mean, SD), Gender (Female):* Control: 55.1, 18.7; Steroids 53.8, 16.2; 15/40	Pneumonia	Methylprednisolone 1 - 2 mg/kg for 3 - 14 days	Primary Outcomes: Length of ICU stay; days of mechanical ventilation
Angus, 2020; multi-center; Australia, Canada, France, Ireland, the Netherlands, New Zealand, the United	403	Patients* 18 years or older; presumed or confirmed SARS-CoV-2 infection; ICU for respiratory or cardiovascular organ support **Age (mean, SD), Gender (Female):* No HC 59.9, 14.6;	COVID-19	Hydrocortisone; Fixed dose of hydrocortisone 50mg or 100mg IV q6h for 7 days; OR Shock-dependent course with hydrocortisone 50mg IV q6h while in shock for up to 28 days.	Primary Outcomes: Organ-support free days up to 21 days (days alive and free of ICU-based respiratory or cardiovascular support) Secondary Outcomes:

Kingdom, and the United States.		Fix Dose HC 60.4, 11.6; Shock HC 59.5, 12.7; 111/384			In- Hospital mortality; length of ICU stay; length of hospital stay; composite outcome of progression to invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO) or death among those not ventilated at baseline; WHO ordinal scale (range, 0-8, where 0 = no illness, 1-7 = increasing level of care, and 8 = death) assessed at day 14.19,20
Dequin, 2020; multi-center; France	149	Patients* at least 18 years admitted to 1 of the 9 participating French ICUs for acute respiratory failure could be included if they had a biologically confirmed (reverse transcriptase–polymerase chain reaction) or suspected (suggestive chest computed tomography scan result in the absence of any other cause of pneumonia) COVID-19 **Age (median, IQR), Gender (Female):* Placebo 66.3 (53.5-72.7); HC 63.1 (51.5-70.8); 45/149	COVID-19	IV infusion at 200 mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days. If the patient's respiratory and general status had sufficiently improved by day 4, a short treatment regimen was used (200 mg/d for 4 days, followed by 100 mg/d for 2 days and then 50 mg/d for the next 2 days, for a total of 8 days).	Primary Outcome: Treatment failure on day 21 (defined as death or persistent dependency on mechanical ventilation/high-flow oxygen therapy) Secondary Outcomes: Use of tracheal intubation; Use of prone position; Extracorporeal membrane oxygenation or inhaled nitric oxide; PaO2:FIO2 ratio (days 1-7, 14, 21); Proportion of patients with nosocomial infections recorded during the ICU stay up to day 28.
Horby, 2020; multi-center; UK	1007	Hospitalized patients* with clinically suspected or laboratory-confirmed SARS-CoV-2 infection **Age (mean, SD), Gender (Female):* Usual Care: 65.8, 15.8; Dex: 66.9, 15.4; 2338/6425	COVID-19	Dexamethasone; 6mg PO/IV daily for up to 10 days	Primary Outcome: 28-day all-cause mortality Secondary Outcomes: Time until hospital discharge; subsequent receipt of invasive mechanical ventilation, ECMO, death
Tomazini, 2020; multi-center; Brazil	299	Patients* at least 18 years old, had confirmed or suspected COVID-19 infection, and were receiving mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with PaO2:FIO2 of 200 or less. **Age (mean, SD), Gender (Female):*	COVID-19	Dexamethasone 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge, whichever occurred first	Primary Outcome: Ventilator-free days during the first 28 days (alive and free of mechanical ventilation) Secondary Outcomes: All-cause mortality during 28 days; ICU-free days up to day 28; Mechanical

		Control: 62.7, 13.1; Dex: 60.1, 15.8; 112/299			ventilation duration at 28 days; SOFA scores (48 hrs, 72 hrs, 7 days)
DEXA-COVID19; multi-center; Spain	19	Patients* 18 years or older; Mechanical ventilation; Moderate to severe ARDS per Berlin criteria; Confirmed COVID-19 **Age (median, IQR), Gender (Female):* Control: 60 (52-69); Dex: 62 (48-68); 6/19	COVID-19	Dexamethasone; 20 mg/d IV for 5 days and then 10 mg/d IV for 5 days	Primary Outcome: 60-day mortality Serious Adverse Events: Secondary infections of pneumonia, sepsis, or other similar; Pulmonary Embolism
COVID STEROID; multi-center; Denmark	29	Patients* 18 years or older; Oxygen supplementation (≥10 L/min) or mechanical ventilation or continuous CPAP; Confirmed COVID-19 **Age (mean, SD), Gender (Female):* Control: 62 (55-71); HC 57 (52-75); 6/29	COVID-19	Hydrocortisone 200 mg/d intravenously × 7 d (continuous infusion or bolus injection every 6 h)	Primary Outcome: Days alive without life-support at 28 days Secondary Outcomes/Serious Adverse Events: Mortality at 28 days; New episodes of septic shock (Sepsis 3 criteria); Invasive fungal infection; GI bleeding
Steroids-SARI; multi-center; China	47	Patients* admitted to ICU; PaO2:FIO2 <200 mm Hg on positive pressure ventilation or high-flow nasal canulae >45 L/min; Confirmed COVID-19 **Age (mean, SD), Gender (Female):* Control: 62 (54-68); Methylpred: 67 (61-74); 12/47	COVID-19	Methylprednisolone 40 mg IV every 12 h for 5 days	Primary Outcome: Lower LIS score at 7d and 14d Secondary Outcomes: Mortality at 30 days; Secondary bacterial infections; barotrauma; Severe hyperglycemia; GI bleed requiring transfusion; Acquired weakness
Jeronimo 2020; single center; Brazil	393	Hospitalized patients* were included if they had clinical AND/OR radiological suspicion of COVID-19, aged 18 years or older at the time of inclusion, with SpO2 ≤ 94% at room air OR in use of supplementary oxygen OR under IMV **Age (mean, SD), Gender (Female):* Placebo: 57, 15; MP 54,15; 139/393	COVID-19	Methyprednisolone 0.5 mg/kg x 5 days	Primary Outcome: 28-day mortality Secondary Outcomes: early mortality (Days 7 and 14); orotracheal intubation by Day 7; patients with PaO2 /FiO2 < 100 by Day 7

GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Narrative Summary
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
16 [a]	randomised trials	not serious	not serious [b]	borderline serious[v]	borderline serious[w]	none	453/1245 (36.4%)	693/1545 (44.9%)	**RR 0.82** (0.72 to 0.95)	**80 fewer per 1,000** (from 125 fewer to 22 fewer)	⊕⊕⊕◯ MODERATE	Corticosteroids probably reduce mortality compared to no corticosteroids
Duration of Mechanical ventilation												
9 [c]	randomised trials	serious [d]	not serious [e]	serious[v]	not serious	none	614	633	-	MD 4.04 lower (5.53 lower to 2.53 lower)	⊕⊕◯◯ LOW	Corticosteroids may reduce duration of mechanical ventilation compared to no corticosteroids
Length of ICU stay												
4 [h]	randomised trials	serious [i]	serious [j]	serious[v]	serious [k]	none	184	153	-	MD 0.78 higher (4.11 lower to 5.68 higher)	⊕◯◯◯ VERY LOW	Corticosteroids have an uncertain effect on length of ICU stay compared to no corticosteroids

Certainty assessment							№ of patients		Effect		Certainty	Narrative Summary
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
Length of Hospital stay												
4 [l]	randomised trials	serious [m]	not serious [e]	serious[v]	not serious	none	188	156	-	MD 8.05 lower (12.98 lower to 3.12 lower)	⨁⨁◯◯ LOW	Corticosteroids may reduce length of hospital stay compared to no corticosteroids
Neuromuscular weakness												
2 [n]	randomised trials	not serious	serious [o]	serious[v]	serious [k]	none	30/152 (19.7%)	22/119 (18.5%)	**RR 1.29** (0.79 to 2.09)	**54 more per 1,000** (from 39 fewer to 202 more)	⨁◯◯◯ VERY LOW	Corticosteroids have an uncertain effect on neuromuscular weakness compared to no corticoteroids
Gastrointestinal bleeding												
5 [p]	randomised trials	not serious	not serious	serious[v]	serious [k]	none	9/217 (4.1%)	7/219 (3.2%)	**RR 1.20** (0.43 to 3.34)	**6 more per 1,000** (from 18 fewer to 75 more)	⨁⨁◯◯ LOW	Corticosteroids may increase gastrointestinal bleeding compared to no corticosteroids
Serious hyperglycemia												

Certainty assessment							№ of patients		Effect		Certainty	Narrative Summary
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
6 [s]	randomised trials	not serious	not serious	serious [t,v]	not serious	none	282/480 (58.8%)	229/435 (52.6%)	**RR 1.11** (1.01 to 1.23)	**58 more per 1,000** (from 5 more to 121 more)	⨁⨁⨁◯ MODERATE	Corticosteroids probably increase serious hyperglycemia compared to no corticosteroids

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

Explanations

a. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , COVID STEROID 2020, DEXA-COVID19 2020, Horby, 2020, Jeronimo 2020, Tomazini 2020, Steroids-SARI 2020, Dequin 2020, Derek 2020

b. isquared is mildly high, however, however, the majority of studies favour corticosteroids with only 2 very small unpublished studies showing a non-significant benefit with placebo.

c. Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , Tomazini 2020, Zhifang 2016, Zhou 2014, Steroids-SARI 2020

d. Of the 10 included studies, 3 are at high risk of bias (Rezk 2013, Zhou 2014, Zhi-fang 2016) and 1 has some concerns (Steroids-SARI 2020)

e. High isquared, however, all studies favour corticosteroids

h. Liu 2012, Meduri 2007, Steinberg 2006, Zhi-fang 2016

i. Out of the 4 included studies, one had high risk of bias (Zhi-fang 2016) and the other had some concerns (Liu 2012)

j. High isqaured with variable effects across studies

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

l. Meduri 2007, Steinberg 2006, , Zhou 2014, Steroids-SARI 2020

m. Out of the 4 included studies, one had high risk of bias (Zhou 2014) and two had some concerns (Steroids-SARI 2020)

n. Meduri 2007, Steinberg 2006

o. Low isquared, however variable effects across studies

p. Annane 2006, Meduri 1998, Tongyoo 2016, , COVID-STEROID 2020, Steroids-SARI 2020

q. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , COVID STEROID 2020, Tomazini 2020

r. Different studies measured superinfection differently

s. Meduri 1998, Meduri 2007, Tongyoo 2016, Villar 2020, Tomazini 2020, Steroids-SARI 2020

t. Defined differently across studies. Meduri 2007 defined as requiring insulin, whereas other studies had different glucose cutoffs (150 mg/dl vs. 180 mg/dl).

u. Wide confidence interval doesn't exclude no effect.

v. Not all included studies had ARDS as inclusion criteria (COVID-19 studies, Annane 2006). However, we did not downgrade one whole level because there was no subgroup differences and effect sizes were similar between studies that strictly defined ARDS and studies that did not.

w. Optimal information size not reached by TSA

x. Rated as critically important from patient perspective

y. Rated as important from patient perspective

z. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , DEXA-COVID19 2020, Tomazini 2020

Summary of Judgements: Corticosteroids for Acute Respiratory Distress Syndrome

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of Recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	✓	○

ROB Assessments

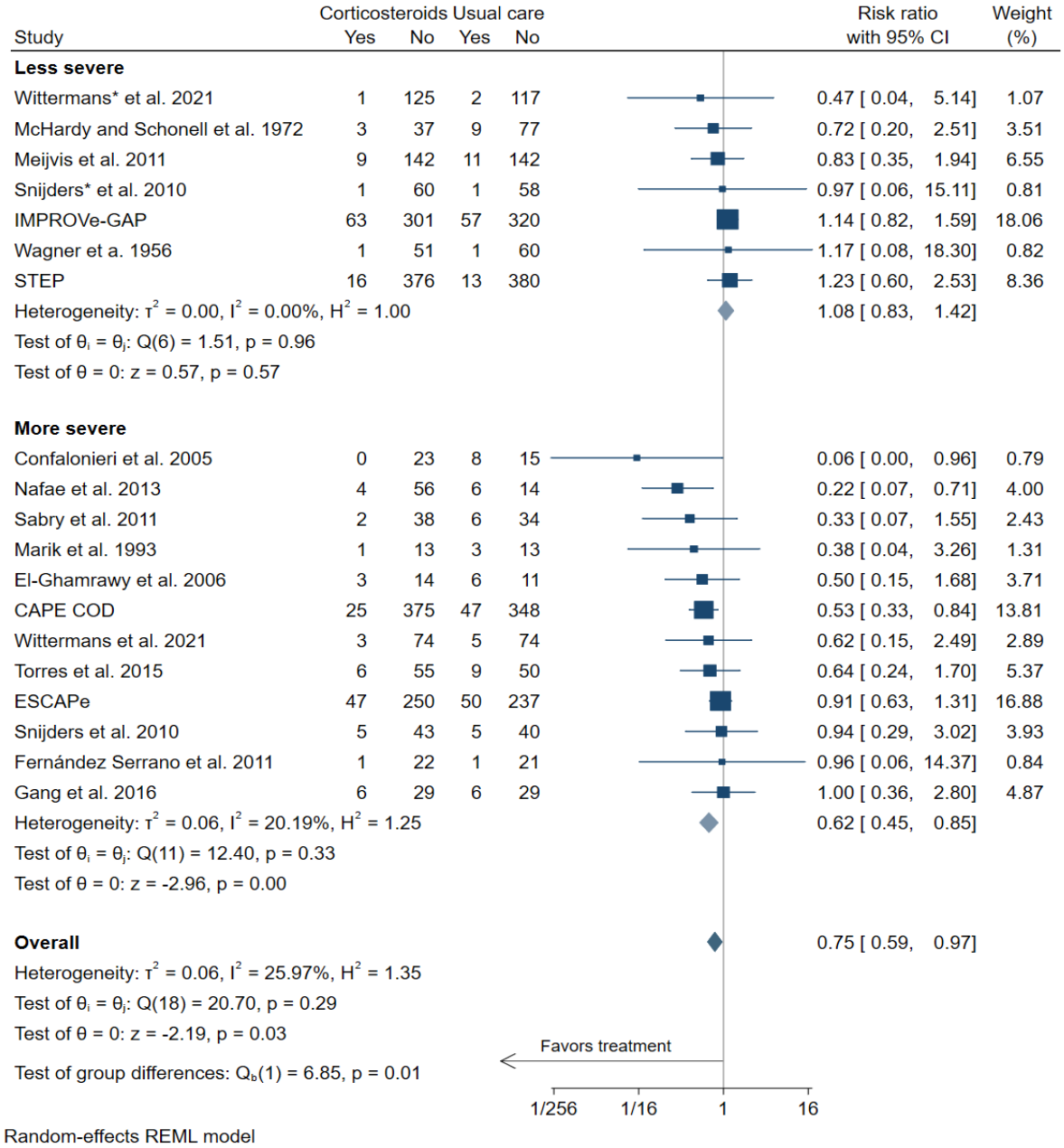
Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias for the outcome of Mortality
Steinberg, 2006	Low	Low	Low	Low	Low	Low
Meduri, 2007	Low	Low	Low	Low	Low	Low
Liu, 2012	Some concerns	Low	Low	Low	Low	Some concerns
Rezk, 2013	High	Low	Low	Low	Low	High
Tongyoo, 2016	Low	Low	Low	Low	Low	Low
Villar, 2020	Low	Low	Low	Low	Low	Low
Meduri, 1998	Low	Some concerns	Low	Low	Low	Some concerns
Annane, 2006	Low	Low	Low	Low	Low	Low
Zhou, 2014	Some concerns	Some concerns	Low	Low	Some concerns	High
Zhifang, 2016	Some concerns	Some concerns	Low	Low	Some concerns	High
Horby, 2020	Low	Low	Low	Low	Low	Low
Tomazini, 2020	Low	Low	Low	Low	Low	Low
DEXA-COVID19	Low	Low	Low	Low	Low	Low
COVID STEROID	Low	Low	Low	Low	Low	Low
Steroids-SARI	Some concerns	Low	Low	Low	Low	Some concerns
Jeronimo, 2020	Low	Low	Low	Low	Low	Low
Dequin, 2020	Low	Low	Low	Low	Low	Low
Derek, 2020	Low	Low	Low	Low	Low	Low

Supplemental Digital Content 9C

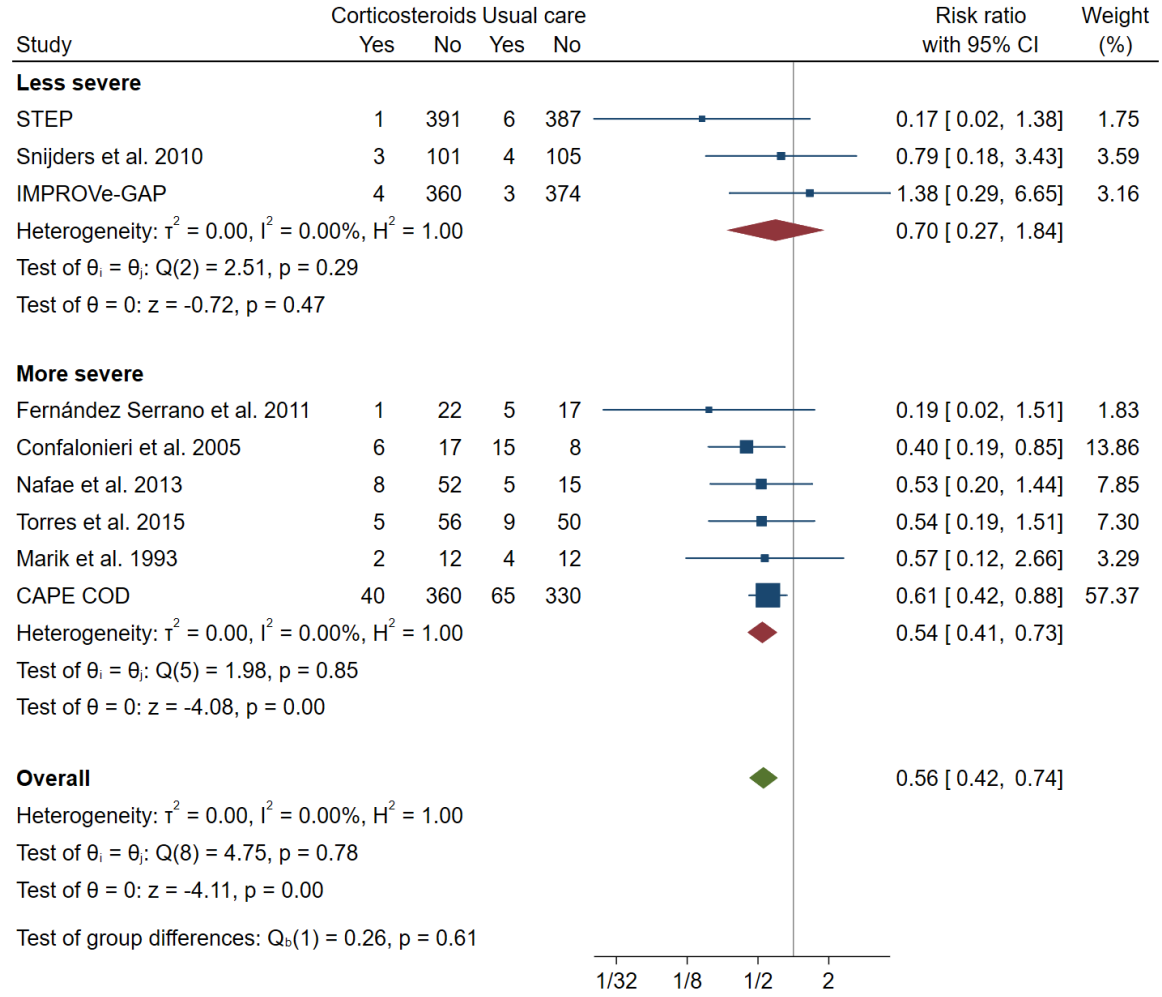
Question: Should corticosteroids be administered to hospitalized patients with community acquired pneumonia?

Forest plots

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Hospital Mortality.

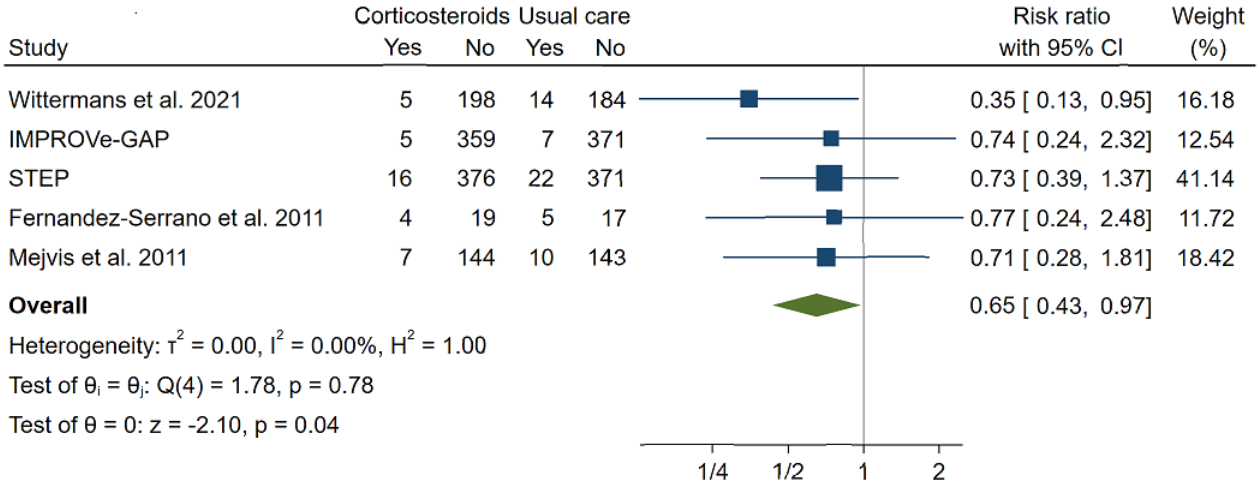


Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Need for Invasive Mechanical Ventilation.



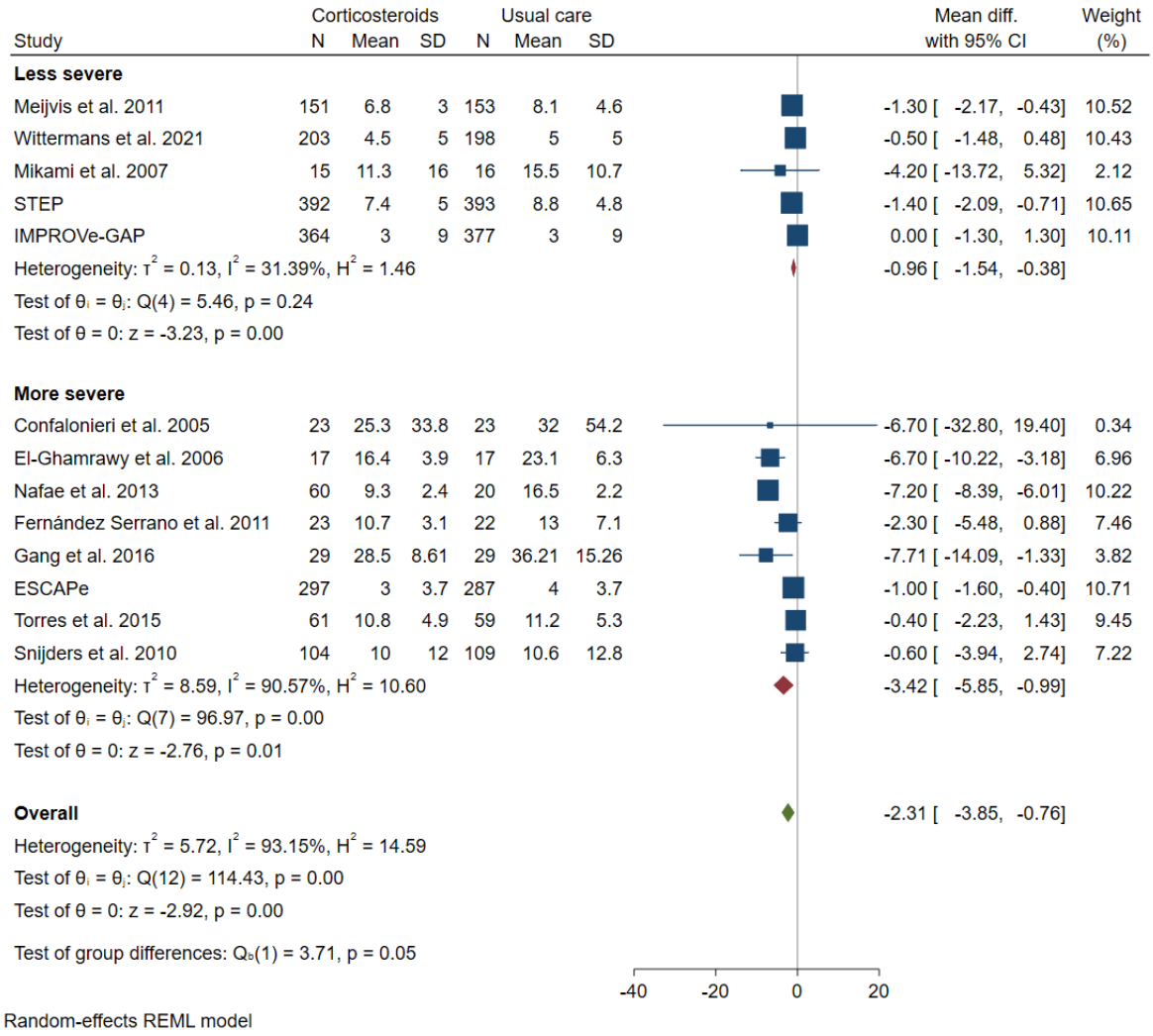
Random-effects REML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in patients with less severe CAP. Need for ICU admission.

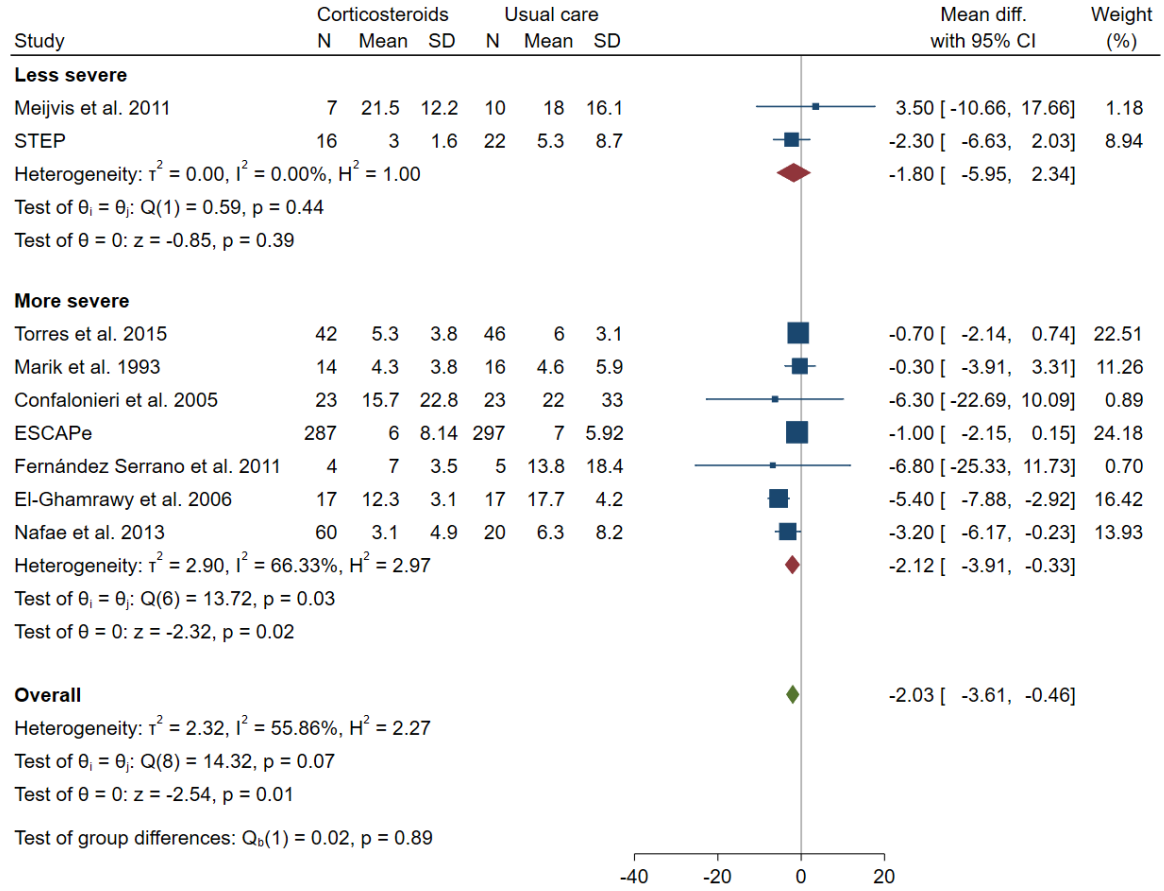


Random-effects REML model

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Duration of Hospitalization

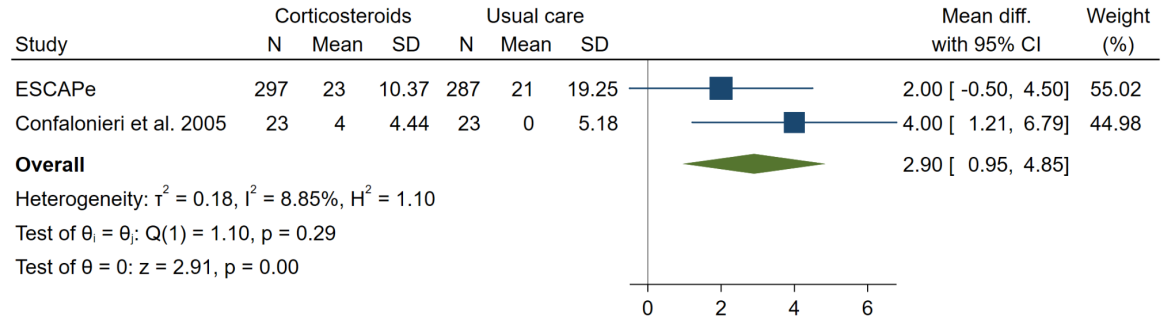


Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Duration of ICU Stay



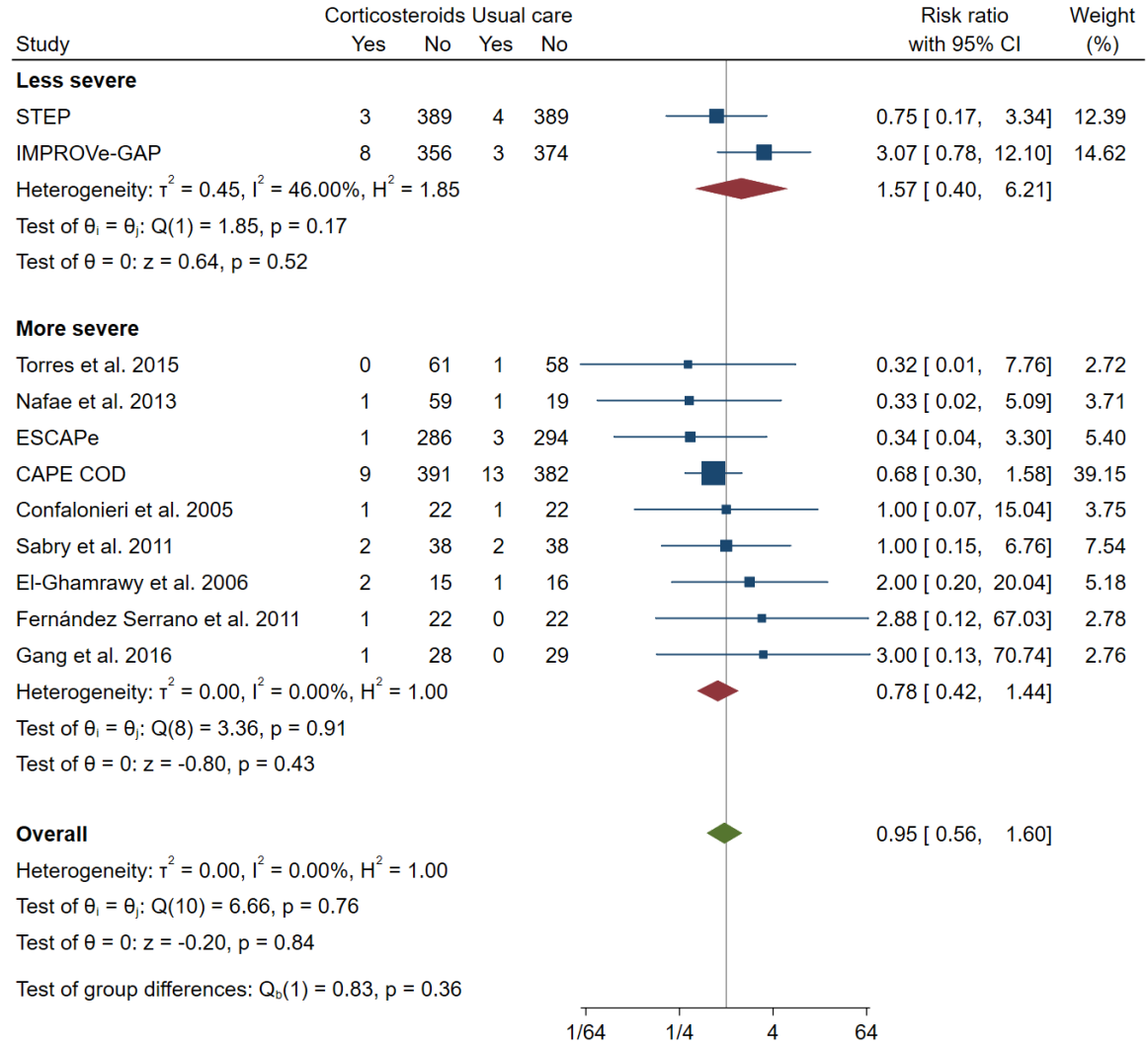
Random-effects REML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in patients with severe CAP. Ventilator-free Days



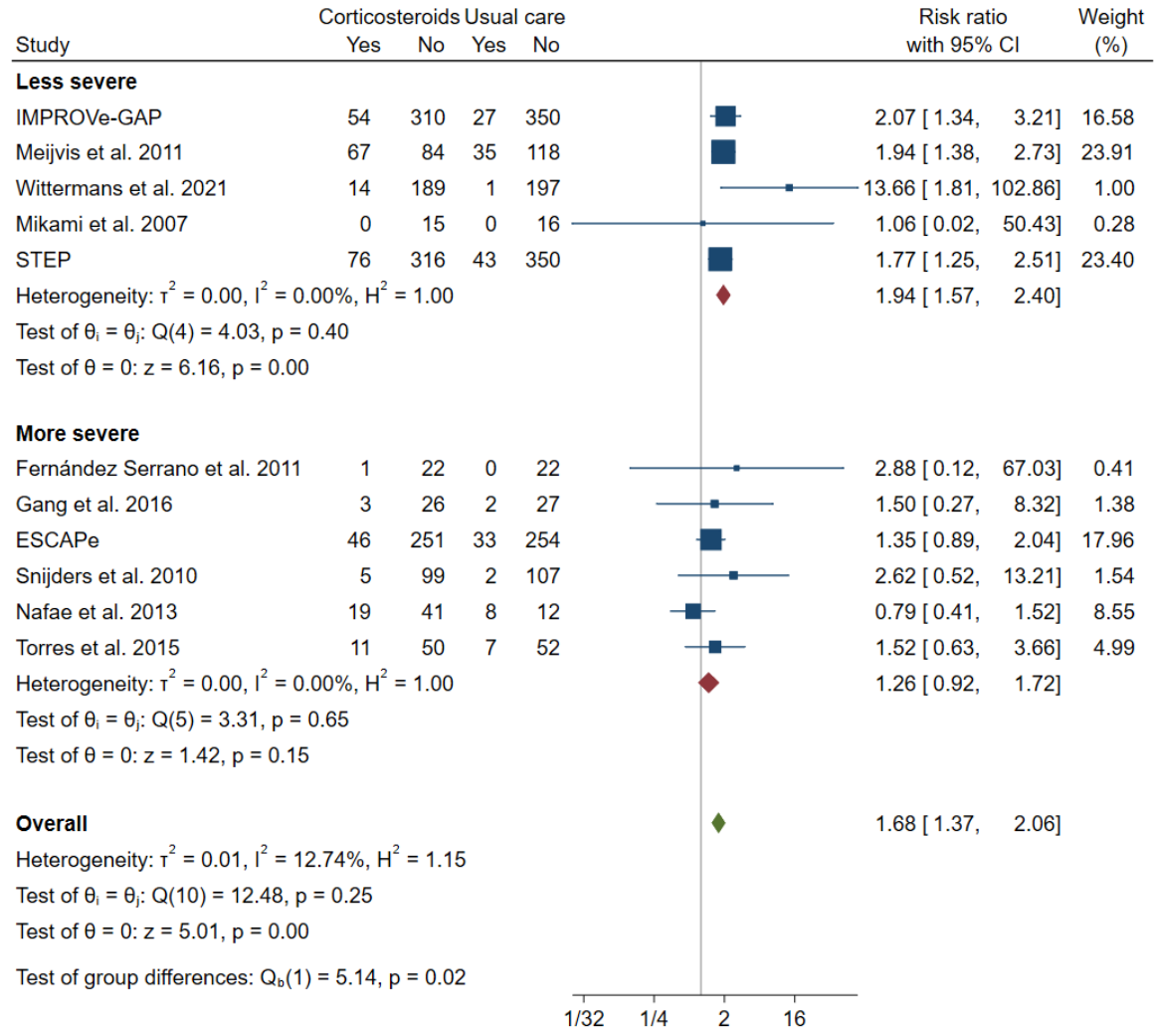
Random-effects REML model

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Gastrointestinal Bleed



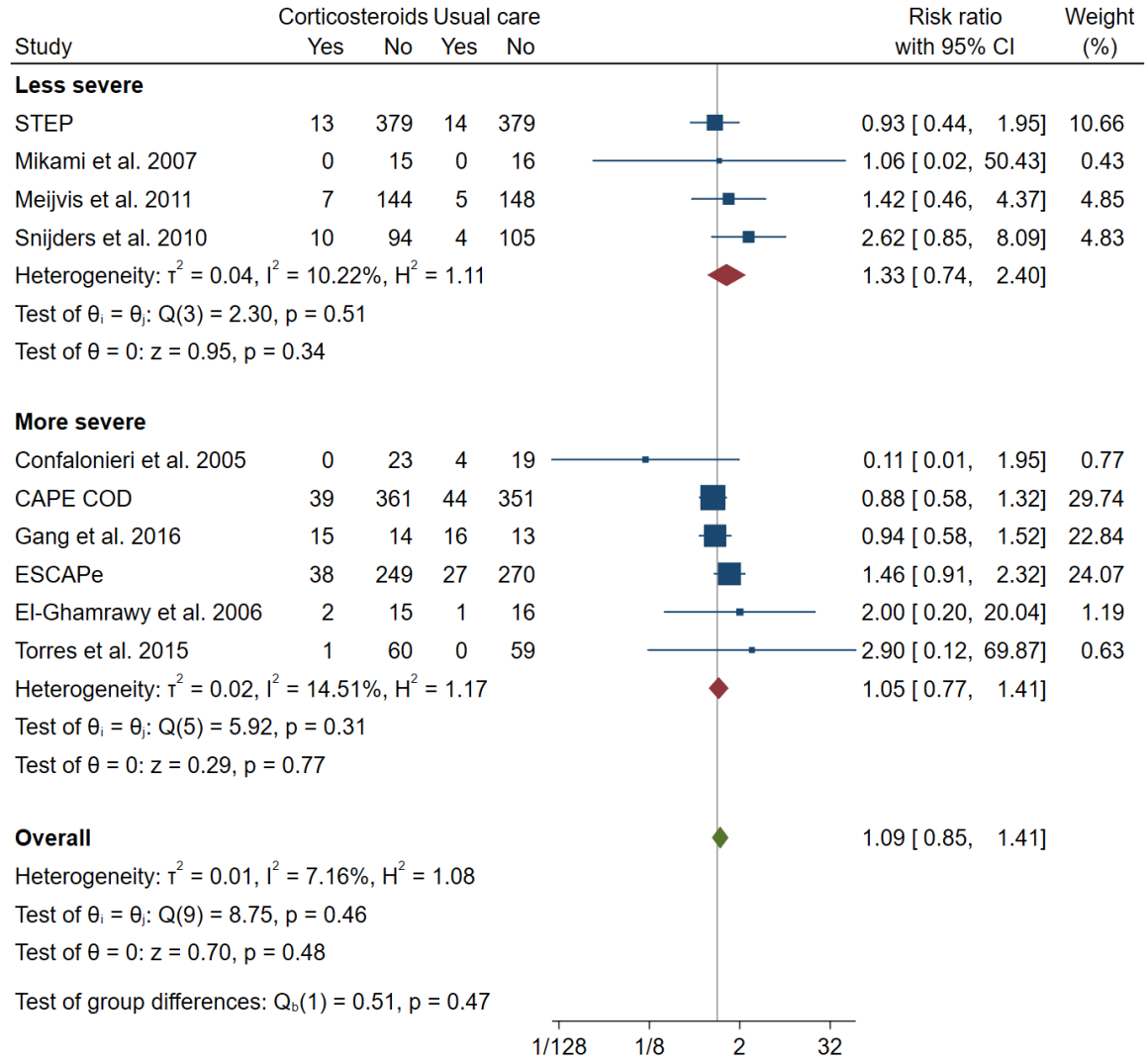
Random-effects REML model

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Hyperglycemia



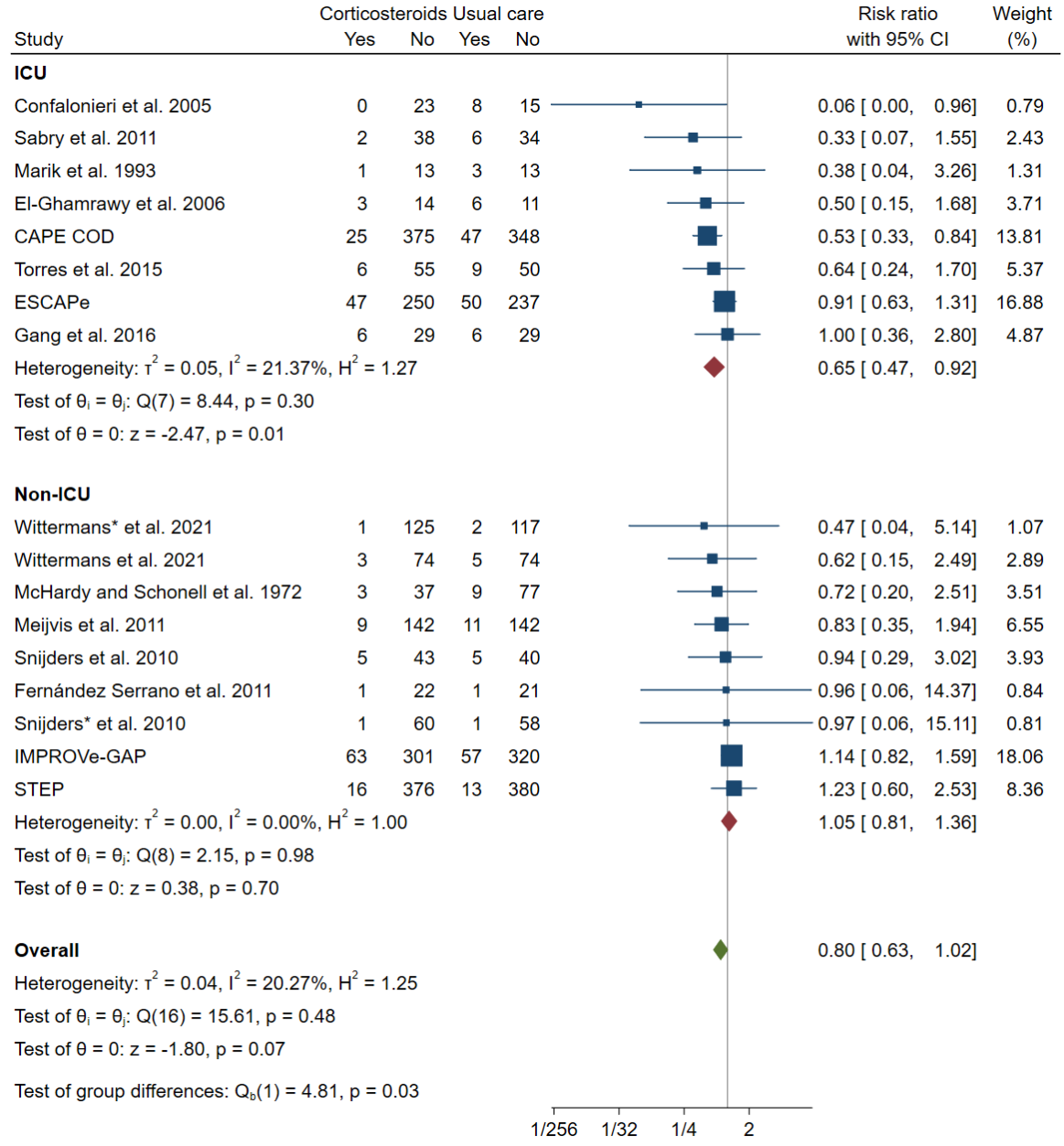
Random-effects REML model

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Secondary Infections



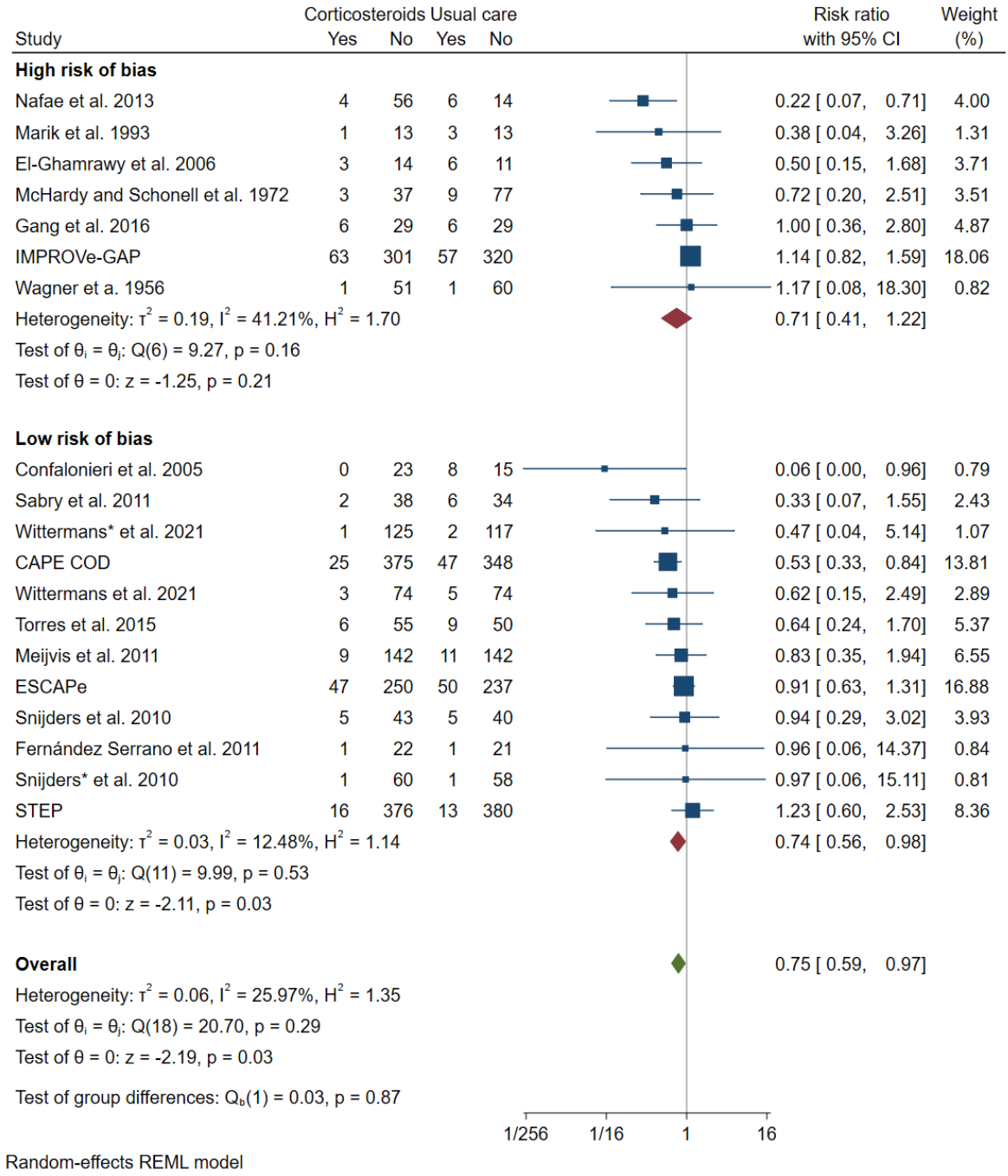
Random-effects REML model

Forest plot: ICU vs non-ICU Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality

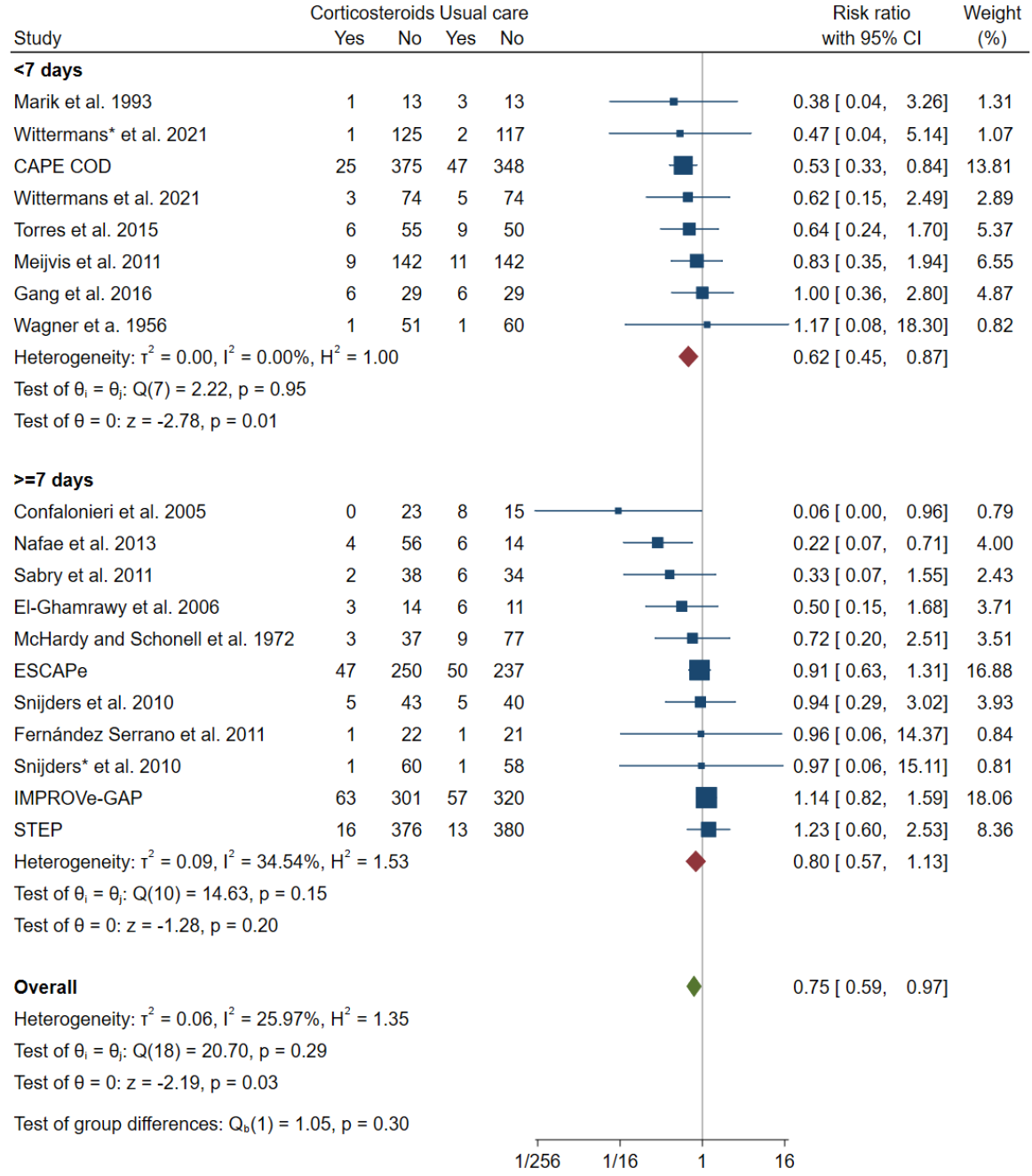


Random-effects REML model

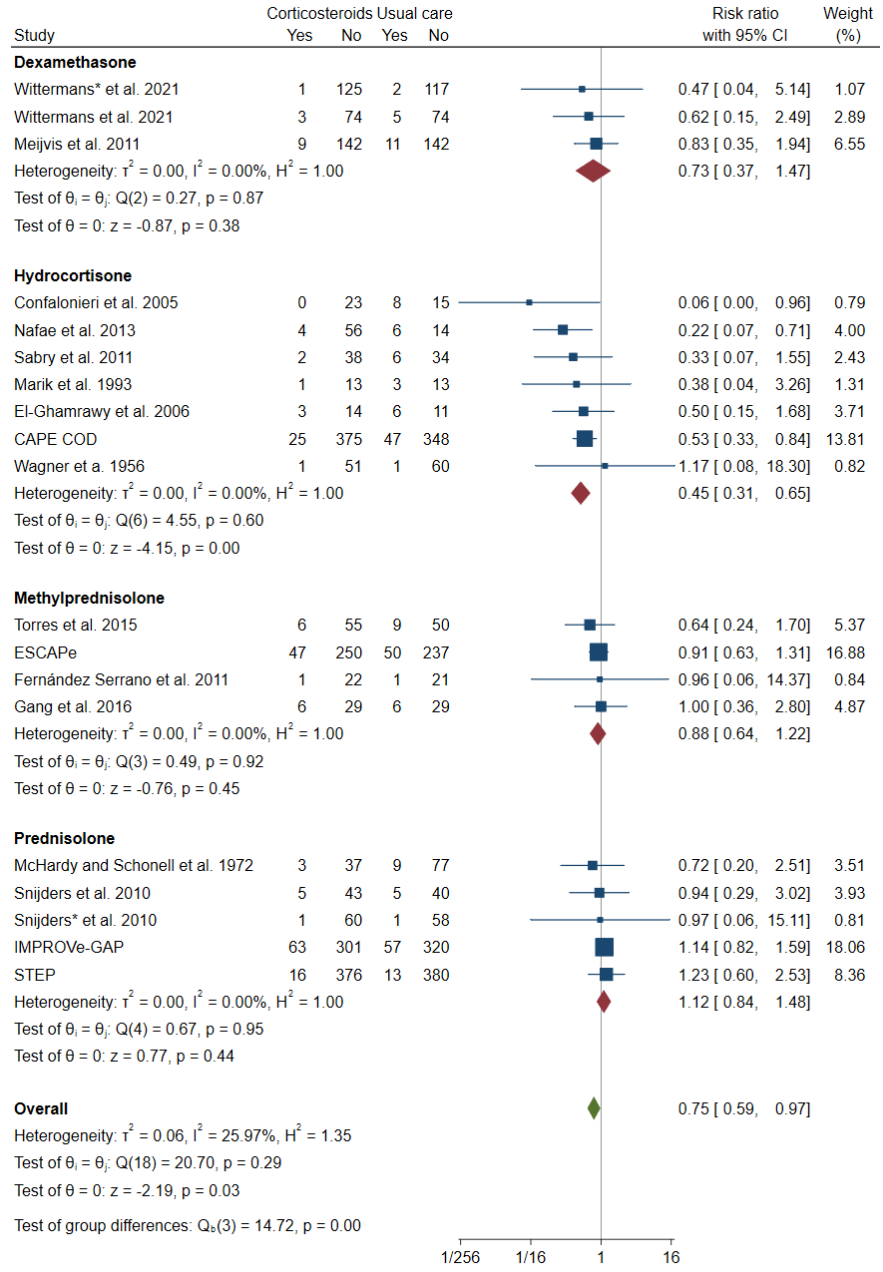
Forest plot: Risk of Bias Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality



Forest plot: Duration of Treatment (<7 days or >/= 7 days) Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality

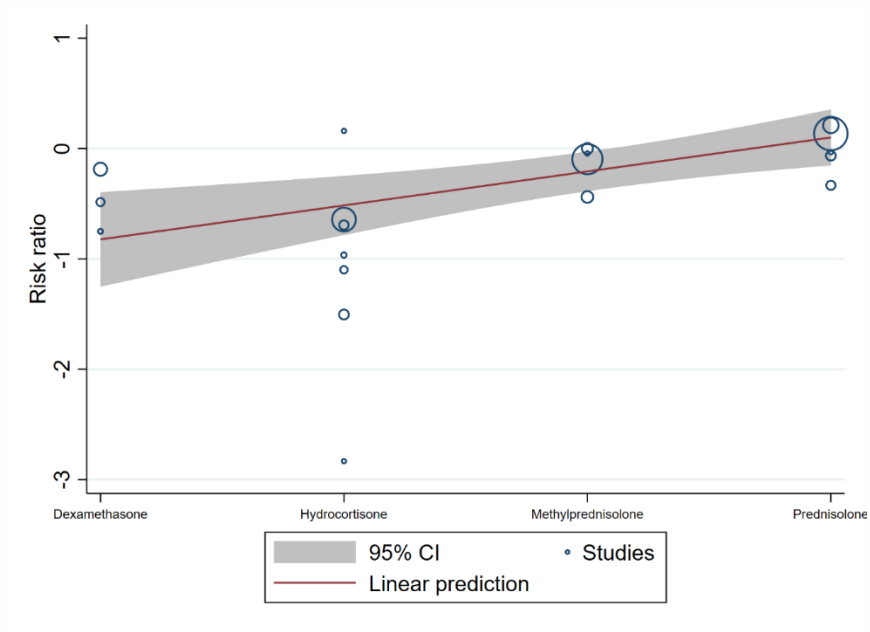


Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality

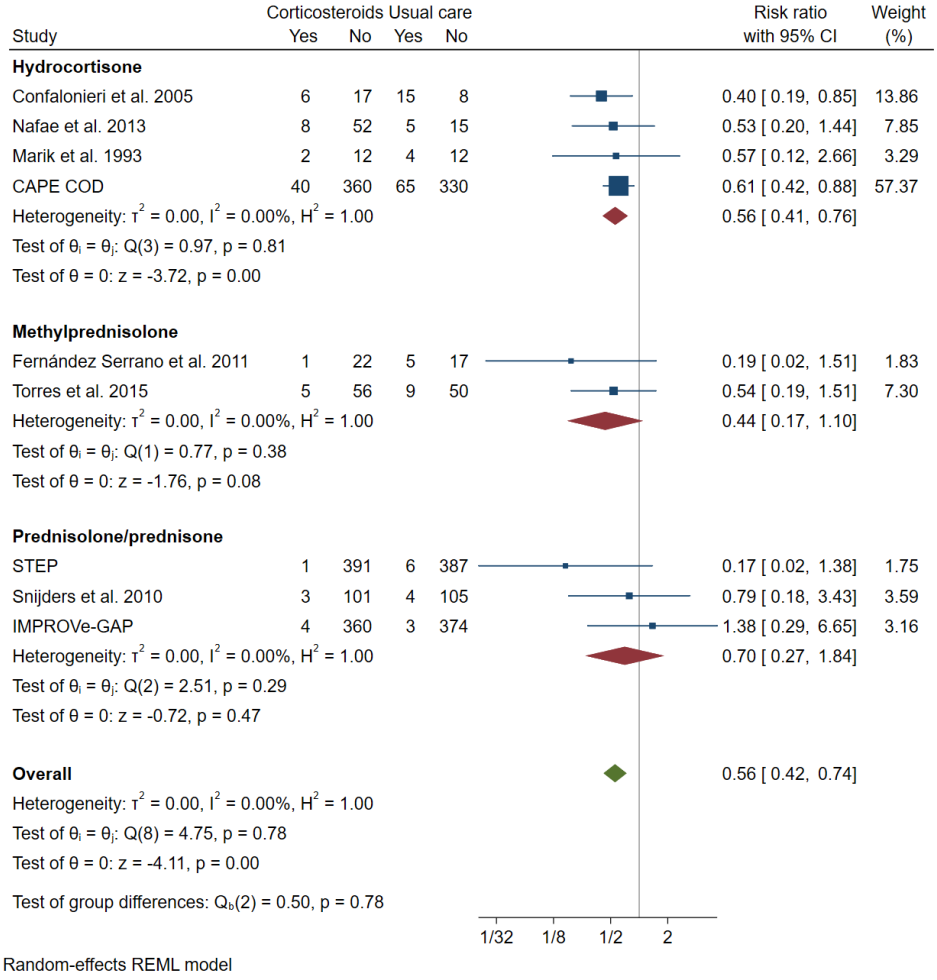


Random-effects REML model

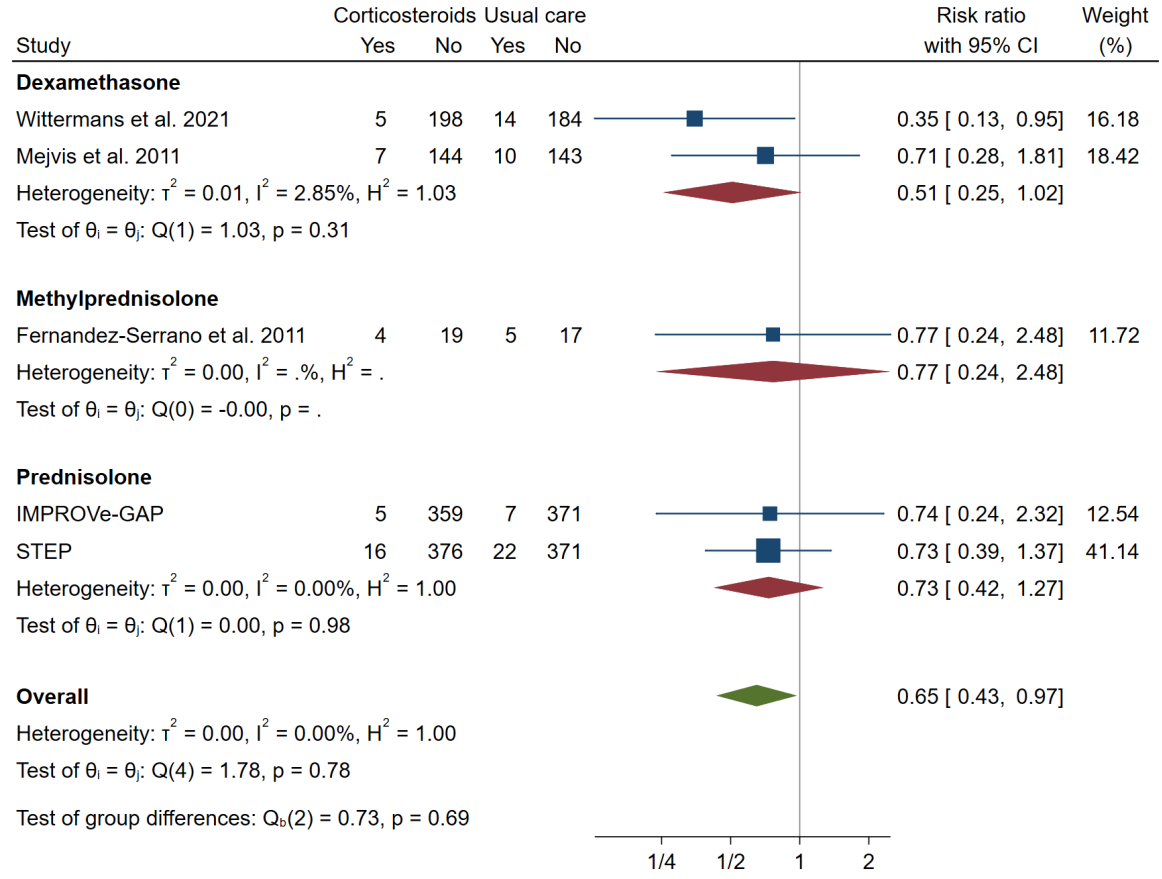
Mortality meta-regression in all patients with CAP based on molecule (p=0.001)



Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Need for Invasive Mechanical Ventilation

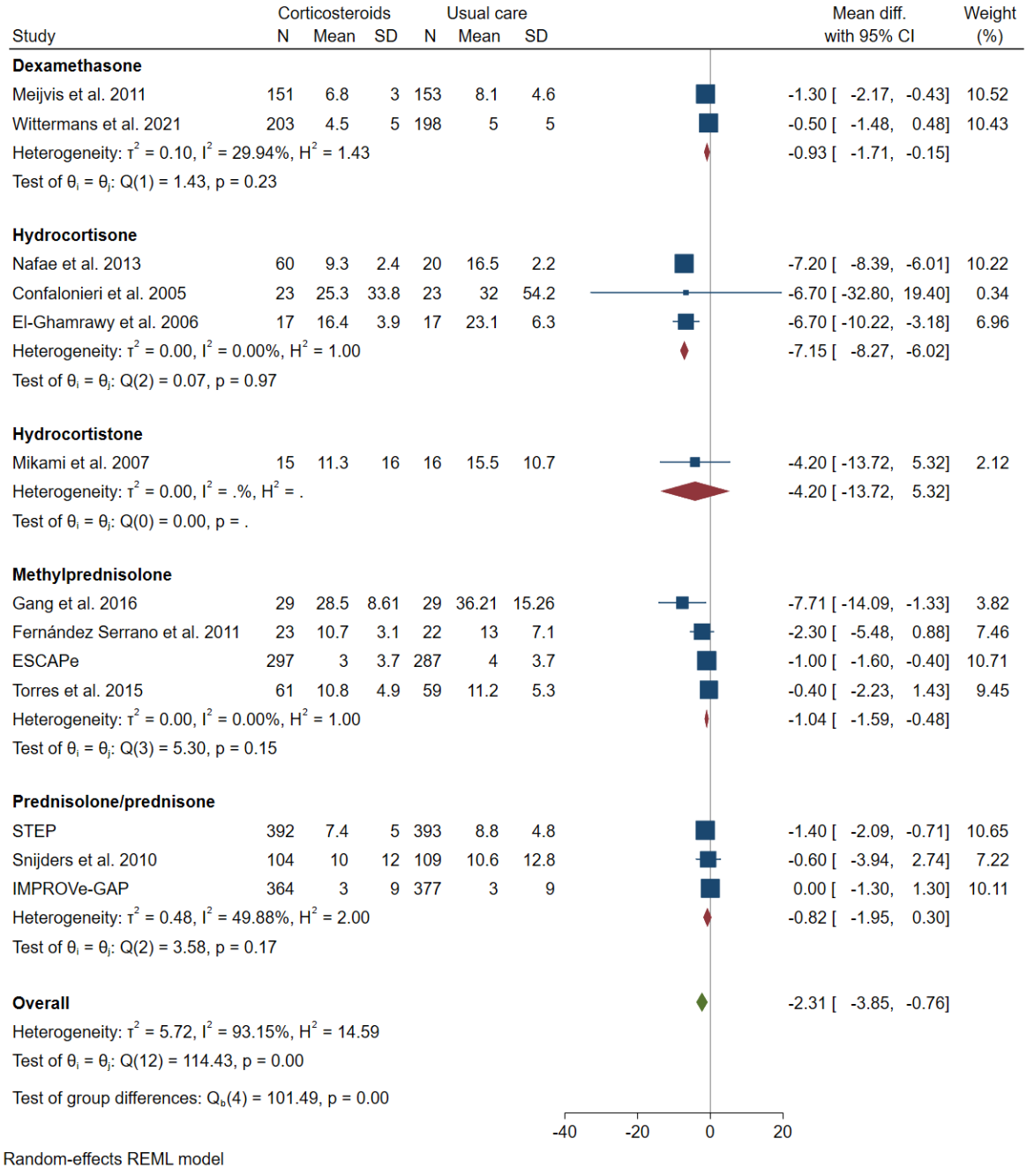


Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Need for ICU Admission.

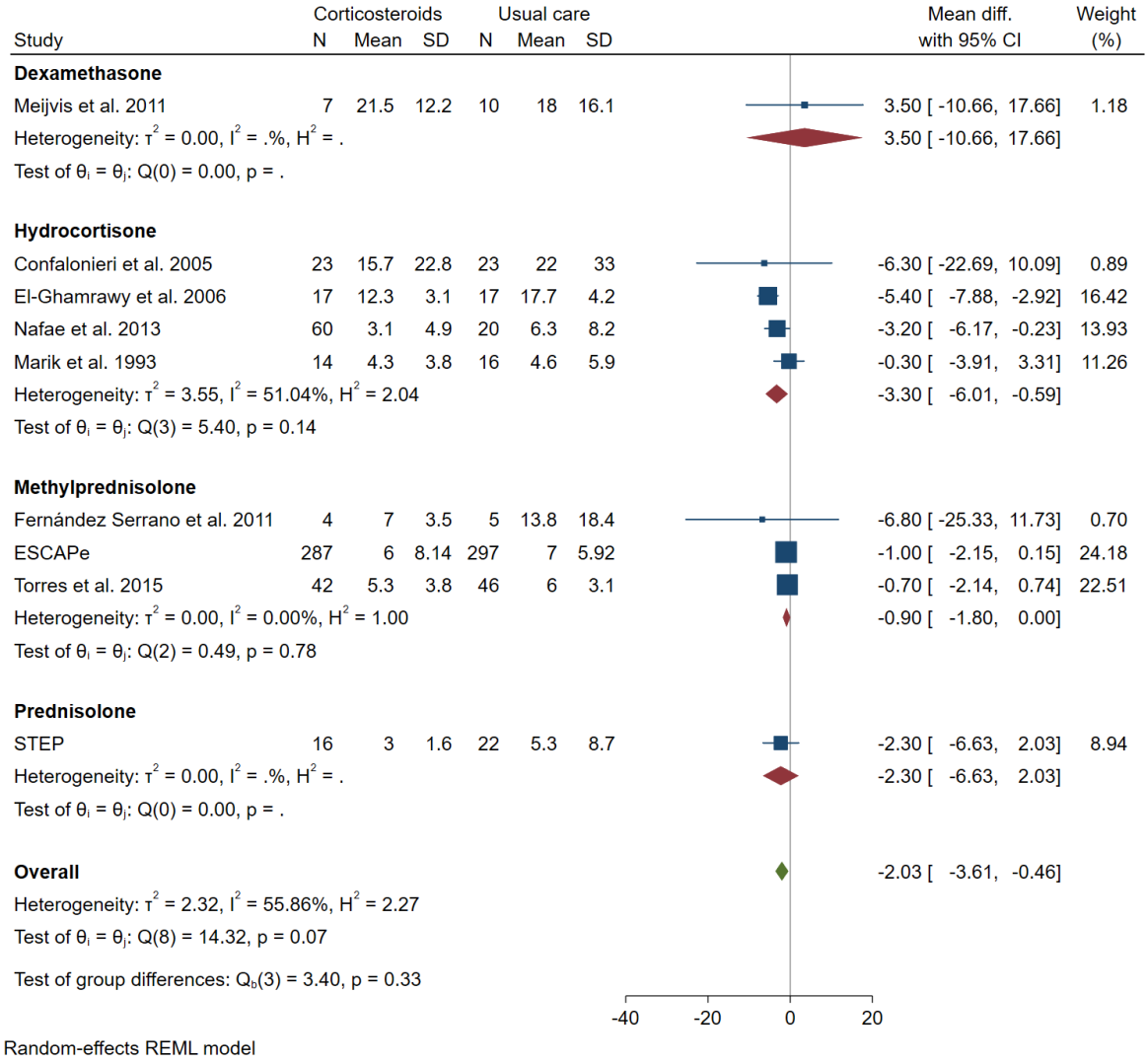


Random-effects REML model

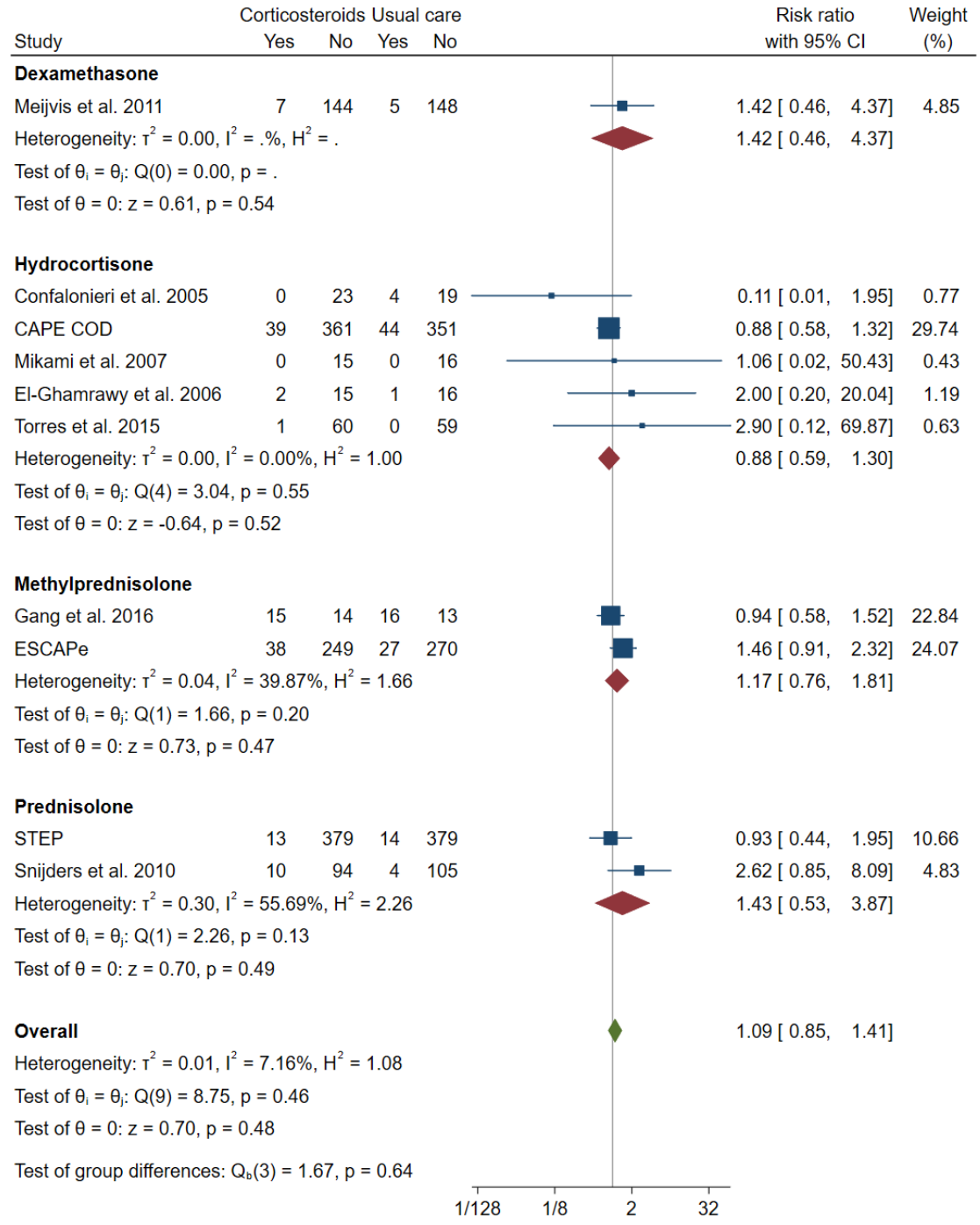
Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Duration of hospitalization.



Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Duration of ICU Stay.

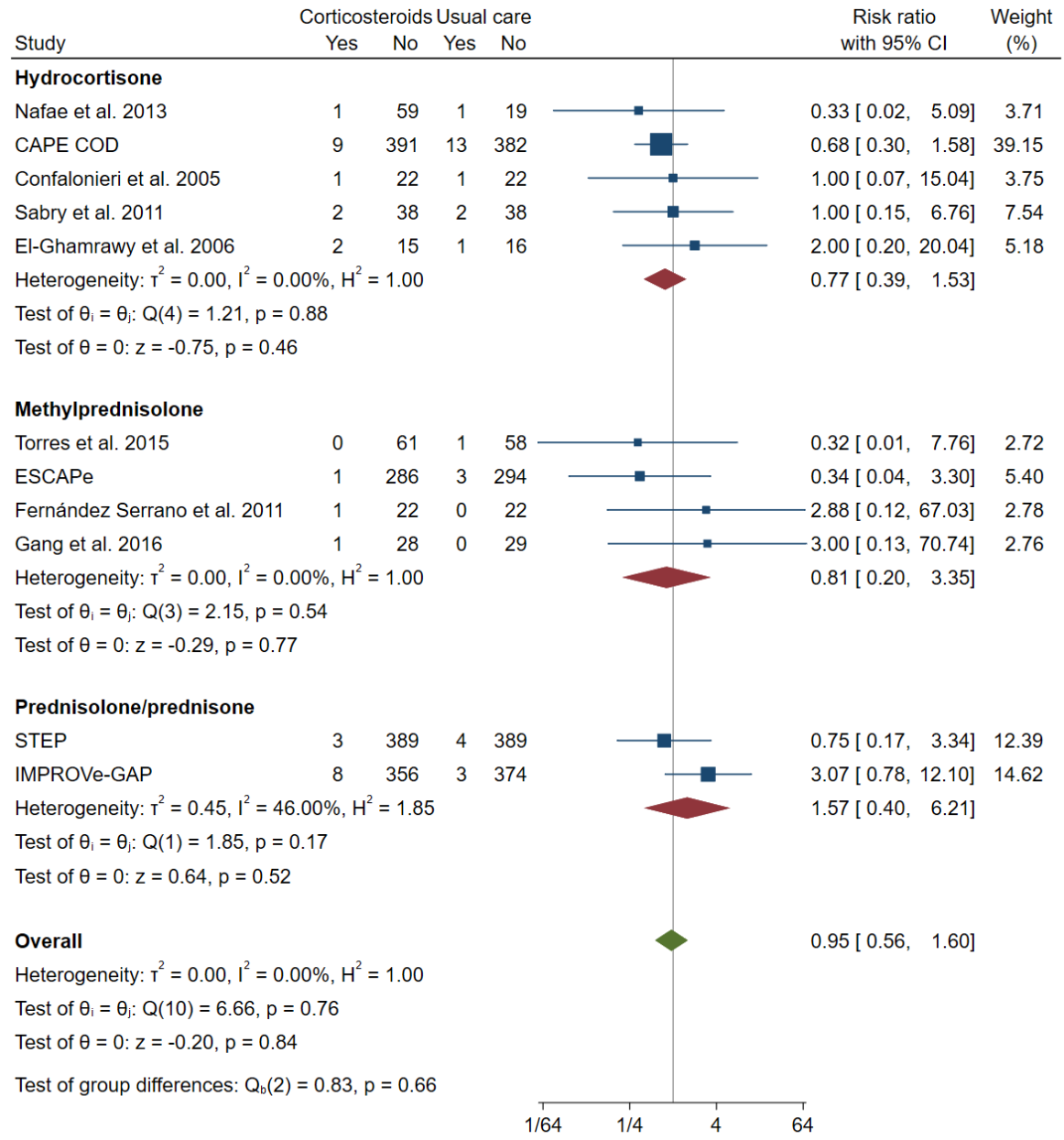


Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Secondary Infections.



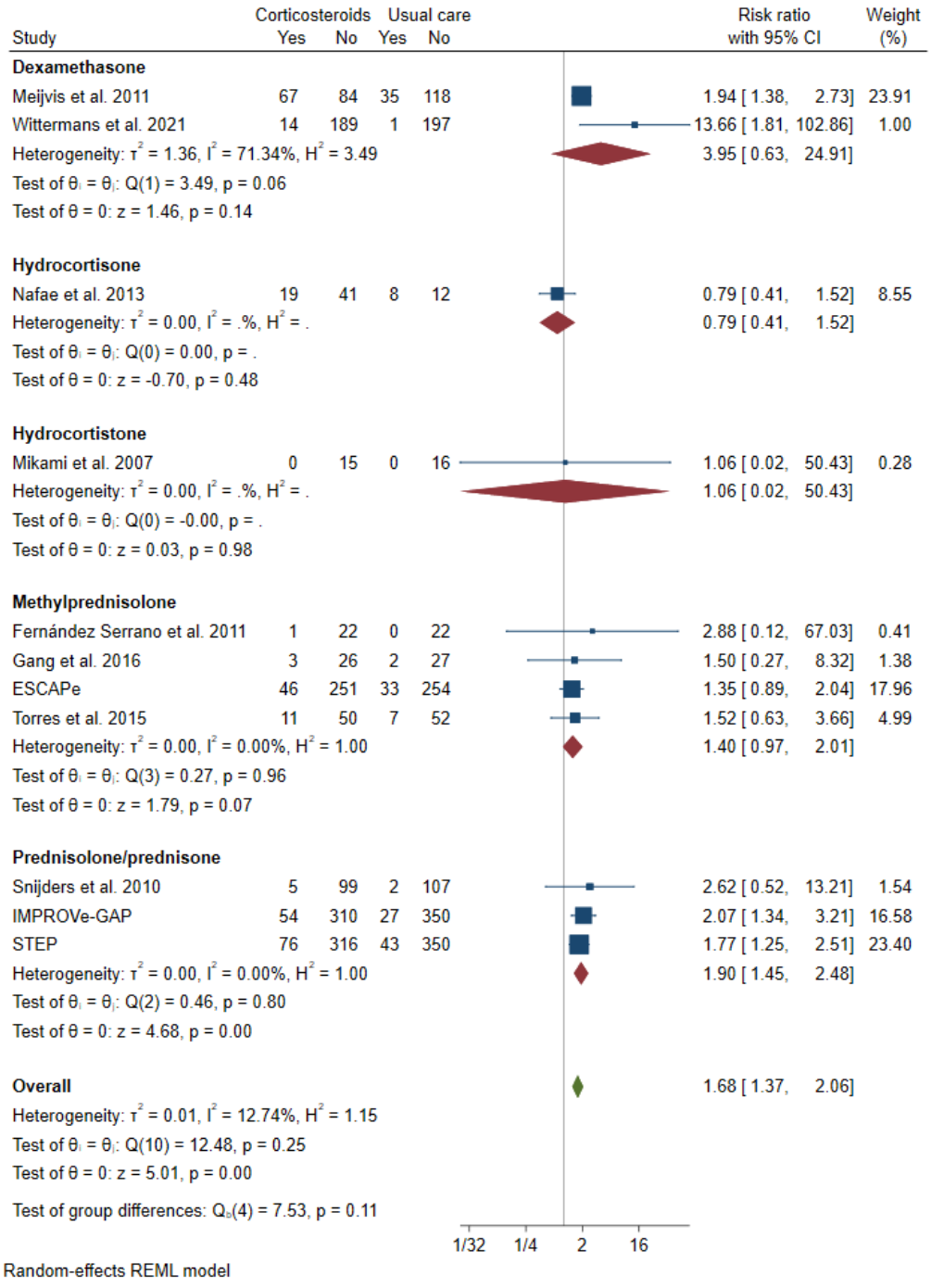
Random-effects REML model

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Gastrointestinal Bleed.



Random-effects REML model

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Hyperglycemia.



GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality (More severe)												
12	randomised trials	not serious	not serious	serious[a]	not serious	none	103/1070 (9.6%)	152/991 (15.3%)	**RR 0.62** (0.45 to 0.85)	**56 fewer per 1,000** (from 81 fewer to 22 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (Less-severe)												
7	randomised trials	not serious	not serious	serious[a]	serious[b]	none	94/1186 (7.9%)	94/1248 (7.5%)	**RR 1.08** (0.83 to 1.42)	**6 more per 1,000** (from 13 fewer to 32 more)	⨁⨁◯◯ Low	CRITICAL
Invasive mechanical ventilation												
9	randomised trials	not serious	not serious	not serious	serious[c]	none	70/1371 (5.1%)	116/1298 (8.9%)	**RR 0.56** (0.42 to 0.74)	**36 fewer per 1,000** (from 48 fewer to 21 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Secondary infections												
10	randomised trials	not serious	not serious	serious[d]	serious[c]	none	125/1440 (8.7%)	115/1447 (6.5%)	**RR 1.09** (0.85 to 1.41)	**7 more per 1,000** (from 12 fewer to 32 more)	⨁⨁◯◯ Low	IMPORTANT
Hyperglycemia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	usual care	Relative (95% CI)	Absolute (95% CI)		
11	randomised trials	not serious	not serious	serious[e]	not serious	none	251/1689 (14.9%)	127/1673 (7.6%)	**RR 1.76** (1.46 to 2.14)	**58 more per 1,000** (from 35 more to 87 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Gastrointestinal bleeding												
11	randomised trials	not serious	not serious	not serious	very serious[f]	none	29/1687 (1.7%)	29/1659 (1.7%)	**RR 0.95** (0.56 to 1.60)	**1 fewer per 1,000** (from 8 fewer to 10 more)	⨁⨁◯◯ Low	IMPORTANT
Duration of hospitalization												
13	randomised trials	serious[g]	not serious[h]	not serious	serious[f]	none	1739	1703	-	MD **2.31 days fewer** (3.85 fewer to 0.76 fewer)	⨁⨁◯◯ Low	IMPORTANT
Duration of ICU stay												
9	randomised trials	serious[i]	not serious	not serious	serious[f]	none	470	456	-	MD **2.06 days fewer** (3.61 fewer to 0.46 fewer)	⨁⨁◯◯ Low	IMPORTANT
Ventilator free days												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	usual care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	serious[c]	none	320	310	-	MD **2.9 days more** (0.95 more to 4.85 more)	⨁⨁⨁◯ Moderate	CRITICAL
ICU admission												
5	randomised trials	not serious	not serious	not serious	serious[b]	none	37/1133 (3.3%)	58/1144 (5.1%)	**RR 0.65** (0.43 to 0.97)	**18 fewer per 1,000** (from 29 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Explanations

a. Heterogenous definition of severity.
b. The confidence intervals include our 1% MID
c. Does not seem the optimal information size
d. Heterogenous definition of infections
e. Out outcome of interest was hyperglycemia requiring intervention, but most trials reported only hyperglycemia
f. The confidence intervals cross our MID in both directions
g. Statistically significant subgroup effect, with most benefit from high risk of bias trials.
h. Critical heterogeneity.
i. Although there was no statistically significant different in subgroups of risk of bias, most of the benefit is derived from three high risk of bias trials.

Study Characteristics and Severity Classification

Study	Trial registration	Country	Male (%)	Age	ICU (%)	Mechanical ventilation	Severity	CRP (mg/L)	Intervention	Number randomized
Lloyd 2019 (IMPROVe-GAP)	NCT02835040	Australia	57	76.1	10.5	NR	Non-severe [50% of patients with CORB scores <2]	88.2	Prednisone 50mg daily for 7 days	816

Gang 2016	NR	China	NR	NR	100	NR	Severe [Majority ICU patients]	NR	MP 80 mg daily for 7 days	58
Nafae 2013	NR	Egypt	56.2	49	NR	0	Severe [Based on baseline vitals indicating mean CORB score >2]	92.3	HCT 200 mg IV load, then 10 mg/hr IV infusion for 7 days	80
Sabry 2011	NCT01228110	Egypt	72.5	62.2	100	75	Severe [Majority ICU patients]	568.5	HCT 200 mg IV load, then 12.5 mg/hr IV infusion for 7 days	80
Confaloni eri 2005	NR	Italy	69.5	63.5	100	73.9	Severe [Majority ICU patients]	420	HCT 200 mg IV load, then 10 mg/hr IV infusion for 7 days	46
Mikami 2007	NR	Japan	74.2	72	0	0	Non-severe [PSI I-III >50%]	19.7	Prednisolone 40 mg IV daily for 3 days	31
Meijvis 2011 (Ovidius)	NCT00471640	Netherlands	56.5	63.6	0	0	Non-severe [PSI I-III >50%]	217	DXM 5 mg IV daily for 4 days	304
Witterma ns 2021	NCT01743755	Netherlands	67.4	67.5	0	0	Non-severe [PSI I-III >50%]*	204.5	DXM 6 mg PO daily for 4 days	401
Snijders 2010	NCT00170196	Netherlands	58.2	63.5	10.3	NR	Non-severe [PSI I-III >50%]^	235.9	Prednisolone 40 mg daily for 7 days (IV or PO)	213
El-Ghamraw y 2006	NR	Saudi Arabia	61.8	61.8	100	NR	Severe [Majority ICU patients]	NR	HCT 200 mg IV bolus, then 10 mg/hr IV infusion for 7 days	34
McHardy and Schonell 1972	NR	Scotland	48.4	60.3	0	NR	Non-severe [Defined by trials, most patients classified as mild-moderate]	NR	Prednisolone 5 mg every 6 hours for 7 days	126
Fernández Serrano 2011	ISRCTN22426306	Spain	66.7	61 (placebo),66 (MPDN)	0	0	Severe [Fine scores IV-V >50%]	NR	MP 200 mg IV bolus, then 20 mg IV every 6 hours for 3 days, then 20 mg IV every 12 hours for three days, then 20 mg IV for 3 days	45
Torres 2015	NCT00908713	Spain	61.4	65.3	75	2.5	Severe [PSI scores IV-V >50%]	258.7	MP 0.5 mg/kg every 12 hours for 5 days	120
Blum 2015 (STEP)	NCT00973154	Switzerland	62	74 (prednisone),73(placebo)	0	0	Non-severe [PSI I-III >50%]	161.5	Prednisone 5 mg PO daily for 7 days	785

Marik 1993	NR	UK	NR	36.44	100	NR	Severe [mean Apache II score 13, all ICU patients]	NR	HCT 10 mg/kg IV once, 30 min prior to antibiotics	30
Wagner 1956	NR	USA	67.3	NR	NR	NR	Non-severe [As defined by authors]	NR	HCT PO taper over 5 day (Starting with 200 mg/day, down to 2 mg/day)	113
Meduri 2022 (ESCAPe)	NCT01283009	USA	96	68.8	100	33	Severe [PSI scores IV-V >50%]	NR	MP 40 mg IV bolus, then 40 mg per day for 7 days, then taper for 20 days	584
Dequin 2023 (CAPE COD)	NCT02517489	France	69.4	67	100	22.2	Severe [PSI scores IV-V >50%]	250	HCT 200 mg IV daily for 4 days, then taper duration (8 or 14 days) determined by clinical criteria. HCT discontinued on ICU discharge.[+]	795

CORB = Confusion, Oxygenation, Respiratory Rate, and Blood Pressure Scale, DXM = dexamethasone, HCT = hydrocortisone, IV = intravenous, MP = methylprednisolone, NR = not reported, PO = per os (by mouth), PSI = Pneumonia Severity Index

* For mortality, we used in-study subgroups reported based on PSI scores (I-IV vs V)

^ For mortality, used in-study subgroups of PSI class IV/V vs I-III.

& For mortality, we used in-study subgroups of vasopressor only patients vs non-MV patients

[+] Methylprednisolone 40 mg IV bolus, then 40 mg per day for 7 days, then 20 mg per day for 7 days, then 12 mg per day for 3 days, then 4 mg per day for 3 days (IV infusion in ICU, then divided twice daily IV or PO after ICU discharge)

[+]The decision to shorten treatment assumed that all of the following criteria were present on day 4: patient breathing spontaneously; PaO2:FiO2 ratio greater than 200; Sequential Organ Failure Assessment (SOFA) score on day 4 less than or equal to SOFA score on day 1; high probability (as estimated by the clinician in charge) that the patient will be able to be discharged from the ICU on day 14. In all cases, treatment was discontinued upon discharge from the ICU.

Trials were defined as severe if 50% or more of participants had severe pneumonia scores (Pneumonia Severity Index of IV or V, CURB-65 scores of >=3, CORB scores of >=2, or SMART-COP scores of >=4) or if most patients were admitted to the ICU at the time of randomization or required intravenous continuous vasopressor therapy. Severe CAP is also defined by ATS/IDSA criteria in patients meeting at least one major criterion or 3 or more minor criteria, but this was not used in our analysis to classify severe CAP.

Summary of Judgements: Corticosteroid administration in hospitalized patients with community acquired pneumonia

More Severe

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of Recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**

○	○	○	○	✓

Less Severe

	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of Recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	✓	○	○

ROB Assessments

Study	Outcome	1) Bias arising from the randomization process	2) Bias due to deviations from the intended intervention	3) Bias due to missing outcome data	4) Bias in measurement of the outcome	5) Bias in selection of the reported results
Confalonieri et al. 2005	Duration of hospitalization	Low	Low	Low	Low	Low
El-Ghamrawy et al. 2006	Duration of hospitalization	Probably high	Probably high	Low	Low	Low
ESCAPe	Duration of hospitalization	Low	Low	Low	Low	Low
Fernández Serrano et al. 2011	Duration of hospitalization	Probably low	Low	Low	Low	Probably high
Gang et al. 2016	Duration of hospitalization	High	High	Probably high	Probably low	Probably high
IMPRoVE-GAP	Duration of hospitalization	Probably high	Probably high	Probably high	Low	Low
Mikami et al. 2007	Duration of hospitalization	Probably high	Probably high	Low	Probably high	Probably low
Nafae et al. 2013	Duration of hospitalization	Probably high	High	Low	Probably low	Probably low
Ovidius	Duration of hospitalization	Low	Low	Low	Low	Low
Snijders et al. 2010	Duration of hospitalization	Probably low	Low	Low	Low	Probably low
STEP	Duration of hospitalization	Low	Low	Low	Low	Low
Torres et al. 2015	Duration of hospitalization	Low	Low	Low	Low	Low
Wittermans et al. 2021	Duration of hospitalization	Low	Low	Low	Low	Low
Confalonieri et al. 2005	Duration of ICU	Low	Low	Low	Low	Low
ESCAPe	Duration of ICU	Low	Low	Low	Low	Low
Fernández Serrano et al. 2011	Duration of ICU	Probably low	Low	Low	Low	Probably high
IMPRoVE-GAP	Duration of ICU	Probably high	Probably high	Probably high	Low	Low
Marik et al. 1993	Duration of ICU	Probably high	Probably high	Low	Probably low	Probably high
Nafae et al. 2013	Duration of ICU	Probably high	High	Low	Probably low	Probably low
Ovidius	Duration of ICU	Low	Low	Low	Low	Low
STEP	Duration of ICU	Low	Low	Low	Low	Low
Torres et al. 2015	Duration of ICU	Low	Low	Low	Low	Low
Confalonieri et al. 2005	Gastrointestinal bleeding	Low	Low	Low	Low	Low
ESCAPe	Gastrointestinal bleeding	Low	Low	Low	Low	Low
Gang et al. 2016	Gastrointestinal bleeding	High	High	Probably high	Probably low	Probably high

IMPRoVE-GAP	Gastrointestinal bleeding	Probably high	Probably high	Probably high	Low	Low
IMPRoVE-GAP	Gastrointestinal bleeding	Probably high	Probably high	Probably high	Low	Low
Nafae et al. 2013	Gastrointestinal bleeding	Probably high	High	Low	Probably high	Probably low
Sabry et al. 2011	Gastrointestinal bleeding	Probably low	Low	Low	Low	Probably low
STEP	Gastrointestinal bleeding	Low	Low	Low	Low	Low
Torres et al. 2015	Gastrointestinal bleeding	Low	Low	Low	Low	Low
Wittermans et al. 2021	Gastrointestinal bleeding	Low	Low	Low	Low	Low
Confalonieri et al. 2005	Hyperglycemia	Low	Low	Low	Low	Low
ESCAPe	Hyperglycemia	Low	Low	Low	Low	Low
Gang et al. 2016	Hyperglycemia	High	High	Probably high	Probably low	Probably high
IMPRoVE-GAP	Hyperglycemia	Probably high	Probably high	Probably high	Low	Low
Nafae et al. 2013	Hyperglycemia	Probably high	High	Low	Probably high	Probably low
Ovidius	Hyperglycemia	Low	Low	Low	Low	Low
Snijders et al. 2010	Hyperglycemia	Probably low	Low	Low	Low	Probably low
STEP	Hyperglycemia	Low	Low	Low	Low	Low
Torres et al. 2015	Hyperglycemia	Low	Low	Low	Low	Low
Wagner et al. 1956	Hyperglycemia	Probably high	Probably high	Low	Low	Low
Wittermans et al. 2021	Hyperglycemia	Low	Low	Low	Low	Low
IMPRoVE-GAP	ICU admission	Probably high	Probably high	Probably high	Low	Low
STEP	ICU admission	Low	Low	Low	Low	Low
Confalonieri et al. 2005	Infections	Low	Low	Low	Low	Low
El-Ghamrawy et al. 2006	Infections	Probably high	Probably high	Low	Low	Low
Gang et al. 2016	Infections	High	High	Probably high	Probably low	Probably high
Mikami et al. 2007	Infections	Probably high	Probably high	Low	Probably high	Probably low
Ovidius	Infections	Low	Low	Low	Low	Low
Snijders et al. 2010	Infections	Probably low	Low	Low	Low	Probably low
STEP	Infections	Low	Low	Low	Low	Low
Torres et al. 2015	Infections	Low	Low	Low	Low	Low
Confalonieri et al. 2005	Invasive mechanical ventilation	Low	Low	Low	Low	Low
Fernández Serrano et al. 2011	Invasive mechanical ventilation	Probably low	Low	Low	Low	Probably high

IMPRoVE-GAP	Invasive mechanical ventilation	Probably high	Probably high	Probably high	Low	Low
Marik et al. 1993	Invasive mechanical ventilation	Probably high	Probably high	Low	Probably low	Probably high
Nafae et al. 2013	Invasive mechanical ventilation	Probably high	High	Low	Probably low	Probably high
Snijders et al. 2010	Invasive mechanical ventilation	Probably low	Low	Low	Low	Probably low
STEP	Invasive mechanical ventilation	Low	Low	Low	Low	Low
Torres et al. 2015	Invasive mechanical ventilation	Low	Low	Low	Low	Low
Confalonieri et al. 2005	Mortality	Low	Low	Low	Low	Low
El-Ghamrawy et al. 2006	Mortality	Probably high	Probably high	Low	Low	Low
ESCAPe	Mortality	Low	Low	Low	Low	Low
Fernández Serrano et al. 2011	Mortality	Probably low	Low	Low	Low	Probably high
Gang et al. 2016	Mortality	High	High	Probably high	Probably low	Probably high
IMPRoVE-GAP	Mortality	Probably high	Probably high	Probably high	Low	Low
Marik et al. 1993	Mortality	Probably high	Probably high	Low	Probably low	Probably high
McHardy and Schonell et al. 1972	Mortality	High	High	Low	Low	Probably high
Nafae et al. 2013	Mortality	Probably high	High	Low	Probably low	Probably low
Ovidius	Mortality	Low	Low	Low	Low	Low
Sabry et al. 2011	Mortality	Probably low	Low	Low	Low	Probably low
Snijders et al. 2010	Mortality	Probably low	Low	Low	Low	Probably low
STEP	Mortality	Low	Low	Low	Low	Low
Torres et al. 2015	Mortality	Low	Low	Low	Low	Low
Wagner et al. 1956	Mortality	Probably high	Probably high	Low	Low	Low
Wittermans et al. 2021	Mortality	Low	Low	Low	Low	Low
Confalonieri et al. 2005	Ventilator free days	Low	Low	Low	Low	Low
ESCAPe	Ventilator free days	Low	Low	Low	Low	Low