Contents lists available at ScienceDirect

Journal of Critical Care

Efficacy and safety of corticosteroids for the treatment of community-acquired pneumonia: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

ABSTRACT

Background: The role of corticosteroids in the treatment of community-acquired pneumonia (CAP) remains uncertain. We conducted an updated meta-analysis to investigate the effectiveness and potential effect modifiers of adjunctive corticosteroids in patients with CAP.

Methods: The protocol of this meta-analysis was registered with PROSPERO (CRD42022354920). We searched MEDLINE, Embase, the Cochrane Library and trial registers from inception till March 2023 to identify randomized controlled trials (RCTs) investigating corticosteroids in adult patients with CAP. Our primary outcome was the risk of all-cause mortality within 30 days after randomization (if not reported at day 30, we extracted the outcome closest to 30 days). Risk ratios (RR) and mean differences (MDs) were pooled under a random-effects model.

Results: Fifteen RCTs ($n = 3252$ patients) were included in this review. Corticosteroids reduced the risk of all-cause mortality in CAP patients (RR: 0.69, 95% CI: 0.53–0.89; high certainty). This significant result was restricted to hydrocortisone therapy and patients with severe CAP. Additionally, younger patients demonstrated a greater reduction in mortality. Corticosteroids reduced the incidence of shock and the need for mechanical ventilation (MV), and decreased the length of hospital and ICU stay (moderate certainty).

Conclusions: Corticosteroids reduce the risk of all-cause mortality, especially in younger patients receiving hydrocortisone, and probably decrease the need for MV, the incidence of shock, and the length of hospital and ICU stay in patients with CAP. Our findings indicate that patients with CAP, especially severe CAP, will benefit from adjunctive corticosteroid therapy.

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1. Introduction

Community-acquired pneumonia (CAP) is defined as the infection of the lung parenchyma occurring outside the hospital environment i.e., in the community. Despite therapeutic and medical advancements, CAP remains a major cause of morbidity and mortality worldwide. [1] It is the leading cause of infectious death in developed countries and is associated with increased hospitalization rates and significant health-care costs. [2,3] The clinical presentation varies from mild illness to severe CAP with an increased rate of complications, hospitalization, and a reported rate of mortality between 21% and 54%. [4]

Investigations have shown that the high mortality rate in CAP may be attributable to a cytokine-mediated uncontrolled inflammatory response. [5,6] This may be attenuated through the anti-inflammatory actions of corticosteroids. [2] Randomized controlled trials (RCTs) over several decades have compared the safety and efficacy of different corticosteroids (hydrocortisone, prednisolone, methylprednisolone, and dexamethasone) in the treatment of patients with CAP, and have shown a trend towards improved outcomes with corticosteroid administration. Despite some encouraging results, corticosteroid administration remains disputed since current guidelines present differing recommendations. The current American and British guidelines [7,8] do not endorse the routine use of corticosteroids for the management of patients with severe CAP. However, the European and Latin American guidelines [9] recommend the use of corticosteroids for severe CAP with concurrent shock, and the South African guidelines [10] recommend a combination of the standard of care and corticosteroids in patients with CAP who require admission in an ICU.

In the past, several systematic reviews and meta-analyses [5,11-14] investigated the use of corticosteroids for the treatment of patients with CAP with conflicting results, particularly in terms of mortality benefit; however, they are either outdated and/or do not include all eligible RCTs, or are biased by the inclusion of quasi-randomized trials and studies with bundled interventions. [12] In addition, the factors associated with the success or failure of corticosteroid therapy are not well characterized and have not been adequately explored in previous studies. The results from the largest trial conducted to date with a total of 800 patients, the CAPE COD trial, [15] have recently been released, demonstrating a significant reduction in mortality at 28 days with hydrocortisone use. Therefore, we aimed to perform an updated meta-analysis by including the CAPE COD trial to provide a better assessment of the safety and efficacy of the use of adjunctive corticosteroids in patients with CAP and explore potential factors that may modify the effectiveness of corticosteroid therapy.

2. Methods

This meta-analysis was performed according to the guidance presented in the *Cochrane Handbook for Systematic Reviews of Interventions* and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Supplementary Table 1). [16,17] The protocol was prospectively registered with PROSPERO (CRD42022354920).

2.1. Data sources and searches

We performed an electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Library), MEDLINE (via Ovid), Embase (Elsevier), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) portal from their inception to November 2022 (updated March 2023) using an extensive search strategy. We also screened reference lists of included studies and similar systematic reviews to identify further relevant studies. The detailed search strategy is included in Supplementary Table 2.

2.2. Eligibility criteria

The inclusion criteria were as follows: (1) study design: RCTs; (2) patient population: adults (>18 years of age) with CAP as defined by the trials; (3) intervention: corticosteroids irrespective of the type, dosing regimen or route of administration; and (4) comparator: placebo or standard of care.

The exclusion criteria were: (1) all study designs other than RCTs, such as quasi-randomized trials and observational studies; (2) studies conducted on animals or children; (3) trials evaluating corticosteroids as part of an intervention bundle; and (4) trials including COVID-19 patients No language or date restrictions were applied.

2.3. Study selection and data abstraction

The studies yielded by our search strategy were imported into Mendeley Desktop 1.19.8 (Mendeley Ltd., Amsterdam, The Netherlands) where duplicate articles were searched and removed. Two authors (MEUR and AS) thoroughly reviewed the full texts of the remaining articles and finalized studies that met the pre-specified eligibility criteria. In the event of any disagreements concerning study selection, a senior investigator (HAC) was consulted to facilitate discussion and resolution.

Data regarding study characteristics (including authors, study design, and diagnostic criteria), patient population (including age, gender, and severity of CAP), interventions (including type, dosage, and duration of drug administration), and primary and secondary outcomes were abstracted.

2.4. Outcomes

The primary outcome was the risk of all-cause mortality within 30 days after randomization (if not reported at day 30, we extracted the outcome closest to 30 days). The secondary outcomes included length of hospital stay, length of ICU stay, need for mechanical ventilation (MV), rate of clinical failure, development of shock (need for vasopressors), development of acute respiratory distress syndrome (ARDS), any adverse events (AEs), adverse cardiac events, gastrointestinal (GI) bleeding, hyperglycemia, secondary infection, and neuropsychiatric effects.

2.5. Risk of bias assessment

We used the revised Cochrane Risk of Bias Tool for RCTs (RoB 2.0) [18] to evaluate the risk of bias in the studies included in our analysis. RoB 2.0 assesses bias in five domains: (1) bias resulting from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Two investigators (AM and AE) evaluated the risk of bias for each included study as either high, low or some concerns of bias. Any discrepancies regarding the risk of bias assessment were settled by a senior investigator (HAC).

2.6. Data synthesis

Review Manager (RevMan, Version 5.4; The Cochrane Collaboration, Copenhagen, Denmark) was used to conduct the meta-analyses. For dichotomous outcomes, we extracted risk ratios (RRs) and corresponding 95% confidence interval (CI) from each trial. We reported continuous outcomes as mean difference (MD) along with 95% CI. We used a random-effects model to perform meta-analyses. The Chi-square test and the Higgins I^2 statistic were calculated to evaluate the statistical heterogeneity.

Publication bias was assessed visually in funnel plots for outcomes with >10 studies. We ran Egger's test to check funnel plot asymmetry

using Stata 17.0 (StataCorp LLC, College Station, Texas, USA). We performed a sensitivity analysis on the primary outcome by excluding studies at a high risk of bias to check the robustness of our results.

Subgroup analyses based on the type of corticosteroid used, the severity of CAP, and whether a loading dose was used or not were conducted for the primary outcome. Severe CAP was defined as Pneumonia Severity Index (PSI) ≥ 4 or equivalent. Trials that included patients with varying severity of pneumonia and did not provide a subgroup analysis for these patients were categorized as being of severe CAP if the mortality rate in the control arm was 9% or more, based on a PSI IV mortality rate of 9.3%. In addition, we conducted meta-regression using Stata 17.0 on the primary outcome with the mean age of the intervention group and the duration of therapy as the covariates. A *P*-value <0.05 was considered statistically significant for the test for subgroup differences.

2.7. Certainty of evidence assessment

Two authors (A.E and A.A.P) independently assessed the certainty of the evidence according to the five Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. [19,20] Each body of evidence was rated as being of high, moderate, low or very low certainty.

3. Results

After reviewing for eligibility, 15 studies were selected out of a total of 8207 through an extensive screening process outlined in the PRISMA Flowchart (Fig. 1). [15,21-34] A total of 3252 patients with severe or non-severe CAP were included. In these 15 RCTs conducted across 11 countries, 1829 patients received corticosteroid therapy and 1824 patients were assigned to the control group. Six RCTs evaluated hydrocortisone [15,21-23,25,34] while the rest used other types of corticosteroids. Seven RCTs included only patients with severe CAP, [15,21-26] three RCTs enrolled patients with both severe and non-severe CAP and provided data for these two subgroups separately, [28,29,32] and two RCTs were classified as being of severe CAP due to a mortality rate of $\geq 9\%$ in the control arm. [27,34] Further details of the study characteristics are shown in Table 1.

3.1. Risk of bias in included studies

Nine studies were found to be of low risk of bias and two studies were found to have some concerns of bias due to issues in the randomization process and selection of the reported results (Fig. 2). An inadequate randomization process, deviations from the intended interventions, and flawed measurement of the outcome led to a high risk of bias in four studies. The most common shortcoming of studies with a high risk of bias included the lack of blinding amongst participants and personnel delivering the intervention.

3.2. Effects of interventions

3.2.1. Primary outcome: all-cause mortality

Our meta-analysis shows a statistically significant association between corticosteroid treatment and a lower rate of all-cause mortality, compared with the control group (RR: 0.69, 95% CI: 0.53–0.89, *P*-value = 0.004; Fig. 3). The level of heterogeneity approximated was low (I^2 = 12%). Egger's test depicted no evidence of funnel plot asymmetry (*P*-value = 0.080; Supplementary Fig. S1). The overall quality of evidence was evaluated to be high due to the absence of any significant concerns in the GRADE domains (Table 2).

Sensitivity analysis, by excluding trials with a high risk of bias, did not change the results substantially (RR 0.69, 95% CI: 0.50–0.94; I^2 = 29%; Supplementary Fig. S2).
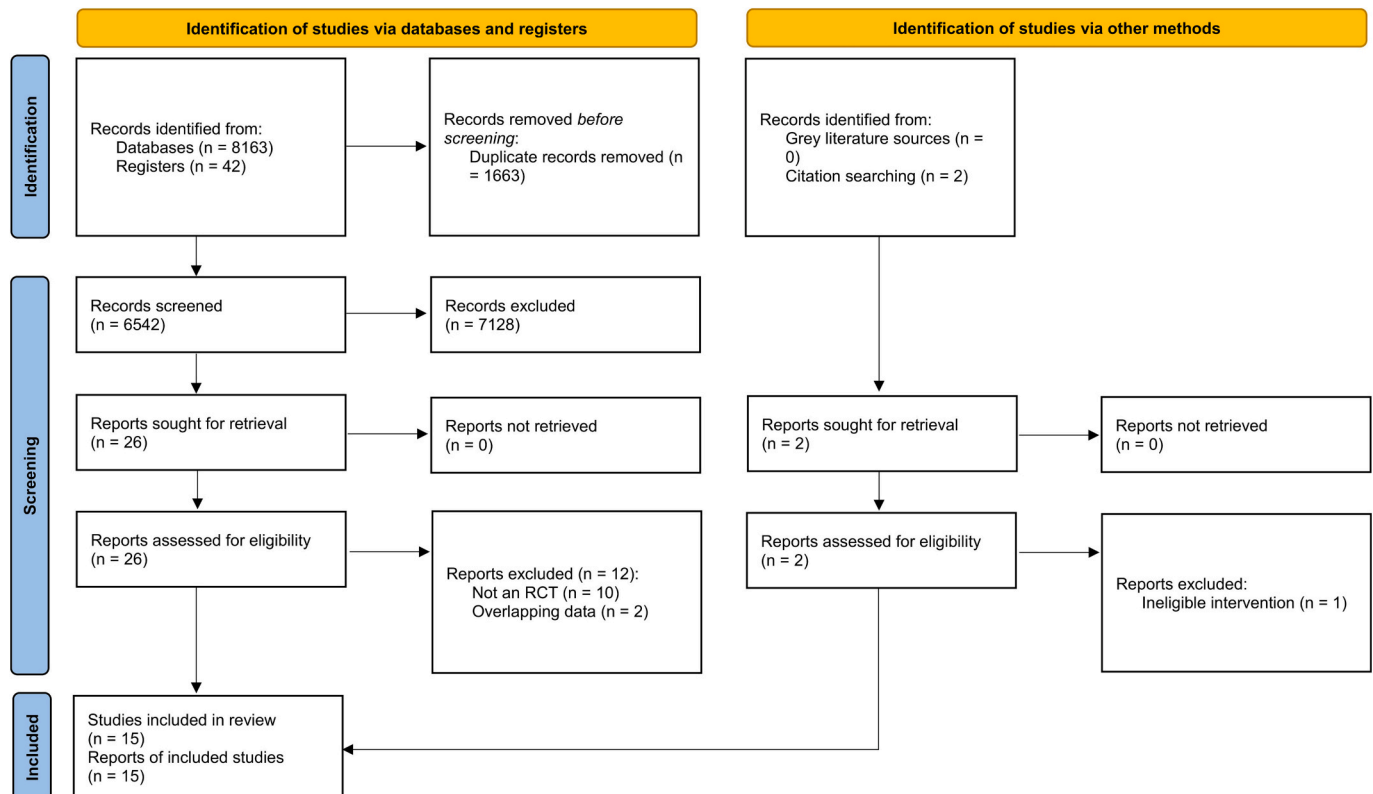

Fig. 1. PRISMA 2020 flowchart of the study selection process.

Table 1
Characteristics of the included studies.

Study ID	Country	Number of patients	Study Follow-up	Severity of pneumonia	Age (years) Mean (SD)	Male (%)	Patients not on MV at randomization, n (%)	Corticosteroid Type	Corticosteroid Dosage	Corticosteroid Duration (days)	Loading Dose
McHardy 1972 [27]	United Kingdom	126 (40 vs 86)	> 12 weeks	Severe CAP	62.3 vs 59.4	48.4	NR	Prednisolone	20 mg by mouth daily (5 mg/6 h)	7 days	No
Meduri 2022 [26]	USA	584 (297 vs 287)	12 months	Severe CAP	69 (10.8) vs 68.6 (11.1)	96.2	391 (67)	Methylprednisolone	IV 40 mg loading bolus was followed by 40 mg/day through day 7 and progressive tapering during the treatment course	20 days	Yes
Meijvis 2011 [30]	Netherlands	304 (151 vs 153)	1 month	Non-severe CAP	64.5 (18.7) vs 62.8 (18.2)	56.3	NR	Dexamethasone	Bolus of 5 mg followed by 5 mg IV dexamethasone daily	4 days	Yes
Mikami 2007 [31]	Japan	31 (15 vs 16)	NR	Non-severe CAP	75.9 (16.0) vs 68.4 (22.8)	74.2	NR	Prednisolone	IV 40 mg daily	3 days	No
Blum 2015 [32]	Switzerland	785 (392 vs 393)	1 month	Mixed	72.67 (16.3) vs 72 (15.56)	62	NR	Prednisone	Oral 50 mg daily	7 days	No
Confalonieri 2004 [22]	Italy	46 (23 vs 23)	2 months	Severe CAP	60.4 (17.3) vs 66.6 (14.7)	69.5	12 (26)	Hydrocortisone	IV 200 mg loading bolus followed by 10 mg/h infusion (240 mg in 500 cm^3 0.9% saline)	7 days	Yes
Fernández-Serrano 2011 [33]	Spain	45 (23 vs 22)	1 month	Non-severe CAP	58.3 (13.3) vs 61.67 (15.56)	NR	NR	Methylprednisolone	IV 200 mg bolus followed by a maintenance IV dose 20 mg/6 h for 3 days, then 20 mg/12 h for 3 days, and 20 mg/day for another 3 days.	10 days	Yes
Marik 1993 [25]	South Africa	30 (14 vs 16)	During hospitalization in ICU	Severe CAP	31.7 (12.8) vs 40.6 (14.7)	NR	NR	Hydrocortisone	IV single dose of 10 mg/kg	1 day	No
Nafae 2013 [34]	Egypt	80 (60 vs 20)	In hospitalization	Severe CAP	50.1 (13.3) vs 45.8 (13.1)	56.25	NR	Hydrocortisone	200 mg IV bolus then maintenance dose of 10 mg/h	7 days	Yes
Sabry 2011 [21]	Egypt	80 (40 vs 40)	8 days	Severe CAP	61.95 (6.97) vs 62.5 (4.26)	72.25	20 (25)	Hydrocortisone	200 mg IV bolus then maintenance dose of 12.5 mg/h	7 days	Yes
Snijders 2010 [28]	Netherlands	213 (104 vs 109)	30 days	Mixed	63.0 (17.9) vs 64.0 (18.7)	52.9 vs 63.3	NR	Prednisolone	40 mg of prednisolone oral or IV daily	7 days	No
Torres 2015 [24]	Spain	120 (61 vs 59)	In hospitalization	Severe CAP	64.5 (19.1) vs 66.1 (20.1)	57 vs 66	105 (88)	Methylprednisolone	IV bolus of 0.5 mg/kg/12 h	5 days	No
El-Ghamrawy 2006 [23]	Saudia Arabia	34 (17 vs 17)	In hospitalization	Severe CAP	62.9 (15.6) vs 60.6 (15.2)	NR	NR	Hydrocortisone	IV 200 mg bolus followed by maintenance IV dose 240 mg in 500 mL 0.9% saline at a rate of 10 mg/kg/h	7 days	Yes
Dequin 2023 [15]	France	795 (400 vs 395)	In hospitalization	Severe CAP	67.3 (14.1) vs 67.7 (14.8)	70.3 vs 68.6	442 (56)	Hydrocortisone	IV 200 mg continuous infusion daily	8–14 days	Yes
Wittermans 2021 [29]	Netherlands	401 (203 vs 198)	30 days	Mixed	66.9 (14.2) vs 65.6 (16.4)	57 vs 61	NR	Dexamethasone	Oral 6 mg once daily	4 days	No

MV: mechanical ventilation, CAP: Community-acquired pneumonia, NR: Not reported, SD: Standard Deviation.

Study ID	D1	D2	D3	D4	D5	Overall
Confalonieri 2004	+	+	+	+	+	+
Blum 2015	+	+	+	+	+	+
Dequin 2023	+	+	+	+	+	+
El Ghamrawy 2006	!	!	+	-	!	-
Fernandez-Serrano 2011	!	+	+	+	!	!
Marik 1993	-	-	+	-	!	-
McHardy 1972	!	-	+	+	!	-
Meduri 2022	+	+	+	+	+	+
Meijvis 2011	+	+	+	+	!	+
Mikami 2007	-	!	+	+	!	-
Nafae 2013	+	+	+	+	+	+
Sabry 2011	!	+	+	+	+	!
Snijders 2010	+	+	+	+	+	+
Torres 2015	+	+	+	+	+	+
Wittermans 2021	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Fig. 2. Quality assessment of included trials.

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Blum 2015	16	392	13	393	10.5%	1.23 [0.60, 2.53]
Confalonieri 2004	0	23	7	23	0.8%	0.07 [0.00, 1.10]
Dequin 2023	25	400	47	395	20.3%	0.53 [0.33, 0.84]
El-Ghamrawy 2006	3	17	6	17	4.1%	0.50 [0.15, 1.68]
Fernández-Serrano 2011	1	23	1	22	0.9%	0.96 [0.06, 14.37]
Marik 1993	1	14	3	16	1.4%	0.38 [0.04, 3.26]
McHardy 1972	3	40	9	86	3.9%	0.72 [0.20, 2.51]
Meduri 2022	47	286	50	277	27.6%	0.91 [0.63, 1.31]
Meijvis 2011	9	151	11	153	7.9%	0.83 [0.35, 1.94]
Nafae 2013	4	60	6	20	4.5%	0.22 [0.07, 0.71]
Sabry 2011	2	40	6	40	2.6%	0.33 [0.07, 1.55]
Snijders 2010	6	104	6	109	5.0%	1.05 [0.35, 3.15]
Torres 2015	6	61	9	59	6.3%	0.64 [0.24, 1.70]
Wittermans 2021	4	203	7	198	4.1%	0.56 [0.17, 1.87]
Total (95% CI)		**1814**		**1808**	**100.0%**	**0.69 [0.53, 0.89]**
Total events	127		181			

Heterogeneity: Tau² = 0.03; Chi² = 14.77, df = 13 (P = 0.32); I² = 12%
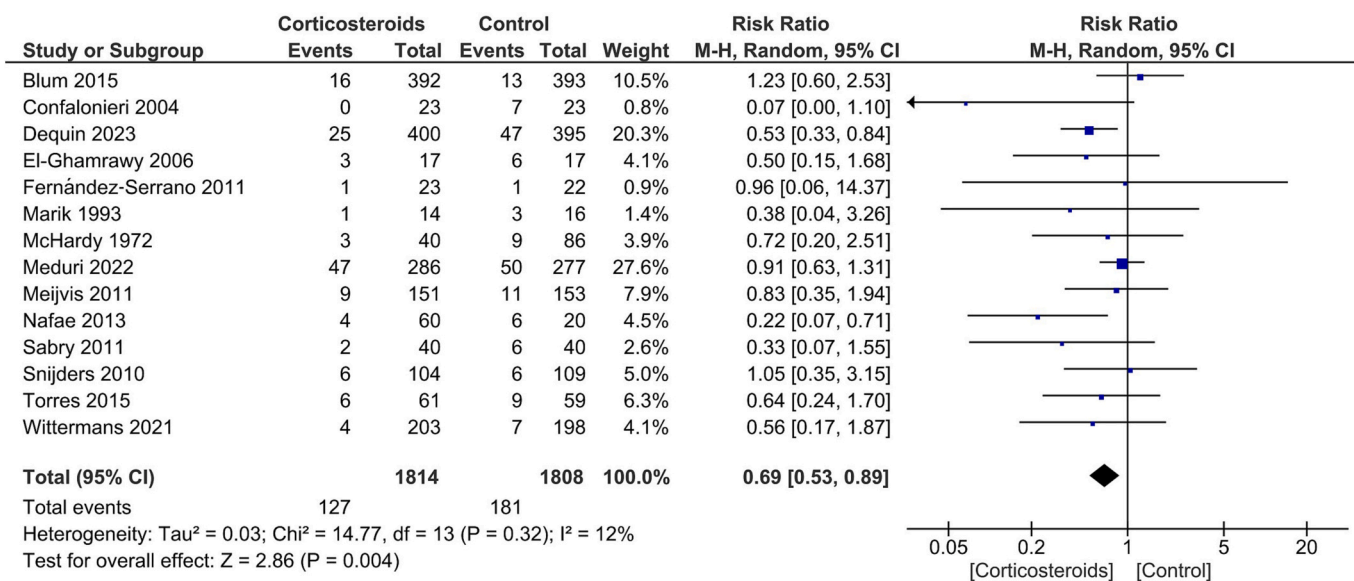Test for overall effect: Z = 2.86 (P = 0.004)

Fig. 3. Effect of corticosteroids on all-cause mortality in patients with community-acquired pneumonia.

3.3. Secondary outcomes

3.3.1. Length of hospital stay

The use of corticosteroids was associated with a statistically significant decrease in the length of hospital stay (MD -2.35 days, 95% CI: −3.70 to −1.00, *P*-value <0.001; Supplementary Fig. S3). A significantly high level of heterogeneity was observed ($I^2 = 93\%$). Egger's test depicted no funnel plot symmetry (*P*-value = 0.305; Supplementary Fig. S4). The overall quality of evidence was rendered as moderate due to concerns of inconsistency (Table 2).

3.3.2. Length of ICU stay

Our meta-analysis reported a statistically significant negative association between the length of ICU stay and the use of corticosteroids (MD -1.45 days, 95% CI: −2.51 to −0.39, *P*-value = 0.007; Supplementary Fig. S5). A considerably high level of heterogeneity was reported ($I^2 = 74\%$). There was no indication of funnel plot asymmetry (Egger's *P*-value = 0.380; Supplementary Fig. S6) The overall quality of evidence was rendered as moderate due to concerns of inconsistency (Table 2).

Table 2

Grading of recommendations assessment, development, and evaluation (GRADE) summary of findings.

Outcome	No. of participants (studies)	Effect estimates (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
All-cause mortality	3622 (14)	RR 0.69 (0.53–0.89)	Not serious	Not serious	Not serious	Not serious	Undetected	⊕ ⊕ ⊕ ⊕ HIGH
Length of hospital stay (days)	2643 (11)	MD -2.35 (−3.70 to −1.00)	Not serious	Serious	Not serious	Not serious	Undetected	⊕ ⊕ ⊕⊝ MODERATE
Length of ICU stay (days)	2791 (10)	MD -1.45 (−2.51 to −0.39)	Not serious	Serious	Not serious	Not serious	Undetected	⊕ ⊕ ⊕⊝ MODERATE
Need for MV	2388 (9)	RR 0.58 (0.42–0.81)	Not serious	Serious	Not serious	Not serious	NA	⊕ ⊕ ⊕⊝ MODERATE
Clinical failure	1164 (4)	RR 0.64 (0.35–1.18)	Not serious	Serious	Not serious	Serious	NA	⊕ ⊕ ⊝⊝ LOW
Shock (need for vasopressor)	1653 (8)	RR 0.37 (0.20–0.68)	Not serious	Serious	Not serious	Not serious	NA	⊕ ⊕ ⊕⊝ MODERATE
ARDS	1497 (5)	RR 0.42 (0.17–1.01)	Not serious	Not serious	Not serious	Serious	NA	⊕ ⊕ ⊕⊝ MODERATE
Any adverse events	2623 (8)	RR 0.96 (0.75–1.23)	Not serious	Serious	Not serious	Serious	NA	⊕ ⊕ ⊝⊝ LOW
Adverse cardiac events	1919 (6)	RR 0.84 (0.58–1.21)	Not serious	Not serious	Not serious	Serious	NA	⊕ ⊕ ⊕⊝ MODERATE
GI bleeding	2569 (9)	RR 0.89 (0.50–1.58)	Not serious	Not serious	Not serious	Serious	NA	⊕ ⊕ ⊕⊝ MODERATE
Hyperglycemia	2532 (8)	RR 1.54 (1.10–2.14)	Not serious	Not serious	Not serious	Not serious	NA	⊕ ⊕ ⊕ ⊕ HIGH
Secondary Infection	1993 (6)	RR 1.05 (0.65–1.68)	Not serious	Not serious	Not serious	Serious	NA	⊕ ⊕ ⊕⊝ MODERATE
Neuropsychiatric effects	1550 (5)	RR 1.61 (0.80–3.23)	Not serious	Not serious	Not serious	Serious	NA	⊕ ⊕ ⊕⊝ MODERATE

CI, confidence interval; MD, mean difference; RR, risk ratio.

3.3.3. Need for mechanical ventilation

Our analysis shows a statistically significant lower incidence of the need for mechanical ventilation in patients treated with corticosteroids in the treatment arm compared with the control group (RR: 0.58, 95% CI: 0.42–0.81, *P*-value = 0.002; Supplementary Fig. S7). A moderate level of heterogeneity was evaluated ($I^2 = 55\%$). The overall certainty of evidence was considered moderate due to concerns of inconsistency (Table 2).

3.3.4. Clinical failure

A statistically insignificant difference was found between the use of corticosteroids in the intervention arm and placebo in the control arm, for reducing the incidence of clinical failure (RR: 0.64, 95% CI: 0.35–1.18, *P*-value = 0.15; Supplementary Fig. S8). The associated level of heterogeneity was found to be high ($I^2 = 60\%$). The overall certainty of evidence was evaluated as low due to concerns of inconsistency and imprecision (Table 2).

3.3.5. Shock (Need for Vasopressors)

Our analysis reveals that the use of corticosteroids significantly reduced the need for vasopressors compared with the control group (RR: 0.37, 95% CI: 0.20–0.68, *P*-value = 0.001; Supplementary Fig. S9). A moderate level of heterogeneity was reported ($I^2 = 54\%$). The overall quality of evidence was assessed as moderate due to concerns related to inconsistency (Table 2).

3.3.6. ARDS

The use of corticosteroids did not show a statistically significant reduction in the incidence of ARDS compared with the control arm (RR: 0.42, 95% CI: 0.17–1.01, *P*-value = 0.05; Supplementary Fig. S10). A moderate level of heterogeneity was observed ($I^2 = 37\%$). The overall certainty of evidence was assessed as moderate as some concerns were related to imprecision (Table 2).

3.3.7. Any adverse events

There was no statistically significant difference in the incidence of adverse events between the two groups (RR: 0.96, 95% CI: 0.75–1.23, *P*-

value = 0.76; Supplementary Fig. S11). A moderate level of heterogeneity was observed ($I^2 = 66\%$). The overall certainty of evidence was considered low due to multiple concerns pertaining to inconsistency and imprecision (Table 2).

3.3.8. Adverse cardiac events

The use of corticosteroids did not significantly reduce the risk of adverse cardiac events compared with the control arm (RR: 0.84, 95% CI: 0.58–1.21, *P*-value = 0.34; Supplementary Fig. S12). No heterogeneity was reported in the results ($I^2 = 5\%$). The overall certainty of evidence was moderate as imprecision was the only concern observed (Table 2).

3.3.9. GI bleeding

Our analysis indicates that the use of corticosteroids had no statistically significant association with the risk of GI bleeding compared with the control group (RR: 0.89, 95% CI: 0.50–1.58, *P*-value = 0.69; Supplementary Fig. S13). No heterogeneity was reported in the results ($I^2 = 0\%$). The overall quality of evidence was graded as moderate due to concerns regarding imprecision (Table 2).

3.3.10. Hyperglycemia

The use of corticosteroids increased the risk of developing hyperglycemia (RR: 1.54, 95% CI: 1.10–2.14, *P*-value = 0.01; Supplementary Fig. S14). A moderate level of heterogeneity was indicated ($I^2 = 52\%$). The overall quality of evidence was graded as high due to the absence of concerns in any domain (Table 2).

3.3.11. Secondary infection

Our meta-analysis shows that no statistically significant difference was found between the corticosteroid and the control arms in the risk of secondary infections (RR: 1.05, 95% CI: 0.65–1.68, *P*-value = 0.85; Supplementary Fig. S15). A low level of heterogeneity was observed ($I^2 = 20\%$). The overall quality of evidence was graded as moderate due to some concerns regarding imprecision (Table 2).

3.3.12. Neuropsychiatric effects

Statistical analysis shows no significant association between the use of corticosteroids and neuropsychiatric effects (RR: 1.61, 95% CI: 0.80–3.23, *P*-value = 0.18; Supplementary Fig. S16). No heterogeneity was reported in the results ($I^2 = 0$%). The overall quality of evidence was evaluated as moderate as only some concerns were observed regarding the imprecision of the results (Table 2).

3.4. Subgroup and meta-regression analysis

3.4.1. Type of corticosteroid: hydrocortisone vs. other corticosteroids

Hydrocortisone reduced the risk of all-cause mortality (RR 0.44, 95% CI: 0.30–0.65; $I^2 = 0$%) but the other corticosteroids had no effect on mortality (RR 0.89, 95% CI: 0.69–1.16; $I^2 = 0$%; *P* for interaction = 0.004; Supplementary Fig. S17).

3.4.2. Severity of CAP: severe vs. non-severe

Corticosteroids reduced the risk of mortality in patients with severe CAP (RR 0.66, 95% CI: 0.50–0.87; $I^2 = 16$%) but had no effect in non-severe CAP (RR 0.87, 95% CI: 0.42–1.80; $I^2 = 0$%). However, the test for subgroup differences was not significant (*P* for interaction = 0.47; Supplementary Fig. S18).

3.4.3. Dosing of corticosteroids: loading dose vs. no loading dose

The effect of corticosteroids on mortality was consistent regardless of the use of a loading dose or not (*P* for interaction = 0.54; Supplementary Fig. S19).

3.4.4. Mean age of the intervention group

Corticosteroids were associated with a greater benefit in younger patients as with increasing age the mortality benefit moved closer to null (coefficient = 0.048, SE = 0.020; *P* = 0.016; Supplementary Fig. S20).

3.4.5. Duration of therapy

The length of therapy of corticosteroids did not modify the effect of corticosteroids on mortality (coefficient = 0.027, SE = 0.018; *P* = 0.137; Supplementary Fig. S21).

4. Discussion

In this updated meta-analysis including 3252 patients, high-quality evidence indicates a significant reduction in risk of all-cause mortality with corticosteroid use, particularly hydrocortisone, in patients with CAP. Concurrent with prior systematic reviews and meta-analyses, [5,11,13,14,35] adjunctive corticosteroid therapy likely reduces the need for vasopressors and MV. Corticosteroids probably also decrease the length of hospital and ICU stay. There were no statistically significant differences in terms of clinical failure, development of ARDS, total adverse events, adverse cardiac events, GI bleeding, secondary infection, and neuropsychiatric effects but corticosteroids were associated with a higher rate of hyperglycemia.

The pathogenesis of CAP is characterized by bacterial or viral respiratory pathogen-mediated inflammation and damage of lung parenchyma. [36] The severity of infection is primarily determined by the intensity of local and systemic inflammatory response. While non-severe CAP often has mild clinical manifestations including dyspnea and cough, severe CAP can progress to sepsis, ARDS, and multi-organ failure.

Our meta-analysis demonstrated a significant reduction in mortality risk with adjunctive corticosteroid therapy. These findings remained consistent when patients were stratified with respect to the use of a loading dose or not. Subgroup analysis according to the severity of CAP and the type of corticosteroid revealed that the mortality benefit with adjuvant corticosteroid therapy was more pronounced in severe CAP and patients receiving hydrocortisone. These findings corroborate those of a previous individual patient data meta-analysis which suggested a higher benefit of corticosteroids in patients with severe CAP. [5] The

beneficial effects of hydrocortisone are supported by the CAPE COD trial, [15] the largest trial conducted to date with a total of 800 patients, which demonstrated a lower risk of mortality at 28 days with hydrocortisone use. In contrast, two other large trials have found no reduction in all-cause mortality with methylprednisolone or prednisone therapy. [26,32] Owing to potent anti-inflammatory properties, adjunctive corticosteroid therapy is hypothesized to have a clinical benefit in ameliorating signs and symptoms, and improving the outcome of CAP, although the complete mechanism of action of steroids in CAP is still unknown. Differences in glucocorticoid activity on the intracellular glucocorticoid receptor numbers and the recovery of the hypothalamic-pituitary-adrenal axis by various agents may explain these findings. [37] Our results should be seen as hypothesis generating, which needs testing in further high-quality RCTs.

In contrast to our results, a recent meta-analysis found no evidence of reduced mortality with corticosteroid therapy. [12] This study included a trial which employed a quasi-randomization method, [38] and another trial which used an intervention bundle, consisting of corticosteroids and other treatments simultaneously, [39] making it difficult to isolate the effects of corticosteroids alone. Another recent meta-analysis demonstrated findings largely similar to ours; [14] however, it has several issues which have been highlighted since its publication including the exclusion of many important studies which biased the results of its subgroup analyses, and post hoc registration of the protocol. [40,41] To overcome these limitations, our meta-analysis focused exclusively on RCTs that employed rigorous randomization methods and studied the effects of corticosteroids as a standalone adjunctive intervention for community-acquired pneumonia. Our meta-analysis also incorporates results from the recent CAPE COD trial and all previously published eligible RCTs which has enhanced the power and reliability of our findings greatly. Moreover, we also investigated several factors that may influence the effectiveness of corticosteroids, such as patient age, disease severity, and duration of therapy. Notably, we found that the benefit of corticosteroids was more pronounced in younger patients. This suggests that age may play a crucial role in determining the efficacy of corticosteroid treatment. Nevertheless, the apparent mortality benefit associated with corticosteroid use in CAP should be interpreted with caution. Across trials, the risk of mortality has typically been assessed in heterogeneous populations including CAP due to varying pathogens and host factors in patients with differing comorbidities. As a result, there is a lack of clarity as to what subpopulation of CAP benefits the most from adjunctive steroid therapy. In future, RCTs designed with prognostic enrichment can potentially derive more statistically determinate results, by studying the effect of corticosteroid therapy in select subgroups more likely to benefit. [42]

The safety of corticosteroids has been a cause of concern pertaining to their use in clinical practice. Our meta-analysis reported no significant treatment-associated complications with corticosteroid use. Although the quality of evidence of these outcomes was mostly moderate to low, these results are in concordance with the findings of previous meta-analyses which attested to the safety of adjuvant corticosteroid treatment in patients hospitalized with CAP, [5,11,13,35] and also with the body of evidence generated during the COVID-19 pandemic on the use of corticosteroids. [43-45]

Clinical evidence has repeatedly identified hyperglycemia as a common adverse effect of corticosteroid therapy. Correspondingly, we found high-quality evidence suggesting an increased risk of hyperglycemia with corticosteroid use. Importantly, the increase in the incidence of hyperglycemia was not accompanied by long-term adverse outcomes and secondary infections. For the most part, the benefits of corticosteroids appear to outweigh the harm in patients with CAP.

Our meta-analysis has several strengths. We employed broad inclusion criteria making this the largest meta-analysis to date on this topic. Along with a strict study protocol, we also limited our analyses to the intention-to-treat population wherever possible. Data were collected from studies with a true randomization process only, thus, excluding any

potential confounding bias due to quasi-randomized studies. Additionally, we included multiple subgroup and meta-regression regression analyses to identify potential effect modifiers of the association between corticosteroid use and patient outcomes in CAP. Furthermore, we evaluated the quality of evidence using the GRADE approach to better understand the implications of our findings and the overall confidence in these results. Lastly, most of our included RCTs had a low risk of bias, and the sensitivity analysis showed that our results were not unduly influenced by the high risk of bias studies.

Our study also has limitations. Despite pooling the largest cumulative sample size to date, our estimates suffered from substantial imprecision as evident in our GRADE assessment and were likely underpowered for key outcomes. Therefore, large-scale RCTs are still required to strengthen the evidence base and to confirm or refute our findings. Additionally, differing routes of administration and varying doses of corticosteroids as well as heterogenous populations across the included studies are potential contributors to the high level of heterogeneity observed in certain outcomes. Moreover, since we did not have access to individual patient data, we were only able to explore a limited number of potential effect modifiers whereas others such as concomitant treatments or specific pathogen types may also be important. Finally, the findings of our subgroup analyses need to be interpreted with caution as these are observational in nature and require confirmation from randomized controlled data.

5. Conclusions

This updated meta-analysis of 3252 CAP patients shows that corticosteroids, particularly hydrocortisone, reduce the risk of all-cause mortality, especially in younger patients with a high disease burden. Corticosteroids probably decrease the need for MV, the need for vasopressors, and the length of hospital and ICU stay in patients with CAP. Our findings indicate that patients with CAP, especially those with severe CAP, will benefit from adjunctive corticosteroid therapy. Large-scale RCTs are required to investigate outcomes in subpopulations of interest.

Funding

No financial support was received for this study.

Human and animal participants

Research involving human participants and/or animals: No animals or human subjects were used in the current study.

Ethics approval and consent to participate

No ethical approval and informed consents were required for the purpose of the current study.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Huzaifa Ahmad Cheema: Conceptualization, Methodology, Formal analysis, Resources, Writing – review & editing, Project administration. **Adeena Musheer:** Methodology, Formal analysis, Resources, Writing – original draft. **Arooba Ejaz:** Formal analysis, Data curation, Writing – original draft. **Anousheh Awais Paracha:** Formal analysis, Investigation, Writing – original draft. **Abia Shahid:** Formal analysis, Investigation, Writing – original draft. **Mohammad Ebad Ur Rehman:** Validation, Writing – original draft. **Alaa Hamza Hermis:** Conceptualization, Investigation, Writing – review & editing. **Harpreet Singh:**

Methodology, Writing – review & editing, Visualization. **Natalie Duric:** Resources, Writing – review & editing. **Faran Ahmad:** Visualization, Writing – review & editing. **Sharjeel Ahmad:** Conceptualization, Writing – review & editing. **Antoni Torres:** Investigation, Writing – review & editing. **Tamas Szakmany:** Writing – review & editing, Supervision, Validation, Project administration.

Declaration of Competing Interest

A. Torres reports participation on Advisory Boards or lectures for Pfizer, GSK, MSD, Biomerieux, Biotest and Jansen. T Szakmany reports participation on Advisory Boards or lectures for PAION UK and ThermoFisher UK. The rest of the authors report no relationships that could be construed as a conflict of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154507.

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