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Glucocorticoids can reduce mortality in patients with severe community-acquired pneumonia: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Severe community-acquired pneumonia (sCAP) is associated with higher morbidity and mortality. The use of glucocorticoids to improve the prognosis of severe community-acquired pneumonia remains a topic of controversy.

Methods Following the guidelines given in the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA), we conducted a systematic review and meta-analysis to evaluate the effects of glucocorticoids on mortality and duration of mechanical ventilation in patients with sCAP. Randomized controlled studies investigating the use of glucocorticoids in the treatment of sCAP were extracted from PubMed, Embase, Cochrane Library, and Web of Science. Statistical analysis was performed to compare the differences in in-hospital mortality, mechanical ventilation duration, gastrointestinal bleeding, secondary infection, and other outcome measures between the glucocorticoid group and the control group.

Results A total of 8 studies involving 1769 patients were included in the analysis. The hospital mortality in the glucocorticoid group was significantly lower than that in the control group [8 studies, relative risk (RR) 0.59; 95% CI 0.47–0.76, $p < 0.01$. $I^2 = 25\%$, low certainty]. The duration of mechanical ventilation in the glucocorticoid group was significantly shorter than that in the control group [Mean Difference (MD) −3.08; 95% CI −4.96 to −1.19, $p < 0.01$; $I^2 = 0\%$, low certainty]. There was no significant difference in the incidence of gastrointestinal bleeding (RR 0.94; 95% CI 0.55–1.63, $p = 0.84$, $I^2 = 0\%$, low certainty) or secondary infection (RR 0.85; 95% CI 0.58–1.25, $p = 0.85$, $I^2 = 2\%$, moderate certainty) between the glucocorticoid group and the control group. In subgroup analysis, mortality was significantly lower in the hydrocortisone group compared to the control group (6.3% vs. 14.6%, RR 0.43; 95% CI 0.29–0.62, $p < 0.01$, $I^2 = 0\%$, very low certainty). However, there was no significant difference in mortality between the methylprednisolone group and the control group (15.6% vs. 19.9%, RR 0.78; 95% CI 0.57–1.08, $p = 0.14$, $I^2 = 0\%$, moderate certainty).

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Conclusion Glucocorticoids can reduce mortality in patients with sCAP, and the effect may vary depending on the type and the dose of glucocorticoids used. Additionally, glucocorticoid treatment can lead to a shorter duration of mechanical ventilation, as well as the length of ICU stay, without increasing the risk of gastrointestinal bleeding or secondary infection in patients with sCAP.

PROSPERO registration: CRD42023416525.

Keywords Pneumonia, Severe community-acquired pneumonia, Corticosteroids, Meta-analysis

Introduction

Community-acquired pneumonia (CAP) is a highly prevalent respiratory infectious disease. In the United States, more than 1.5 million adults are hospitalized with CAP each year [1]. The incidence of CAP typically ranges from 1 to 25 cases per 1000 inhabitants per year. In recent years, there has been a notable increase in hospitalization rates, particularly among older patients and those requiring intensive care, due to CAP. The case fatality rate of CAP varies based on factors such as the healthcare facility, geographic region, patient classification, and age, with rates ranging from 2 to 20% and reaching as high as 50% for patients admitted to the Intensive care unit (ICU) [2]. Severe community-acquired pneumonia often manifests alongside severe infection, shock, or respiratory failure, with mortality rates as high as 30% for patients requiring invasive mechanical ventilation and up to 40% for patients experiencing shock [3, 4].

Pneumonia induces profound lung and systemic inflammation, leading to impaired gas exchange, sepsis, organ failure, and an increased risk of death. Glucocorticoids possess potent anti-inflammatory and immunomodulatory properties that have the potential to mitigate the consequences of pneumonia. Numerous studies, including a meta-analysis conducted in 2022, have demonstrated that glucocorticoids can reduce mortality and improve outcomes in patients with CAP. Severe CAP (sCAP) is accepted terminology used to describe ICU-admitted patients with CAP as they might require organ support [5]. However, controversy persists regarding the efficacy of glucocorticoids specifically in the context of sCAP. While a meta-analysis from 2018 reported no improvements in outcomes with glucocorticoid use in sCAP. However, subsequent randomized controlled trials (RCTs) have produced conflicting findings, suggesting that glucocorticoids can reduce mortality and the need for mechanical ventilation in patients with sCAP. Consequently, whether glucocorticoids can improve the prognosis of sCAP and reduce mortality and the need for mechanical ventilation remains controversial.

To further assess the clinical efficacy of glucocorticoids in patients with sCAP, we conducted a meta-analysis to analyze whether hormone therapy could reduce mortality and improve prognosis in this patient population. Only randomized controlled trial (RCT) studies were included in this study.

Methods

Registration

Following the guidelines given in the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [6], we conducted a systematic review and meta-analysis to assess the effect of glucocorticoids on the prognosis of patients with sCAP. The project was registered on PROSPERO (CRD42023416525).

Information sources

A comprehensive literature search was performed in PubMed, Cochrane Library, Web of Science, EMBASE, and other relevant databases from their inception until April 29, 2023. Additionally, the references list of previously published systematic reviews was screened for potential studies.

Search strategy

The studies were identified using keywords such as "Pneumonia" "adrenocortical hormone" "prednisone" "hydrocortisone" "dexamethasone" "methylprednisolone" and others. The detailed search process is presented in Table S1.

Literature inclusion criteria

Only randomized controlled trials investigating the efficacy of glucocorticoid therapy for sCAP were included in this meta-analysis. Prospective observational studies, retrospective studies, case reports, and case series studies were excluded. Additionally, studies that could not provide extracted or replicable results were also excluded.

Patient inclusion criteria

The clinical diagnosis of CAP was established if any of 1, 3, or 2 of the following criteria was met, excluding conditions such as pulmonary tuberculosis, pulmonary neoplasms, noninfectious pulmonary interstitial diseases, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis.

1. Community morbidity.
2. Pneumonia-related clinical manifestations: (1) Recent cough, sputum, or aggravation of existing respiratory symptoms, with or without purulent sputum, chest pain, dyspnea, and hemoptysis; (2) fever; (3) signs of lung consolidation and/or smell and moist rales; (4) peripheral white blood cell count > 10 × 10^9/L or < 4 × 10^9/L, with or without nuclear a left shift.
3. Imaging examination of the chest revealing new patchy infiltrating shadows, leaf or segment consolidation shadows, ground glass opacities, or interstitial changes, with or without pleural effusion.

Diagnostic criteria for severe community-acquired pneumonia (meeting one of the following conditions):

1. Pneumonia Severity Index (PSI) > 130 (Fine class V) [7].
2. Patients with acute respiratory failure requiring mechanical ventilation (invasive or noninvasive) with PEEP ≥ 5cmH2O.
3. In patients receiving high-flow oxygen therapy, FiO2 ≥ 50%, PaO_2:FiO_2 < 300.
4. A partial rebreathing mask with an oxygen storage bag was used for oxygen therapy, 6L/min ≤ oxygen flow ≤ 10L/min, PaO2 < 30 × oxygen flow (mmHg); or oxygen flow > 10L/min, PaO2 < 300 mmHg.
5. Meeting one or more major criteria or three minor criteria according to the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) [8]:

Major criteria: ① Need for invasive mechanical ventilation; ②Septic shock is treated with vasoconstrictors.

Secondary criteria: ① Respiratory rate (RR) ≥30 times/min; ②Oxygenation index (PaO2/Fi02) ≤250; ③Multiple lobar infiltration; ④Hypothermia (T<36℃); ⑤ Leukopenia (WBC<4.0×10^9/L); ⑥Thrombocytopenia (Platelet < 10.0×10^9/L); ⑦ Hypotension, need strong fluid resuscitation; ⑧Disturbance of consciousness/Disorientation; ⑨Azotemia (BUN≥20mg/dL).

Patient exclusion criteria

1. Age < 18 years;
2. Previous systemic corticosteroid therapy;
3. Aspiration or nosocomial pneumonia;
4. Severe immunosuppression;
5. Active tuberculosis, fungal infection, or cystic fibrosis;
6. Pre-existing health condition with a life expectancy of less than 3 months;
7. Pregnancy;
8. Allergic to corticosteroids;
9. Uncontrolled diabetes;
10. History of hemorrhage within the past 3 months.

Study selection and data extraction

Two independent reviewers (Gu and Yang) performed a literature search and screening. In cases of inconsistencies during the data screening and extraction process, conflicts were resolved through group discussions and consultations with Professor Chen QH. Initially, duplicate literature was removed by the reviewers, then the reviewers assessed the relevance of studies based on their titles and abstracts, eliminating irrelevant ones. Finally, the full texts of the remaining studies were read for further screening. The following information was extracted from the studies: mortality rate, duration of mechanical ventilation, duration of no mechanical ventilation at 28 days, duration of mechanical ventilation at 8 days, length of hospital stay, length of ICU stay, and incidence of adverse events (gastrointestinal bleeding, hyperglycemia, and infection), Glucocorticoid type, dose, timing and whether to tapering. Since different studies reported mortality rates at various periods (28-day mortality rate, 30-day mortality rate, 60-day mortality rate, 90-day mortality rate, ICU mortality rate, and in-hospital mortality rate), we analyzed the in-hospital mortality rate. If extracting the inpatient mortality rate proved difficult, we extracted the 28-day or 30-day mortality rate. To calculate the cumulative dose of corticosteroids, we converted all types of corticosteroids to the equivalent dose of hydrocortisone. Finally, if continuous variables were reported as the median and interquartile range (IQR), they were converted to mean and standard deviation [9, 10].

Outcomes

Primary outcome: mortality rate.

Secondary outcomes: duration of mechanical ventilation, duration of no mechanical ventilation at 28 days, proportion of mechanical ventilation at day 8, length of hospital stay, length of ICU stay, and occurrence of adverse events (gastrointestinal bleeding, hyperglycemia, and infection).

Risk of bias assessment and quality evaluation

All studies were assessed for risk of bias (RoB) using the Risk of Bias 2 (RoB2) tool [11]. Additionally, a Grading of Recommendations Assessment Development and Evaluation (GRADE) was performed [12]. Funnel plots were used to assess publication bias.

Statistics

Data analysis was conducted by two researchers. Meta-analysis was performed using Mantel–Haenszel statistics and inverse variance models. The Review Manager 5.3 software was used for outcome data analysis. The inverse variance model determined the study weights. Relative risk was calculated for dichotomous variables such as mortality. Mean, standard deviation (SD), and 95% confidence intervals (CI) were calculated for continuous variables. Homogeneity was evaluated using the χ^2 test, I^2, where $I^2 \geq 50\%$ indicated high heterogeneity. In cases of high heterogeneity, a random-effects model was used. For primary mortality outcomes, sequential research was conducted to assess if the sample size was sufficient. Trial sequential analysis (TSA) was performed, and the required information size was based on a type I error of 5%, and a beta of 20%. According to the 8 studies we included, the mortality rates were 13%, 15.2%, 26.5%,10%, 12.5%, 8.9%, 10.7%, and 9.1%, respectively. The use of glucocorticoids reduced the mortality rate by about 10%; Therefore, in our TSA, the event occurrence rate is set to 10%, relative risk reduction (RRR) = 20%.

Subgroup analysis and sensitivity analysis

Sensitivity analysis was performed for clinical studies suspected of involving severe community-acquired pneumonia but with uncertain inclusion criteria. Different classes of hormones may affect the prognosis of patients. Therefore, a subgroup analysis of mortality was conducted in patients receiving different glucocorticoid classes. Taking into account the different therapeutic doses of hormones received, the different duration of hormone therapy, and whether hormones are reduced during use may affect the patient's prognosis. We, therefore, performed subgroup analyses of mortality among patients receiving different therapeutic doses of hormones, different durations of hormone therapy, and whether hormones were reduced during use.

Results

A total of 15,973 literature records were retrieved from PubMed ($n = 2074$), Embase ($n = 2549$), Web of SCI ($n = 8556$), and Cochrane Library ($n = 2749$). After removing duplicate literature, a total of 9,345 records were further processed. Following the assessment of titles and abstracts, literature not related to the corticosteroid-assisted treatment of sCAP was excluded. Based on the inclusion and exclusion criteria, a total of 8 RCTs were included in the meta-analysis (Fig. 1).

The included studies were conducted in various countries, including Saudi Arabia [13], USA [13], Italy [14], Egypt [15, 16], Spain [17], United States [18], and France [19]. Among the study sites, 4 [13, 14, 16, 20] were in the ICU, while 4 [15, 17–19] were in mixed wards. Six [13–17, 20] of the seven studies used hydrocortisone and two [18, 19] studies used methylprednisolone (Table 1, Table S2).

Three RCTs [13, 16, 17] had an unclear risk of bias in the randomization process, and one RCT[14] had an unclear risk of bias in the measurement of the outcomes. The other four RCTs [15, 18–20] had a low risk of bias in all domains (Fig. 2, Table 2).

Primary outcomes

All studies reported mortality, among them, Marik's study in 1993 [14], EI Ghamrawy's study in 2006 [13], Confalonierial's study in 2005 [15], Nafae's study in 2013 [17], Torres' study in 2015 [18], and Meduri's study in 2022 [19] reported the hospital mortality rate. Sabry study in 2011 [16] reported the mortality rate on the eighth day. Dequin PF's study in 2023 reported the 28-day mortality rate [20]. Compared to patients in the control group, the corticosteroids group had a lower mortality risk (8 studies, RR 0.59; 95% CI 0.47–0.76, $p < 0.01$, $I^2 = 25\%$, low certainty) (Fig. 3A, Table S3). While the funnel plot exhibited asymmetry, suggesting potential publication bias, the trim and fill method nonetheless confirmed a lower mortality risk in the glucocorticoid group compared to the control group (RR 0.68; 95% CI 0.54–0.86, $p < 0.01$, $I^2 = 35\%$) (Fig. 3B, C). The Z-curve in this experiment crossed the boundary between continuous monitoring and routine ineffectiveness. This suggests that despite falling short of the target sample size ($n = 4780$), the study provides evidence for glucocorticoid's potential to reduce mortality in severe community-acquired pneumonia patients (Fig. 4).

Secondary outcomes

Mechanical ventilation duration and mechanical ventilation on the 8th day

The duration of mechanical ventilation was reported in only 3 [15, 17, 19] out of the 8 studies, and a statistical difference was observed in the duration of mechanical ventilation between patients receiving adjuvant corticosteroid therapy and those receiving standard care alone (MD—3.08; 95% CI −0.496 to −1.19, $p < 0.01$; $I^2 = 0\%$, low certainty (Fig. 5, Table S3). Three studies [15–17] reported mechanical ventilation on day 8, there was no statistical difference between patients who received adjuvant corticosteroid therapy and those who received standard therapy alone. (RR 0.57; 95% CI 0.32–1.00, $p = 0.05$, $I^2 = 63\%$, very low certainty) (Fig. S1, Table S3).

Length of hospital stay and length of ICU stay

The length of hospital stay was reported in four studies [15, 17–19], and there was no statistically significant

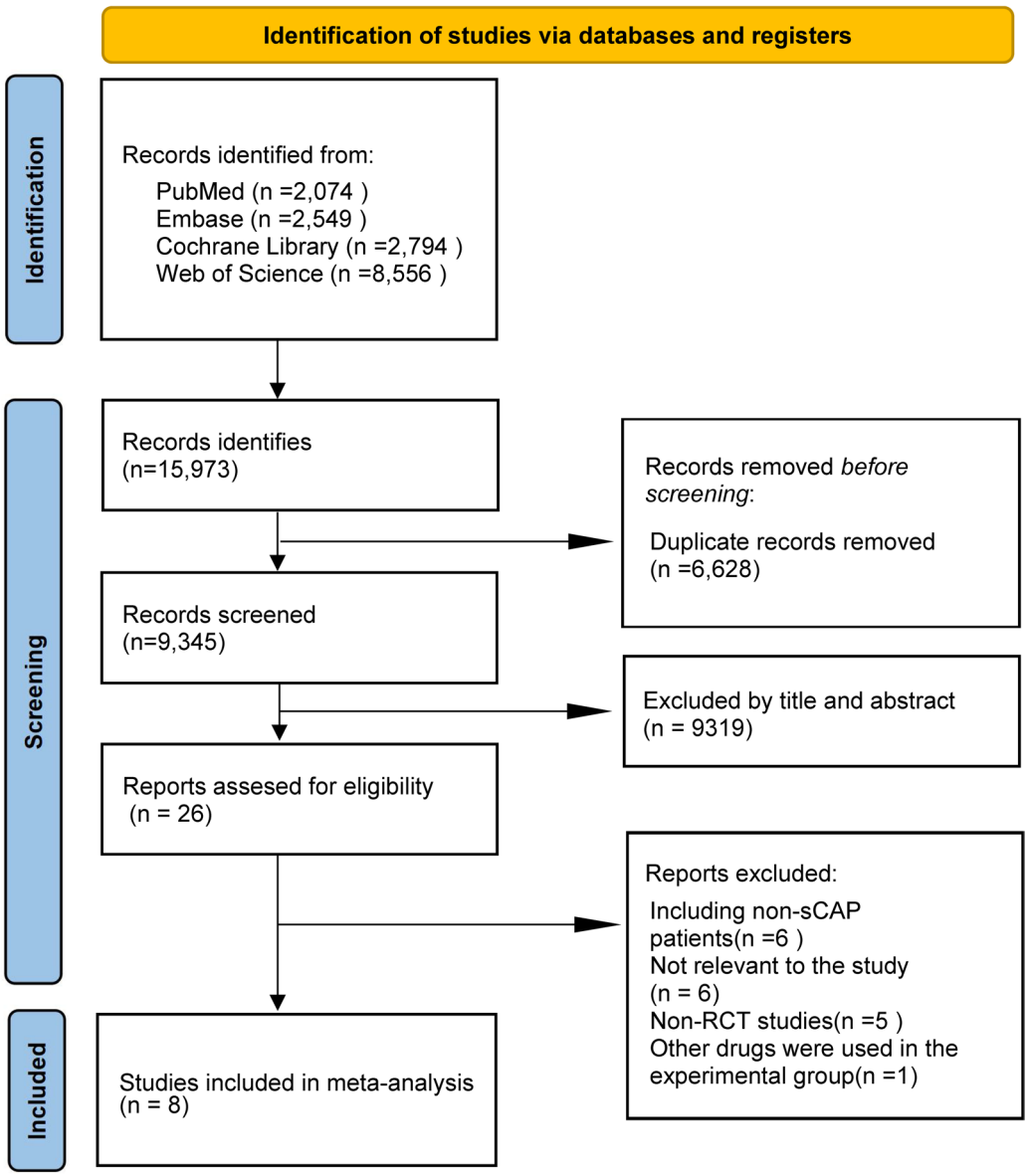


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow chart showing included and excluded trials

difference in the length of hospital stay between patients receiving adjuvant corticosteroid therapy and those receiving standard care alone (MD −3.09; 95% CI −7.39 to 1.21, $p=0.16$, $I^2=95\%$, moderate certainty) (Fig. S2, Table S3). The length of stay in the ICU was reported in six studies [14, 15, 17–20], there was a statistically significant difference in the length of stay in the ICU among patients receiving adjuvant corticosteroid therapy compared with those receiving standard care alone (MD −1.16; 95% CI −1.61 to 0.71, $p<0.01$, $I^2=0\%$, moderate certainty) (Fig. S3A, Table S3). Although the funnel plot showed asymmetry, confirmed by the trim and fill method that there was a statistical difference in the length of ICU stay in the glucocorticoid group compared with the control group (MD −0.88; 95% CI −1.33 to 0.43, $p<0.01$, $I^2=2\%$) (Fig. S3B, Fig. S3 C).

Intubation rate

Only one study [20] reported the cumulative incidence of weather-tube intubation at 28 days in patients who did not receive endotracheal intubation at baseline [60/308(19.5%) vs. 86/310(27.7%)].

Table 1 Baseline characteristics of selected trials

Trials	Country	Participants	Methods	Intervention	Cumulative hydrocortisone equivalent dose (mg)[a]
Marik 1993	USA	30 total patients, 16 control group patients, and 14 steroids group patients. Age: control group 40.6 ± 14.7 years steroids group 31.7 ± 12.8 years APACHE II score: control group 14.2 ± 6.4 steroids group 11.2 ± 1.96	RCT	Hydrocortisone Single dose 10 mg/kg	700
Confalonierial 2005	Italy	46 total patients, 23 control group patients, and 23 steroids group patients. Age: control group 66.6 ± 4.7 years steroids group 60.4 ± 17.3 years Male: control group 65%, steroids group 74% APACHE II score: control group 18.2 ± 4.0 steroids group 17.2 ± 4.1	RCT	Hydrocortisone 7 d IV 200 mg bolus followed by infusion at a rate of 10 mg/hour	1880
El Ghamrawy 2006	Saudi Arabia	34 total patients, 17 control group patients, and 17 steroids group patients. Age: control group 60.6(15.2) years steroids group 62.9 (15.6) years	RCT	Hydrocortisone 7 d loading dose of 200 mg, followed by 240 mg/day	1880
Sabry 2011	Egypt	80 total patients, 40 control group patients, and 40 steroids group patients. Age: control group 62.5(4.26) years steroids group 61.95(6.97)years Male: control group 70% steroids group 75% Average SOFA sccore(SD): control group 8.2(1.46) steroids group 8.5(1.52)	RCT	Hydrocortisone 7 d loading dose of 200 mg over 30 min, followed by 300 mg/day	2300
Nafae 2013	Egypt	80 total patients, 20 control group patients, and 60 steroids group patients. Age: control group 45.8 ± 13.1 years steroids group 50.1 ± 13.3 years Male:control group 65% steroids group 53%	RCT	Hydrocortisone 7 d 200 mg IV once (only at day 1) then 10 mg/h IV infusion	1880
Torres 2015	Spain	120 total patients, 59 control group patients, and 61 steroids group patients. Age: control group 66.1 (20.1) years steroids group 64.5 (19.1) years Male:control group 66% steroids group 57%	RCT	Methylprednisolone 5 d 0.5 mg/kg BD	875
Meduri (ESCAPeStudy)2022	United States	563 total patients, 277 control group patients, and 286 steroids group patients. Age: control group 68.6 ± 11.1 years steroids group 69 ± 10.8 years Male:control group 95% steroids group 97% APACHE III score: control group 53.4 ± 28.7 steroids group 54.3 ± 29.4 Average SOFA sccore(SD): control group 6.29 ± 2.85 steroids group 6.68 ± 3	RCT	Methylprednisolone 20 d 7 days of full dose (40 mg/day), 7 days of half dose (20 mg/day), and 6 days of tapering doses (12 mg/day and 4 mg/day)	2340
P.-F. Dequin 2023	France	795 total patients, 395 control group patients, and 400 steroids group patients. Age: control group 67 (58–78) years steroids group 67 (58–77) years Male:control group 69% steroids group 70% Average SOFA sccore(SD): control group 4 (3–6) steroids group 4 (3–6)	RCT	Hydrocortisone 8d or 14d 200 mg daily for either 4 or 8 days as determined by clinical improvement, followed by tapering for a total of 8 or 14 days	1100 or 1950

RCT randomized controlled trial

[a] Corticosteroid converted to hydrocortisone equivalent dose for 70 kg adult (where prescribed per kilogram of body weight)

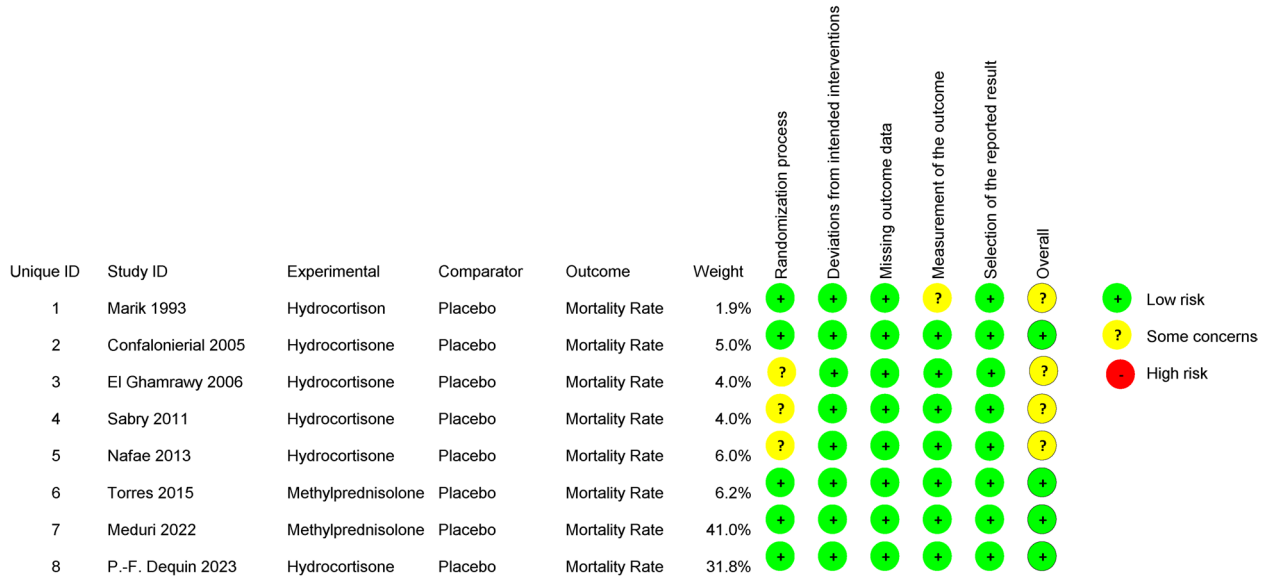


Fig. 2 Risk of bias summary. Review of authors' judgments on the risk of bias items in each included study. The overall risk of bias for each study was determined as follows: If all domains were deemed low risk of bias, then the study was adjusted to be low risk. If there were some concerns in any domain, then the study was adjudged to be of some concern.If any domain was high risk of bias, or some concerns in multiple domains, then the overall risk of bias was deemed high risk

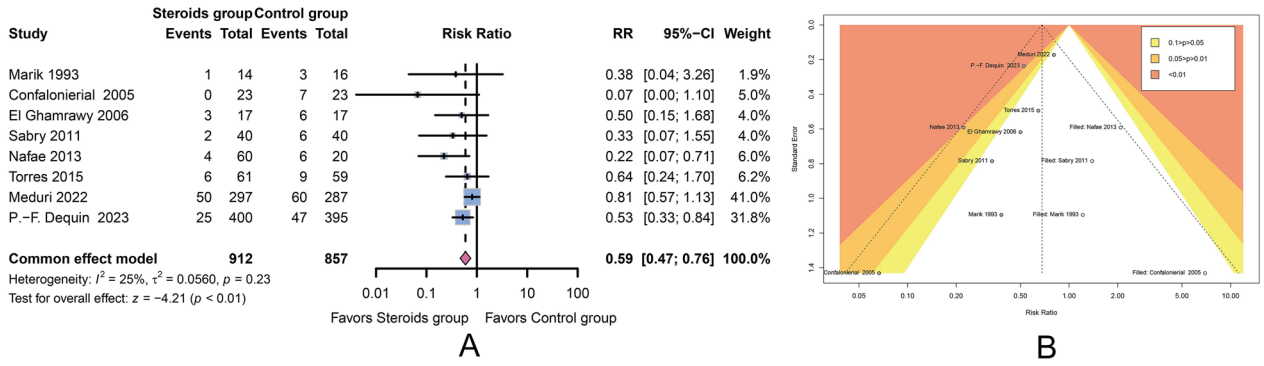
Table 2 Risk of bias summary

Study	Experimental	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Marik 1993	Hydrocortison	Placebo	Low	Low	Low	Some concerns	Low	Some concerns
Confalonierial 2005	Hydrocortisone	Placebo	Low	Low	Low	Low	Low	Low
El Ghamrawy 2006	Hydrocortisone	Placebo	Some concerns	Low	Low	Low	Low	Some concerns
Sabry 2011	Hydrocortisone	Placebo	Some concerns	Low	Low	Low	Low	Some concerns
Nafae 2013	Hydrocortisone	Placebo	Some concerns	Low	Low	Low	Low	Some concerns
Torres 2015	Methylpredni-solone	Placebo	Low	Low	Low	Low	Low	Low
Meduri 2022	Methylpredni-solone	Placebo	Low	Low	Low	Low	Low	Low
P.-F. Dequin 2023	Hydrocortisone	Placebo	Low	Low	Low	Low	Low	Low

Review of authors' judgments on the risk of bias items in each included study

Adverse event

Hyperglycemia was reported in four trials [17–20]. Corticosteroid use was associated with an increased incidence of new hyperglycemic events compared to standard treatment (37.5% vs. 29.6%, RR 1.28; 95% CI 1.12–1.46, $p=0.0002$, $I^2=0\%$, moderate certainty) (Fig. S4, Table S3). There was no increased risk of gastrointestinal bleeding (reported in 7 trials [13, 15–20]) (RR 0.94; 95% CI 0.55–1.63, $p=0.84$, $I^2=0\%$, low certainty) (Fig. S5A, Table S3). There was no significant publication bias found in the risk of gastrointestinal bleeding, it was found that there was no increased risk of gastrointestinal bleeding compared with the control group after confirmed by the trim and fill method (RR 0.97; 95% CI 0.56–1.70, $p=0.92$, $I^2=0\%$) (Fig. S5B, Fig. S5C). Additionally, there was no increased risk of secondary infection (4 trials [13, 15, 18, 20]) (RR 0.85; 95% CI 0.58 –1.25, $p=0.41$, $I^2=2\%$, moderate certainty) (Fig. S6, Table S3).



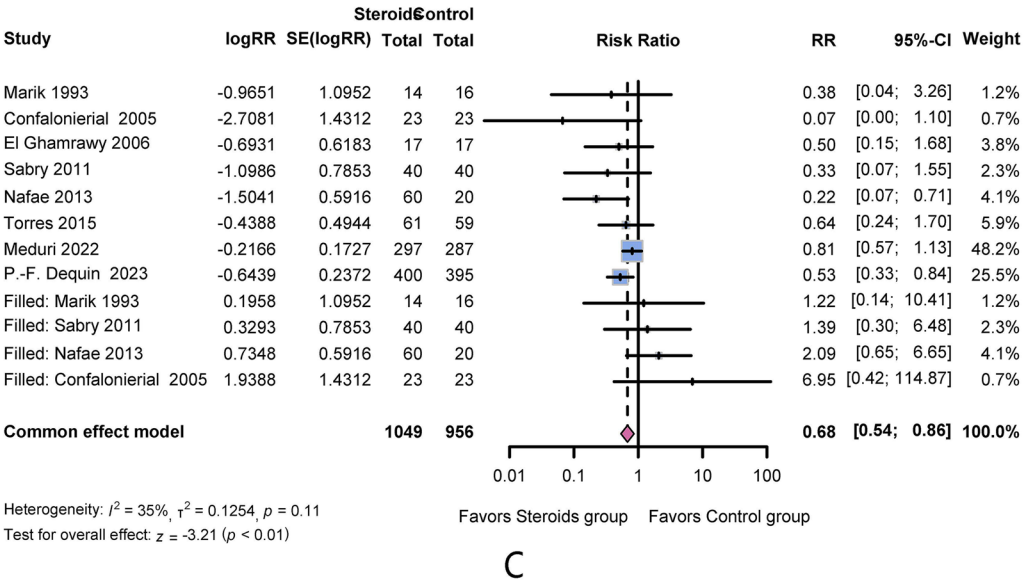


Fig. 3 **A** Forest plot of mortality between the corticosteroids group and the control group. **B** The funnel graph of mortality risk. **C** Forest plot of mortality between the corticosteroids group and the control group confirmed by trim and fill method. *CI* confidence interval, *RR* risk ratio

Sensitivity analysis

In the study conducted by Nafae RM et al. [17], the main study site was the ICU. However, considering the inclusion criteria of the population in their study, we have strong doubts about whether patients with sCAP were included. Therefore, we performed a sensitivity analysis, excluding this study. After excluding Nafae RM et al.'s study, a total of 852 patients receiving standard therapy were compared with 837 patients receiving standard therapy. The analysis revealed a significant difference in mortality between the two groups (10.2% vs. 16.5%, RR 0.62; 95% CI 0.48–0.79, $p < 0.01$, $I^2 = 3\%$, low certainty) (Fig. S7A, Table S3). Although the funnel plot showed asymmetry, confirmed by the trim and fill method that there was a statistical difference in mortality rate in the glucocorticoid group compared with the control group (RR 0.69; 95% CI −0.54 to 0.88, $p < 0.01$, $I^2 = 3\%$) (Fig. S7B, Fig. S7C).

Subgroup analysis

Subgroup analysis was conducted to investigate the effects of different glucocorticoids on the prognosis of patients. There was a significant difference in mortality among 554 patients treated with hydrocortisone [13–17, 20] compared to 511 patients treated with standard care (6.3% vs. 14.7%, RR 0.43; 95% CI 0.29–0.62, $p < 0.01$, $I^2 = 0\%$, very low certainty) (Fig. S8A, Table S3). It was found that the hydrocortisone group still had a lower mortality risk compared with the control group after confirmed by the trim and fill method (RR 0.52; 95% CI 0.36–0.73, $p < 0.01$, $I^2 = 9\%$) (Fig. S8B). However, there was no significant difference in mortality among 358 patients treated with

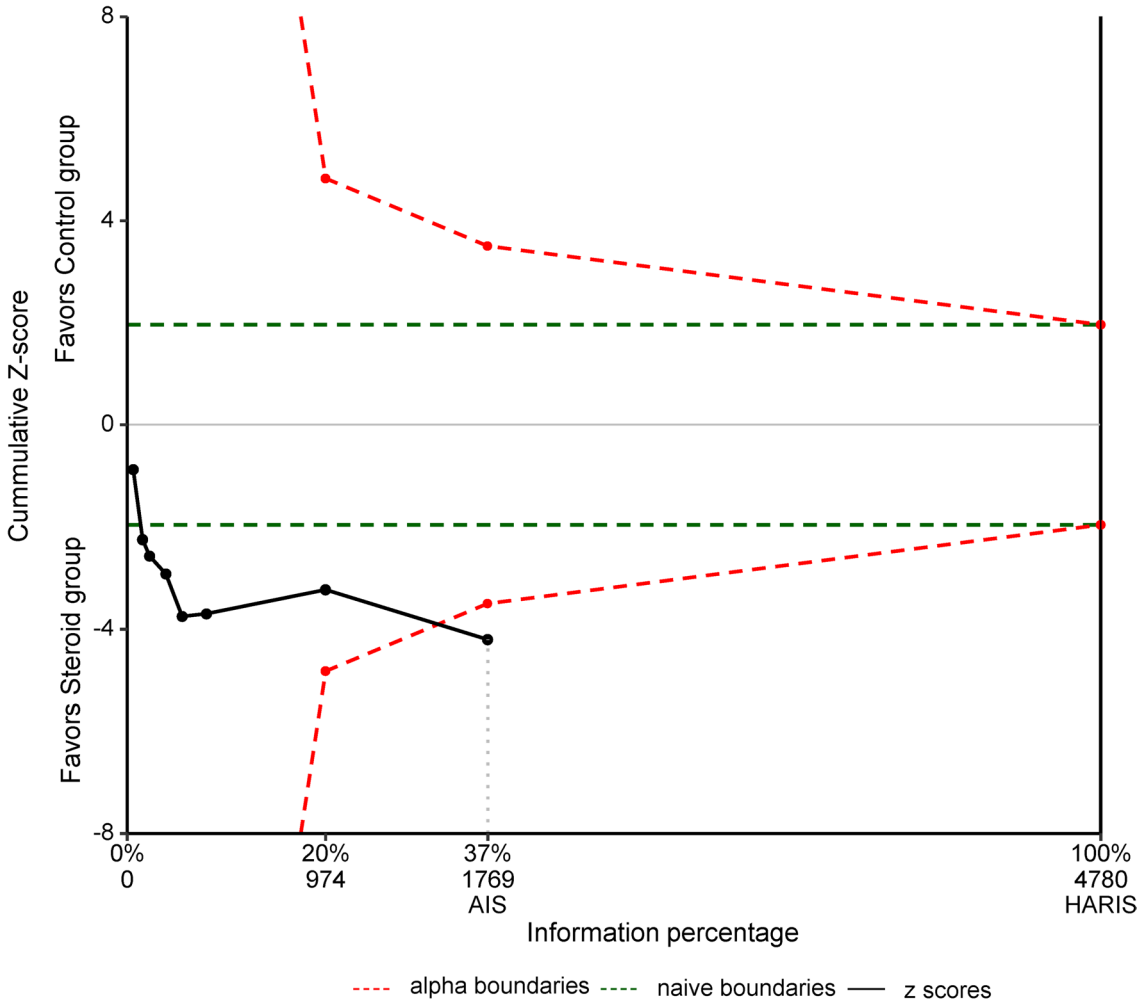


Fig. 4 Line graph showing trial sequential analysis for all-cause mortality in included randomized controlled trials. The uppermost and lowermost curves represent trial sequential monitoring boundary lines for benefit and harm, respectively. Horizontal lines represent traditional boundaries for statistical significance. The cumulative z-curve represents the trial data. The Z-curve crosses the boundaries of continuous monitoring and routine ineffectiveness in the experiment, indicating that although the sample size did not reach the required amount ($n = 4780$) of information, glucocorticoid has been shown to reduce the mortality rate of severe community-acquired pneumonia patients. *TSA* Trial Sequential Analysis

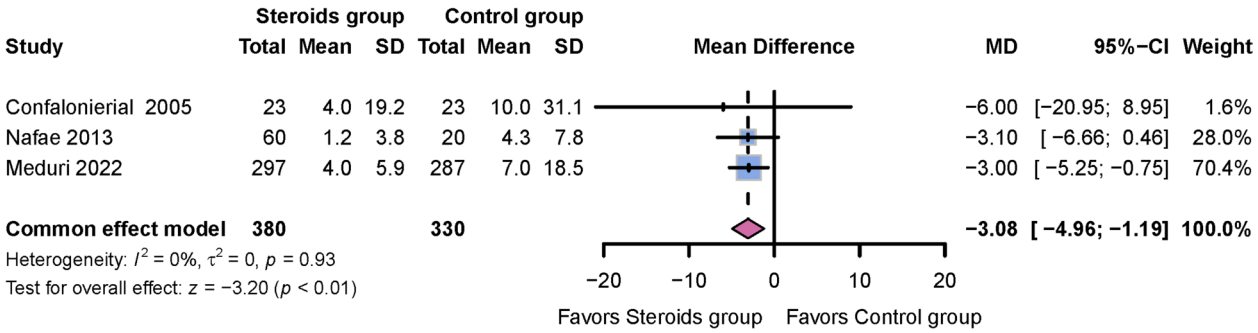


Fig. 5 Forest plot of mechanical ventilation between the corticosteroids group and the control group. *SMD* Standardized Mean Difference, *CI* confidence interval

methylprednisolone [18, 19] compared to 346 patients treated with standard care (15.6% vs. 19.9%, RR 0.78; 95% CI 0.57–1.08, $p=0.14$, $I^2=0\%$, moderate certainty) (Fig. S8A, Table S3). The Z-curve crosses the conventional boundary but does not cross the continuous monitoring boundary of the experiment, and the sample size does not meet the required information amount, requiring more experiments to confirm ($n=5593$) (Fig. S9), hydrocortisone has been shown to reduce the mortality rate of severe community-acquired pneumonia patients. We performed a subgroup analysis of the effect of glucocorticoid tapering or non-tapering on prognosis. There was a significant difference in mortality among 215 patients treated with glucocorticoid non-tapering [13–18] compared to 175 patients treated with standard care (7.4% vs. 21.1%, RR 0.36; 95% CI 0.21–0.62, $p<0.01$, $I^2=0\%$, moderate certainty) (Fig. S10, Table S3). Moreover, there was also a significant difference in mortality among 697 patients treated with glucocorticoid tapering compared to 682 patients treated with standard care (10.8% vs. 15.7%, RR 0.68; 95% CI 0.52–0.90, $p<0.01$, $I^2=53\%$, moderate certainty) (Fig. S10, Table S3). Although both tapering group and non-tapering group can reduce mortality, the tapering meta regression coefficient β value was 0.58 (95% CI −0.04 to 1.20), $P=0.07$, and the results were not statistically different. We performed a subgroup analysis of the effects of different doses of glucocorticoids on prognosis. According to the principles for clinical application of glucocorticoids (2023 edition) [21], corticosteroid converted to hydrocortisone equivalent dose for 70 kg adult, High dose: > 280 mg/d; Middle dose: 140 ~ 280 mg/d; Low dose: < 140 mg/d. There was a significant difference in mortality among 561 patients who received middle doses of glucocorticoids compared to 514 patients who received standard care (6.8% vs. 14.6%, RR 0.46; 95% CI 0.32–0.66, $p<0.01$, $I^2=3\%$, low certainty) (Fig. S11, Table 1, Table S3). There was no significant difference in mortality between patients treated with low and high doses of glucocorticoids (5.6% vs. 16.1%, RR 0.35; 95% CI 0.1–1.22, $p=0.10$, $I^2=0\%$, moderate certainty) (Fig. S11, Table 1, Table S3). We conducted a subgroup analysis of the effects of different days of glucocorticoid use on prognosis. There were significant differences in mortality among 898 patients treated with glucocorticoids for 5 to 7 days (7.5% vs. 21.4%, RR 0.36; 95% CI 0.20–0.62, $p<0.01$, $I^2=0\%$, moderate certainty) (Fig. S12, Table S3) and > 7 days (10.8% vs. 15.7%, RR 0.68; 95% CI 0.52–0.90, $p<0.01$, $I^2=53\%$, moderate certainty) (Fig. S12, Table S3) compared with 841 patients treated with standard care. There was no significant difference in mortality among patients treated with glucocorticoids for 1 day.

Discussion

In this latest meta-analysis, which included eight studies and a total of 1769 patients, the use of glucocorticoids was associated with a reduced risk of death compared to standard treatment, and this effect was found to be dependent on the specific type of hormone used. Additionally, glucocorticoids were found to decrease the need for mechanical ventilation. Although the incidence of hyperglycemia was increased with glucocorticoid use, there was no significant increase in the risk of gastrointestinal bleeding or serious infection.

PSI V is defined as patients with a score > 130 and a case fatality rate of 27–31.1% requiring ICU hospitalization. In our meta-analysis, only 2 trials included patients with PSI V. In the 2015 Torres et al. 's study, 41 patients with PSIV were included (22 in the glucocorticoid group and 19 in the control group)0.2023 Dequin PF et al. 's study included 374 patients with PSI V (181 in the glucocorticoid group and 193 in the control group), while the inclusion criteria of other studies did not include patients with PSI V. In their opinion, PSI V does not necessarily mean sCAP. Whether patients with PSIV should be included should be further explored in our future studies.

The question of whether glucocorticoids can improve the prognosis of sCAP remains controversial. A meta-analysis by Briel M et al. [20] demonstrated that adjuvant therapy with glucocorticoids in hospitalized patients with CAP reduced the time to clinical stabilization and length of stay (LOS) by about 1 day, but did not have a significant effect on mortality. On the other hand, a meta-analysis by Saleem N et al. [22] showed that glucocorticoid therapy was associated with a lower incidence of CAP inpatients progressing to requiring mechanical ventilation, without any significant association with mortality, treatment failure, or adverse events. However, few large multicenter trials have evaluated the effect of glucocorticoids in ICU patients with sCAP. In a review by Stern et al. [23], corticosteroids significantly reduced mortality in adults with severe pneumonia but did not affect mortality in adults without severe pneumonia. Our results suggest that the use of glucocorticoids can reduce the risk of death and the need for mechanical ventilation in patients with severe community-acquired pneumonia. This observation may be influenced by the inclusion of a recent study by Dequin PF et al. [20] in our analysis. Their randomized controlled trial, which involved 795 patients with sCAP treated in the intensive care unit, demonstrated that patients treated with hydrocortisone had a lower risk of death at day 28 compared to those treated with a placebo. However, this study did not measure the

duration of mechanical ventilation. Furthermore, Villar J et al. [24] showed that the early use of dexamethasone reduced the duration of mechanical ventilation and overall mortality in patients with moderate-to-severe acute respiratory distress syndrome (ARDS).

Glucocorticoids do not increase the risk of gastrointestinal bleeding or serious infection. However, they can increase the incidence of hyperglycemia in patients. The trial [25, 26] and meta-analysis [24, 27, 28], reported an increase in the incidence of hyperglycemia, which is consistent with the pharmacodynamic effects of glucocorticoids. It is worth noting that the increase in glucose levels associated with glucocorticoid use is usually short-lived [27].

Corticosteroids are involved in many physiological processes, including the stress response, immune response, inflammation regulation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior. Corticosteroids are widely available and inexpensive. According to one cost-effectiveness study [29], the use of steroids would be associated with savings in those with sCAP, but the effect in patients with sCAP with shock remains unknown. Critical illness-related corticosteroid insufficiency (CIRCI) is characterized by a lack of cortisol in critically ill patients, which further exacerbates the inflammatory response. Studies have shown that serum cortisol concentration is associated with the severity and mortality of CAP, with nearly half of the patients with sCAP having CIRCI. Additional corticosteroids have been shown to benefit survival [30, 31]. It has been suggested that the response to glucocorticoid therapy may be influenced by the severity of systemic inflammatory disorders [18, 32, 33]. In a meta-regression analysis, it was found that the reduction in mortality may only be evident in patients at high risk of death [34].The optimal type and dosage of glucocorticoids have not been determined. In our subgroup analysis, although both tapering group and non-tapering group can reduce mortality, the RR value of non-tapering group was 0.36 (0.21–0.62), which was significantly less than that of tapering group 0.68 (0.47–0.76). Although there was no statistical difference in the meta regression results, the p value is close to 0.05. We speculate that non-tapering may reduce mortality compared with tapering, but there were differences in drug dose, drug type, use time and other factors between tapering group and non-tapering group in different studies, it was still difficult to determine whether tapering and non-tapering can reduce mortality. The impact of non-tapering and tapering on the prognosis of patients remains to be further verified by RCT studies. Middle doses of glucocorticoids were associated with reduced mortality, while low and high doses of glucocorticoids were not associated with reduced mortality. It has been suggested that low doses of dexamethasone may reduce mortality in patients with acute respiratory distress syndrome [25, 35].This could be due to low-dose regimens striking the right balance between anti-inflammatory and immunosuppressive effects, as higher doses of corticosteroids were associated with a greater risk of harm in an earlier sepsis trial [36]. In our subgroup analysis, treatment with hydrocortisone was associated with reduced mortality compared to standard care, while treatment with methylprednisolone did not show a significant association with reduced mortality. A meta-analysis by Gibbison B et al. [37] on the use of corticosteroids in septic shock showed that high-dose methylprednisolone increased the risk of death compared to high-dose dexamethasone, while high-dose dexamethasone reduced the risk of death at 28 days compared to placebo. Studies have shown that methylprednisolone has a higher concentration in the lungs than other types of hormones because it has a larger volume of distribution, a longer residence time, and a longer and wider area of retention in the alveolar epithelium. In addition, methylprednisolone rebounded less than hydrocortisone after disuse and had an advantage over hydrocortisone in reducing levels of interleukin-6 (IL-6) and C-reactive protein (CRP). Methylprednisolone is an exogenous hormone, which needs to be transformed by the liver in the body, with moderate and weak effects, mainly distributed in the lungs. It is recommended to use in ARDS, which can reduce pulmonary interstitial edema and prevent pulmonary fibrosis. Hydrocortisone is an endogenous hormone, that does not need to be transformed in the body, has short effects and weak effects, and uses a large dose. Surviving sepsis campaign is recommended that patients with refractory septic shock may be treated with adjuvant hydrocortisone[38]. Therefore, the specific choice of glucocorticoid still needs further research.

Compared with the meta-analysis by Jheng-YanWu et al. [39], we conducted subgroup analysis based on the types of corticosteroids, time of use, dosage used, and whether tapering or not. Our study extended its analysis beyond the duration of MV in the corticosteroid and control groups by additionally examining MV use on the eighth day. While some funnel plots exhibited significant asymmetry, suggestive of potential publication bias, we employed trim and fill methods to validate our findings. Compared with the meta-analysis conducted by Xin Ya See et al. [40], the study included the studies of Wittermans [40], Snijders [41], and Fernandez-Serrano [42]. However, the study population in the three papers was not sCAP. The study by Wittermans E et al. explored the population of non-ICU hospitalized patients. Therefore, we postulated that this might affect their findings. Unlike the two aforementioned meta-analyses, our study

employed TSA for both the corticosteroid and hydrocortisone groups. TSA helps minimize the risk of false-positive or false-negative results due to random errors commonly encountered in meta-analyses. Furthermore, we implemented the GRADE approach to minimize both random and systematic errors through a comprehensive search strategy and rigorous evaluation of the included studies.

Limitations

Our study has some limitations: Firstly, the optimal type, dosage, and duration of glucocorticoids have not been determined. The choice of corticosteroids may have an impact on the results. Our subgroup analysis revealed a significant reduction in mortality for patients receiving hydrocortisone treatment with a mid-range dosage, administered for either 5–7 days or exceeding 7 days. These findings suggest that hydrocortisone, administered in mid-range doses for 5–7 days or longer, could be a potential therapeutic option for sCAP treatment. However, further investigation is warranted to confirm these observations and establish the optimal corticosteroid regimen. Future controlled trials are needed to evaluate the potential benefits of optimal hormone types, dosages, and durations. Secondly, the 2023 guidelines for severe pneumonia [6] recommend the use of corticosteroids if a shock occurs in patients with sCAP (conditional recommendation, low-quality evidence). However, due to the unavailability of data on shock patients in our study, we were unable to conduct subgroup analysis for patients with or without shock. Finally, the use of glucocorticoids may yield different outcomes for community-acquired pneumonia caused by different pathogens. However, the number of identified pathogens in our study was insufficient to explore the effects of specific pathogens on patients. Even in a detailed microbiological assessment study, up to 62% of patients with community-acquired pneumonia had no detectable pathogens [43], limiting our ability to perform subgroup analyses for specific pathogenic agents.

Conclusion

Glucocorticoids can reduce mortality in patients with sCAP, and the effect may vary depending on the type and the dose of glucocorticoids used. Additionally, glucocorticoids can reduce the duration of mechanical ventilation, as well as the length of ICU stay, without increasing the risk of gastrointestinal bleeding or secondary infections in patients.

Abbreviations

CAP	Community-acquired pneumonia
ICU	Intensive care unit
RCTs	Randomized controlled trials
RCT	Randomized controlled trial
SCAP	Severe community-acquired pneumonia
PSI	Pneumonia severity index
PEEP	Positive end expiratory pressure
FiO2	Fraction of inspired oxygen
PaO2	Partial pressure of oxygen
IDSA	Infectious Diseases Society of America
ATS	American Thoracic Society
WBC	White blood cells
BUN	Blood urea nitrogen
RR	Respiratory rate
MD	Mean difference
IQR	Interquartile range
RoB	Risk of bias
GRADE	Grading of Recommendations Assessment Development and Evaluation
SD	Standard deviation
CI	Confidence intervals
RR	Relative risk
TSA	Trial sequential analysis
RRR	Relative risk reduction
LOS	Length of stay
ARDS	Acute respiratory distress syndrome
HPA	Hypothalamic-pituitary-adrenal
GCS	Glucocorticoid
CIRCI	Critical illness-related corticosteroid insufficiency

Supplementary Information

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Supplementary material 1.

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Author contributions

Xue Gu and Penglei Yang designed the study and performed data analysis and wrote the manuscript; Qihong Chen developed the research theme and managed the research project. Lina Yu,Jun Yuan and Ying Zhang prepared the figures. Zhou Yuan, Xiaoli Zhang and Lianxin Chen embellished the language. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval by an ethics committee was not applicable.

Consent for publication

All authors have agreed to the publication of this manuscript.

Competing interests

The authors declare no competing interests.

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