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RECEIVED 30 June 2024 ACCEPTED 21 October 2024 PUBLISHED 06 November 2024

CITATION

Chen Y, Kuang H, Zhu Y and Luo X (2024) The effect and safety of corticosteroid treatment for severe community-acquired pneumonia: a meta-analysis of randomized controlled trials. *Front. Med.* 11:1457469. doi: 10.3389/fmed.2024.1457469

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The effect and safety of corticosteroid treatment for severe community-acquired pneumonia: a meta-analysis of randomized controlled trials

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Background: There is ongoing debate on the efficacy and safety of corticosteroid therapy for severe community-acquired pneumonia (sCAP). Our aim was to investigate the safety and therapeutic effectiveness of corticosteroids in the sCAP therapy.

Methods: Electronic databases (Cochrane Library, PubMed, Web of Science and Embase) were searched from inception to January 10, 2024. We examined for randomized controlled studies assessing the effectiveness and safety of corticosteroid therapy in individuals with sCAP. The primary outcome was short-term mortality. Subgroup analyses were carried out according to the corticosteroid type. Additionally, trial sequential analysis (TSA) was carried out.

Results: In total, 11 trials, including 1959 patients, met the predetermined standards and underwent analysis. Overall, our meta-analysis exhibited that corticosteroids may considerably lower short-term mortality when compared to control treatment [6 studies (1,582 patients); odds ratio (OR), 0.65; 95% confidence interval (CI) 0.49-0.88; p = 0.005] and C-reactive protein (CRP) levels [5 studies (359 patients); mean difference (MD), -6.97; 95% CI -12.33 to -1.60; p = 0.01, but TSA revealed that the sample size needs to be larger. Moreover, we observed that corticosteroids reduced the hospital length of stay [7 studies (999 patients); MD, -3.56; 95% Cl, -4.28 to -2.84; p < 0.001], need for mechanical ventilation (MV) [7 studies (1,328 patients); OR, 0.60; 95% CI, 0.45-0.79; p = 0.001] and MV duration [4 studies (736 patients); MD, -5.62; 95% Cl, -7.31 to -3.94; p < 0.001], which was in agreement with TSA. However, adverse events, length of hospital and intensive care unit (ICU) stay were not evidently shortened when TSA was utilized. Furthermore, subgroup analysis revealed that all of the above studies benefited from hydrocortisone treatment in comparison to the control group.

Conclusion: Our meta-analysis revealed that corticosteroids, especially hydrocortisone, could decrease the mortality of individuals with sCAP.

Systematic review registration: [https://clinicaltrials.gov/], identifier [CRD42023415555].

KEYWORDS

severe community-acquired pneumonia, corticosteroid, hydrocortisone, mortality, meta-analysis

Introduction

Severe community-acquired pneumonia (sCAP) is defined as patients existing community-acquired pneumonia (CAP) and meeting either one main criteria (respiratory failure needing mechanical ventilation or septic shock requiring vasopressor) or three minor criteria (totally nine variables, such as blood urea nitrogen level, respiratory rate, confusion, white blood cell count, etc.) (1, 2). sCAP is the most critically life-threatening form of community-acquired pneumonia and is characterized by rapid progression, critical illness and high morbidity and mortality (3-5). In the United States (US), the estimated number of patients hospitalized with sCAP is 356,326 per year, resulting in 167,474 deaths within 1 year (6). In Europe, the mortality rate of sCAP with invasive mechanical ventilation (MV) in the ICU is 33% (7). Moreover, sCAP has been reported to cause a substantial financial burden on the current medical system (8, 9). Despite advances in life support measures and antimicrobial treatment, the mortality of sCAP remains unacceptably high, suggesting that we need to focus on reducing mortality in other ways (10).

According to previously published studies, sCAP may lead to dysregulated pulmonary and systemic inflammatory responses, which results in deleterious effects and poor prognosis (11-13). Corticosteroids, as inhibitors of inflammation, can act on many cytokines by binding to their specific receptors and decrease the generation of the major inflammatory cytokines (IL-1b, TNFa, IL-6 along with IL-8). Corticosteroids are known to suppress inflammatory responses in specific tissues as well as in the entire body (14, 15). However, the recommendations among international guidelines with regards to the use of corticosteroids in sCAP are divergent. According to a recent European and Latin American guideline, corticosteroids should be considered for use in patients with sCAP if shock occurs (1). The recommendation level is low. In another international guidelines, corticosteroids is only recommended for bacterial sCAP patients, not including viral sCAP (16).

Current evidences report differential results, there is still ongoing debate regarding the use of corticosteroids in sCAP, such as which types of corticosteroids are most effective, and the optimal duration for their use (14, 17, 18). To enhance the clinical prognosis of sCAP, novel therapy options or adjuvant medicines are therefore desperately needed.

The results of two recently published large RCTs (19, 20) remain controversial. One study (19) showed that hydrocortisone could reduce mortality in patients with sCAP. On the other hand, methylprednisolone did not appear to provide any appreciable benefit for individuals with sCAP, according to another research (20). We implemented a meta-analysis of randomized controlled trials (RCTs) to investigate this contentious topic and determine the efficacy of corticosteroids as an adjuvant therapy option in sCAP patients.

Methods

This research was implemented based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO (registration number: CRD42023415555) (21, 22).

Eligibility criteria

We implemented a comprehensive systematic search of Cochrane Library, PubMed, Web of Science and Embase databases for articles that were published between the creation of the databases and January 10, 2024, with appropriate predefined search terms. The supplemental material contains the specifics of the search method. All peerreviewed, published trials comparing the safety and effectiveness of corticosteroid therapy to either conventional care or a placebo were found through a comprehensive literature search. The only RCTs considered were those that determined the safety and therapeutic effectiveness of corticosteroids in treating adult sCAP individuals.

The following were the inclusion criteria: (1) population: individuals with sCAP as defined by the included studies; (2) intervention: patients treated with corticosteroids plus conventional therapy; (3) comparison: placebo or standard care; (4) outcomes: all-cause short-term mortality. We defined 28-day (28d) or 30-day (30d) mortality as all-cause short-term mortality in the current metaanalysis. Secondary outcomes are length of hospital and ICU stay, hospital mortality, need for mechanical ventilation (MV), MV time, C-reactive protein (CRP) level and adverse events. (5) Study type: the inclusion criteria were open-ended and included only peer-reviewed RCTs with no limitations on publication date, language, age, sample size, sex, or ethnicity.

We excluded trials that (1) only provided data from *post hoc* analysis; (2) focused on individuals with septic shock or those under the age of 18; (3) were published only as case reports, case series, conference posters, or single-arm studies; (4) did not report relevant outcomes; or (5) were pharmacokinetic studies.

Data extraction

To assess the possible investigations, two researchers, Yang Chen and Xing Luo, independently examined the abstracts and titles. Arguments were resolved by consensus or by discussion with Youfeng Zhu, the third author. Utilizing a standardized data extraction form, we retrieved the study features (first author, study design, year of publication, number of participants, study site), full study information, controls, interventions, corticosteroid kinds, and outcomes.

Assessment of risk of bias

With the Cochrane risk-of-bias tool, two researchers (Yang Chen and Huanming Kuang) independently evaluated the risk of bias for all the studies. A third adjudicator (Xing Luo) resolved any disagreements (23).

Statistical analysis

Review Manager version 5.4 was applied to carry out the statistical analysis. For categorical variables, we computed the OR with a 95% CI, and for continuous variables, we computed the MD with a 95% CI. After determining whether the distribution was skew and normal, continuous variables like the length of hospital and ICU stay, and CRP level—all of which are expressed as medians and interquartile

ranges—were transformed into means and standard deviations in accordance with earlier research (24, 25). Random-effects models were applied to pool the data. The I² statistic was utilized to evaluate heterogeneity. Substantial heterogeneity was defined as I² > 50% or p < 0.10.

Subgroup analysis

According to previously published studies, the type and duration of corticosteroid treatment might influence the effect of corticosteroids (17, 18, 26). Therefore, we performed subgroup analyses on the basis of the type and length of corticosteroid therapy.

Trial sequential analysis

To determine the dependability of our meta-analysis, we employed TSA software (version 0.9.5.10 Beta, Copenhagen Trial Unit, Copenhagen, Denmark) (27). We constructed the O'Brien-Fleming monitoring boundaries with the Lan-DeMets methodology and identified the best informativeness, i.e., an alpha of 0.05, a relative risk reduction of 20%, and a two-sided beta of 0.80. This allowed for the calculation of the required information size (RIS) for primary and secondary outcomes. Next, in order to assess the strength of the evidence, we investigate the relationship between the cumulative Z-curve and the TSA border or RIS.

Grading the quality of evidence

The quality of evidence for each outcome measure was evaluated utilizing the GRADE methodology (GRADEpro; McMaster University 2014, Hamilton, Canada) (28). The following certainty assessments indirectness, inconsistency, risk of bias, imprecision, as well as other factors—were applied to lower the quality. Following that, the overall quality of evidence was rated as "high," "moderate," "low" as well as "very low."

Results

Search strategy

In the first search, 526 articles were included. Of these, 138 were duplicates and a further 364 studies were excluded through abstract screening. Following the assessment of the full text, 24 studies were eliminated for diverse reasons (Figure 1). Lastly, our study comprised a total of 11 RCTs (19, 20, 29–37). Figure 1 displays the study selection flow diagram.

Study characteristics

The features of the studies are indicated in Table 1. The analysis comprised a total of 1959 individuals, 988 of whom underwent corticosteroid intervention throughout the study period and 971 of whom received placebo therapy. Nonetheless, the included trials

differed in the types of corticosteroids used and the length of the intervention. Six trials administered hydrocortisone (19, 29, 34–37), and five studies administered nonhydrocortisone (20, 29–31, 34). In three trials, patients were given corticosteroids for a period of less than or equal to 5 days (20, 29, 36), and eight trials administered corticosteroids for more than 5 days (19, 20, 31–35, 37).

Quality assessment

In accordance with the risk of bias assessment, two studies were determined to be at high risk of bias (Supplementary Figure S1). There were seven research (29, 31–35, 37) that did not offer approaches for allocation concealment or random sequence generation. The blinding approach may have been violated in four trials, which might have led to an overestimation or underestimation of the magnitude of effect (29, 31, 32, 35). Additionally, six trials (29, 31–33, 35, 37) had an uncertain risk of other bias assigned to them, as these trials have been subject to uncertainty in previous assessments.

Primary outcome

Overall, our research displayed that the corticosteroid intervention group had a reduced short-term mortality rate than the control group (OR, 0.65; 95% CI 0.49–0.88; p=0.005, six RCTs (15, 16, 27, 31–33), 1,582 patients, low certainty; Table 2; Figure 2A). However, the TSA-adjusted CIs ranged from 0.40 to 1.06 (Supplementary Figure S2). The cumulative Z-curve crossed the traditional benefits monitoring line, but not the O'Brien-Fleming monitoring line. In addition, it did not cross either the uselessness monitoring line or the RIS, suggesting that currently, there may be false-positive results. Therefore, additional large RCTs are needed to confirm our findings.

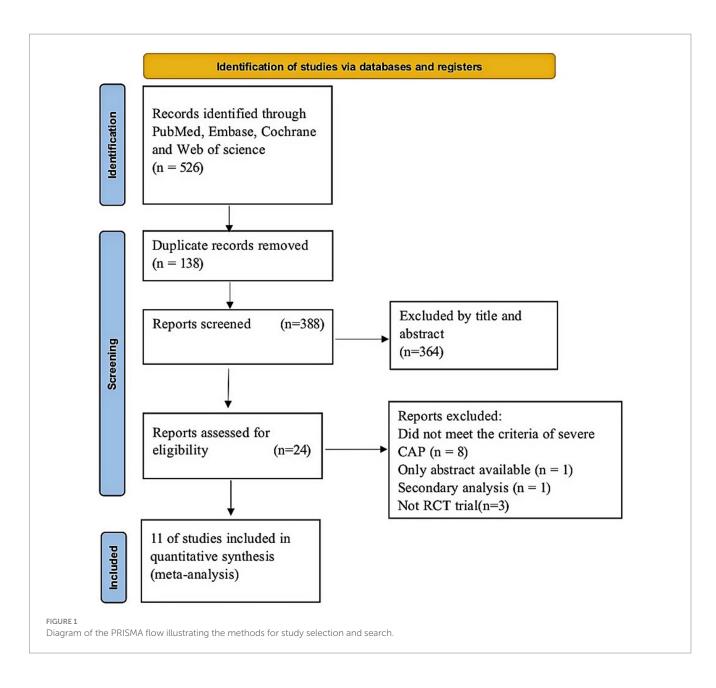
Furthermore, our subgroup analysis revealed that the hydrocortisone subgroup resulted in a considerable decrease in the short-term mortality of sCAP patients, and the TSA results were consistent with this result (OR, 0.44; 95% CI, 0.28–0.70; p=0.005; Figure 2B; Supplementary Figure S2). Nevertheless, these benefits were not observed in the nonhydrocortisone subgroup (Figure 2B).

Moreover, the subgroup analysis revealed that corticosteroid therapy longer than 5 days may significantly lower short-term mortality (OR, 0.66; 95% CI 0.49–0.89; p = 0.007; Figure 2C).

Secondary outcomes

Hospital mortality

Eight studies reported hospital mortality (20, 29, 30, 32–36), and there was no apparent difference in mortality rates in hospitalization between both groups (OR, 0.70; 95% CI 0.47–1.03; p=0.07, 8 studies, 1,021 patients, moderate certainty; Table 2, Figure 3A). The TSA-adjusted CIs were between 0.30 and 1.69, which is in agreement with the findings of the earlier study (Supplementary Figure S3). Cumulative Z-curves did not cross the conventional boundary values, nor did they cross the benefit boundary. Furthermore, there was no statistically significant difference in the effectiveness between the control group and the



intervention group since the accumulated information gathered did not reach the anticipated level of RIS, and more RCTs are needed to prove this.

However, subgroup analysis revealed that patients treated with hydrocortisone (OR, 0.21; 95% CI 0.09–0.50; p=0.0004; Figure 3B) may benefit more than those not treated with hydrocortisone (OR, 1.01; 95% CI 0.64–1.59; p=0.96; Figure 3B). Furthermore, TSA indicated that further studies are required to confirm this finding (Supplementary Figures S4, S5).

Moreover, the duration of corticosteroid treatment was not linked to a noteworthy decrease in hospital mortality (Figure 3C).

ICU stay

The duration of ICU stay was reported in eight research (20, 29, 30, 32, 33, 35–37). There was no discernible variation in the duration of ICU stay between the control and intervention groups (MD, -0.58; 95% CI -1.19 to 0.04; p = 0.07; moderate certainty; Table 2; Figure 4A).

Moreover, the TSA results were in agreement with the study results (TSA-adjusted CI, -3.09 to 1.93; Supplementary Figure S6). Cumulative Z-curves did not cross either the O'Brien-Fleming monitoring line or the conventional boundary. Furthermore, the cumulative information did not meet the futility thresholds or anticipated RIS. Consequently, there was no marked difference between the Control and intervention groups in terms of efficacy, and more RCTs are needed.

Furthermore, subgroup analysis presented that the application of hydrocortisone (OR, -2.41; 95% CI -4.57 to -0.25; p=0.03; Figure 4B) significantly improved the length of ICU stay in contrast to that in the control group (Supplementary Figure S7), and the nonhydrocortisone treatment group did not show this finding (OR, -0.42; 95% CI -1.06 to 0.23; p=0.20; Figure 4B; Supplementary Figure S8). Subgroup analysis did not reveal that the duration of corticosteroid treatment affected the ICU length of stay (Figure 4C).

TABLE 1 Characteristics of the included studies.

Study	Study design	Study site	Sample size	Severe criterion	Population	Interventions	Outcomes
Dequin 2023	Double-blind, randomized placebo-controlled trial	France	400/395	PSI, ICU	All included patients enter the ICU	Hydrocortisone 200 mg iv for 4/8 days, degressive for 8/14 days	Short-term mortality (28/30d), ICU stay, hospital stay, need formechanicalventilation, vasopressors drugs
Meduri 2022	Double-blind, randomized placebo-controlled trial	USA	297/287	ATS, ICU	All included patients enter the ICU	Methylprednisolone 40 mg IV bolus, then 40 mg for 7 days, degressive for 20 days	Short-term mortality (28/30d), In-hospital mortality, ICU stay, hospital stay, need formechanicalventilation, mechanical ventilation time, vasopressors drugs
Ceccato 2016	Double-blind, randomized placebo-controlled trial	Spain	56/50	ATS, ICU, PSI	Adult patients with severe CAP	Methylprednisolo ne 0.5 mg/kg every 12h for 5 days	In-hospital mortality, ICU stay, hospital stay, need for mechanical ventilation, CRP
Torres 2015	Double-blind, randomized placebo-controlled trial	Spain	55/57	ATS, ICU, PSI	ATS criteria or PSI scores V	Hydrocortisone 0.5 mg/kg every 12 h for 5 days	In-hospital Mortality, ICU stay, hospital stay, need for mechanical ventilation
Nafae 2013	Double-blind, randomized placebo-controlled trial	Egypt	60/20	ATS, ICU	Based on baseline vitals indicating Mean CORB score > 2	Hydrocortisone 200 mg iv bolus, then 10 mg/h for 7 days	In-hospital mortality, ICU stay, hospital stay, need for mechanical ventilation
Ugajin 2013	Double-blind, randomized placebo-controlled trial	Japan	30/71	PSI	All included patients PSI scores V	Corticosteroids (median dosage) = 50 mg/day prednisine shorter than 8 days	Short-term mortality (28/30d), CRP
Fernandez- Serrano 2011	Double-blind, randomized placebo-controlled trial	Spain	23/22	PSI, ICU	Adult patients with ICU were included	Methylprednisolone 200 mg iv bolus, then every 6 h for 3 days, then 20 mg every 12 h for 3 days, then 20 mg for 3 days	In-hospital mortality, ICU stay, hospital stay, need for Mechanical ventilation
El-Ghamrawy 2006	Double-blind, randomized placebo-controlled trial	KSA	17/17	ICU	All included patients enter the ICU	Hydrocortisone, 200 mg IV bolus, then 240 mg for 7 days	In-hospital mortality
Kim 2006	Double-blind, randomized placebo-controlled trial	Korea	13/13	ATS	ATS criteria	Hydrocortisone, 200 mg IV bolus, then 240 mg for7 days	Short-term mortality (28/30d), In-hospital mortality, ICU stay, hospital stay, mechanical ventilation time, CRP
Confalonieri 2005	Double-blind, randomized placebo-controlled trial	Italy	23/23	PSI, ICU	All included patients enter the ICU	Hydrocortisone 200 mg iv bolus, then 10 mg/h for 7 days	Short-term mortality (28/30d), In-hospital mortality, ICU stay, hospital stay, need for mechanical ventilation, mechanical ventilation time, CRP
Marik 1993	Double-blind, randomized placebo-controlled trial	USA	14/16	BTS, ICU	All included patients enter the ICU	Hydrocortisone 10 mg/kg, 1 day	Short-term mortality (28/30d), ICU stay, need for mechanical ventilation

ICU, Intensive care unit; PSI, Pneumonia severity index; ATS, The American Thoracic Society; BTS, British Thoracic Society.

Hospital stay

Seven studies (20, 29, 30, 32, 33, 35, 36) demonstrated that hospitalization was shorter in the corticosteroid group in contrast to the control group (MD, -3.56; 95% CI -4.28 to -2.84; p < 0.01; low certainty; Table 2; Figure 5A). TSA identified that the RIS was not met; nevertheless, the Z-curve crossed the benefit boundaries, indicating that corticosteroids were more beneficial than the control treatment (Supplementary Figure S9).

Furthermore, subgroup analysis revealed that both hydrocortisone and nonhydrocortisone reduced the length of hospital stay (Figure 5B; Supplementary Figures S10, S11). A duration of corticosteroid therapy longer than 5 days may reduce hospital stay (MD, -4.17; 95% CI -4.95 to -3.38; p < 0.001; Figure 5C).

Need for MV and MV time

Seven studies reported the need for MV (19, 20, 29, 30, 32, 33, 37), and four studies reported the duration of MV (20, 32, 35, 36). Corticosteroid therapy was linked to a decrease in the need for MV (OR, 0.60; 95% CI 0.45–0.79; *p* = 0.0003; moderate certainty; Table 2; Figure 6A) and MV duration (MD, -5.62; 95% CI -7.31 to -3.94; p < 0.001; moderate certainty; Table 2; Figure 7A). The TSA-adjusted CIs were 0.41–0.88 for the need for MV (Supplementary Figure S12), and the Z-curve crossed the benefit boundaries, indicating that corticosteroid treatment was more beneficial than the control treatment. The TSA-adjusted CIs ranged from -9.1 to -2.2 with regard to the duration of MV, and the Z-curve crossed the RIS and the conventional boundary, indicating that corticosteroids were more beneficial than the control treatments (Supplementary Figure S13).

Subgroup analysis with regard to the type of corticosteroids showed that hydrocortisone was more beneficial for the need for MV (OR, 0.53; 95% CI 0.37–0.76; p=0.0006; Figure 6B; Supplementary Figure S14). Moreover, hydrocortisone subgroup was linked to shorter MV duration (MD, -3.22; 95% CI -5.74 to -0.70; p=0.01; Figure 7B; Supplementary Figure S15), but the nonhydrocortisone subgroup did not show improvement (Supplementary Figure S16).

Furthermore, subgroup analysis of the duration of corticosteroid therapy showed that corticosteroid therapy longer than 5 days may reduce the need for MV (OR, 0.60; 95% CI 0.45–0.82; p=0.001; Figure 6C).

CRP level

Five studies (29, 31, 32, 35, 36) reported the CRP level, and the results showed that CRP level declined more in the corticosteroid group versus the control group (MD, -6.97; 95% CI -12.33 to -1.60; p < 0.05; very low certainty; Table 2; Figure 8A). The TSA-adjusted CIs ranged from -20.4 to 6.5 (Supplementary Figure S17). The cumulative Z-curve did not reach the O'Brien-Fleming monitoring line for benefit, although it did pass the traditional line. Furthermore, neither the RIS nor the futility were crossed by the cumulative Z-curve, suggesting that there may have been false-positive results. Therefore, further large RCTs are needed to prove this hypothesis.

Furthermore, subgroup analysis with regard to the type of corticosteroids exhibited that hydrocortisone treatment caused a considerable decrease in the level of CRP (MD, -34.59; 95% CI -49.60 to -19.58; *p* <0.001; Figure 8B), and the TSA results were in agreement (Supplementary Figure S18).

Severe adverse events

Among the included researches, no significant differences with regard to severe adverse effects were found between the two groups (Figure 9). There were similar risks of gastrointestinal hemorrhage (7 studies, 1,221 patients; OR, 0.74; 95% CI 0.38 to 1.46; p=0.39; $I^2=0\%$), frequency of hyperglycemia requiring treatment (4 studies, 346 patients; OR, 1.12; 95% CI 0.58 to 2.14; p=0.74; $I^2=0\%$), and incidence of hospital-acquired infection (5 studies, 1,096 patients; OR, 0.84; 95% CI 0.55 to 1.28; p=0.41; $I^2=0\%$).

Discussion

It is unknown if adjunctive corticosteroid therapy is safe and effective in treating individuals with sCAP. In fact, there seems to be a survival advantage linked to early corticosteroid therapy in patients with ARDS, coronavirus illness 2019, and septic shock (5, 38, 39). The underlying pathophysiology, driven by lung inflammation, is similar among sCAP and the above diseases. Hence, it is reasonable to extrapolate their potential benefits to patients with CAP.

Recently, the impact of corticosteroid therapy for sCAP was examined in two sizable RCTs, however the findings were debatable (19, 20). The CAPE COD trial showed that hydrocortisone could be expected to reduce mortality in sCAP individuals (RR 0.53 [95% CI 0.33–0.84]) (19). The ESCAPe trial demonstrated that methylprednisolone has no apparent benefit in sCAP individuals (adjusted OR 0.90, 95% CI 0.57–1.40) (20). It was noted that systemic corticosteroids were linked to improved clinical results, especially treatment with hydrocortisone, according to subgroup analyses. This is the most recent meta-analysis on the topic that we are aware of, and we identified that sCAP patients undergoing hydrocortisone treatment had markedly better outcomes than those who did not receive hydrocortisone treatment.

In this up-to-date meta-analysis, we included 1959 patients from 11 studies who fulfilled the predefined criteria. In our included studies, seven studies (20, 31, 32, 34–37) did not report the specific pathogens. Three trials (19, 29, 30) ruled out influenza infection and one study (33) excluded active mycobacterial or fungal infection. As few included RCTs reported the specific pathogen, a further subgroup meta-analysis with regards to the type of pneumonia (bacterial, viral, influenza) could not be performed. Overall, our meta-analysis revealed that in contrast to the individuals in the control group, patients in corticosteroids group had considerably decreased shortterm mortality and CRP levels. TSA demonstrated the cumulative Z-curve crossed the traditional benefits monitoring line, but not the O'Brien-Fleming monitoring line. This suggests that there may be false-positive results in the findings, and further large scale RCTs are needed to verify the authenticity of the results.

In order to avoid the influence of other confounding factors, we conducted a subgroup analysis. Moreover, we observed that corticosteroids could shorter hospital stays, reduce MV demand, and MV duration. On the other hand, the duration of hospital stay in the ICU did not considerably decrease. In addition, we did not find that the use of corticosteroids increased the incidence of adverse events. Subgroup analysis revealed that all of the above studies benefited from hydrocortisone treatment. The TSA results were consistent with regard to short-term mortality, length of hospital stay, duration of MV and CRP level. Moreover, it is reassuring that corticosteroid TABLE 2 The quality of evidence for each outcome measure was assessed following the GRADE.

Corticosteroid co	ompared to Place	cebo for severe comr	nunity-acquir	ed pneumonia		
	atients with severe com	nmunity-acquired pneumonia				
Settings:						
Intervention: Corticoster	roid					
Comparison: Placebo						
Outcomes	Illustrative compa	rative risks* (95% CI)	Relative effect	No of Participants	Quality of the	Comments
	Assumed risk	Corresponding risk	(95% CI)	(studies)	evidence (GRADE)	
	Placebo	Corticosteroid				
Short-term mortality	Study population		OR 0.65	1,582	$\oplus \oplus \ominus \ominus$	
(28/30)	166 per 1,000	115 per 1,000 (89–149)	(0.49 to 0.88)	(6 studies)	low ^{1,2}	
	Moderate					
	246 per 1,000	175 per 1,000 (138–223)	-			
In-hospital mortality	Study population	[OR 0.7	1,021	$\oplus \oplus \oplus \ominus \ominus$	
	133 per 1,000	97 per 1,000 (67-136)	(0.47-1.03)	(8 studies)	moderate ³	
	Moderate	I	1			
	211 per 1,000	158 per 1,000 (112-216)				
Duration of ICU Stay		The mean duration of icu stay in the intervention groups was 0.58 lower (1.19 lower to 0.04 higher)		998 (8 studies)	⊕⊕⊕⊝ moderate⁴	
Hospital stay		The mean hospital stay in the intervention groups was 3.56 lower (4.28–2.84 lower)		999 (7 studies)	$\oplus \oplus \bigcirc \bigcirc$ low ⁵	
Need for mechanical	Study population		OR 0.6	1,382	$\oplus \oplus \oplus \ominus \ominus$	
ventilation	218 per 1,000	143 per 1,000 (111–180)	(0.45-0.79)	(7 studies)	moderate ⁶	
	Moderate					
	227 per 1,000	150 per 1,000 (117–188)				
Mechanical ventilation		The mean mechanical		736	$\oplus \oplus \oplus \ominus$	
time		ventilation time in the intervention groups was 5.62 lower (7.31–3.94 lower)		(4 studies)	moderate ⁷	
CRP		The mean crp in the intervention groups was 6.97 lower		359 (5 studies)	⊕⊖⊝⊖ very low ^{8,9}	

(Continued)

Corticosteroid cor	mpared to Plac	cebo for severe co	mmunity-acquir	ed pneumonia			
Gastrointestinal	Study population		OR 0.74	1,221	$\oplus \oplus \oplus \ominus \ominus$		
hemorrhage	31 per 1,000	23 per 1,000 (12-45)	(0.38–1.46)	(7 studies)	moderate ¹⁰		
	Moderate						
	33 per 1,000 25 per 1,000 (13-47)						
Frequency of	Study population		OR 1.12	346	$\oplus \oplus \oplus \ominus$		
hyperglycemia requiring treatment	116 per 1,000 128 per 1,000 (71–220)		(0.58–2.14)	(4 studies)	moderate ¹¹		
	Moderate						
	95 per 1,000	105 per 1,000 (57–183)					
Incidence of hospital-	Study population		OR 0.84	1,096	$\oplus \oplus \oplus \Theta$		
acquired infection	96 per 1,000 82 per 1,000 (55–119)		(0.55–1.28)	(5 studies)	moderate ¹²		
	Moderate						
	70 per 1,000	59 per 1,000 (40-88)					

TABLE 2 (Continued)

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, Confidence interval; OR, Odds ratio; GRADE Working Group grades of evidence; High quality, Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality, Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality, Further research is very likely to have an important impact on our confidence in the estimate. Very low quality, We are very uncertain about the estimate.

$$\label{eq:approx_star} \begin{split} ^1\text{Does not meet $2/3$ low risk.} \\ ^2\text{OR, 0.65.} \\ ^3\text{95\%CI[0.47, 1.03].} \\ ^4\text{95\%CI[-1.19, 0.04].} \\ ^5\text{1}^2 = 91\%, \text{ unable to explain.} \\ ^6\text{OR, 0.60.} \\ ^7\text{I}^2 = 68\%, \text{ unable to explain.} \\ ^8\text{Simple size <400.} \\ ^8\text{Simple size <400.} \\ ^1\text{95\%CI[0.38, 1.46].} \\ ^1\text{195\%CI[0.58, 2.14].} \\ ^1\text{25\%CI[0.55, 1.28].} \end{split}$$

therapy did not raise the prevalence of adverse effects. Therefore, based on our study, hydrocortisone should be chosen when administering hormone therapy to patients with sCAP, while the use of non-hydrocortisone treatment for specific populations requires further study.

In addition, the subgroup analysis results of a recently published meta-analysis (40) revealed that hydrocortisone treatment resulted in a considerable decrease in all-cause mortality (OR, 0.48; 95% CI 0.30–0.72), but no benefits were shown for methylprednisolone (OR, 0.79; 95% CI 0.57-1.08). The authors did not focus much on this subgroup result and conducted only one mortality analysis, not including the results of two recent large-scale RCTs (19, 20). In our study, we conducted a comprehensive subgroup analysis, and the findings indicated that for sCAP individuals, the mortality in hydrocortisone group was much lower than the non-hydrocortisone group.

However, another recent meta-analysis came to a different conclusion (41). According to Saleem et al., there is no discernible mortality difference between individuals on corticosteroid medication and those on standard care (relative risk, 0.85; 95% CI 0.67–1.07,

p=0.17). It is possible that variations in the criteria for population inclusion account for the discrepancy between our research and the earlier meta-analysis, which included both non-sCAP and sCAP patients in their study.

Pitre et al. implemented a meta-analysis focusing on corticosteroids via pairwise and dose–response analyses (42). They discovered that corticosteroids decreased patients' deaths who had severe pneumonia and decreased the need for invasive MV and ICU admission. The above conclusions are consistent with our observations in sCAP patients, but they focused on bacterial community-acquired pneumonia.

In pharmacological, hydrocortisone functions as a glucocorticoid with both mineralocorticoid and glucocorticoid effects, whereas dexamethasone and methylprednisolone act as synthetic glucocorticoids primarily exerting glucocorticoid effects, with minimal mineralocorticoid activities (43). In summary, hydrocortisone may improve cardiovascular function by restoring effective blood volume through increased mineralocorticoid activity and regulating homeostasis to balance sodium and potassium (44, 45). The dual effect of hydrocortisone, encompassing both glucocorticoid

		Experime	ental	Contr	ol		Odds Ratio	Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	Confalonieri 2005	0	23	7	23	6.7%	0.05 [0.00, 0.88]	
	Dequin 2023	25	400	47	395	40.5%	0.49 [0.30, 0.82]	
	Kim 2006	3	13	4	13	2.8%	0.68 [0.12, 3.87]	
	Marik 1993	1	14	3	16	2.4%	0.33 [0.03, 3.64]	
	Meduri 2022	50	297	47	287	36.3%	1.03 [0.67, 1.60]	+
	Ugajin 2013	6	30	26	71	11.3%	0.43 [0.16, 1.20]	
	0,							
	Total (95% CI)		777		805	100.0%	0.65 [0.49, 0.88]	•
	Total events	85		134				
	Heterogeneity: Chi ² = 9	9.47, df = 5	(P = 0.0	09); l² = 4	7%			0.005 0.1 1 10 200
	Test for overall effect:	Z = 2.80 (P	= 0.005	5)				Favours [experimental] Favours [control]
		Experime	ental	Contr	ol		Odds Ratio	Odds Ratio
	Study or Subgroup	Events				Weight	M-H, Fixed, 95% Cl	
	3.1.1 Hydrocortisone							
	Confalonieri 2005	0	23	7	23	6.7%	0.05 [0.00, 0.88]	
	Dequin 2023	25	400	47	395	40.5%	0.49 [0.30, 0.82]	
	Kim 2006	3	13	4	13	2.8%	0.68 [0.12, 3.87]	
	Marik 1993	1	14	3	16	2.4%	0.33 [0.03, 3.64]	
	Subtotal (95% CI)		450	5	447	52.4%	0.44 [0.28, 0.70]	◆
	Total events	29		61				
	Heterogeneity: $Chi^2 = 2$		(P = 0.4		%			
	Test for overall effect:							
	3.1.2 Not Hydrocortis	one						
	Meduri 2022	50	297	47	287	36.3%	1.03 [0.67, 1.60]	
	Ugajin 2013	6	30	26	71	11.3%	0.43 [0.16, 1.20]	
	Subtotal (95% CI)		327		358	47.6%	0.89 [0.60, 1.32]	T
	Total events	56		73				
	Heterogeneity: Chi ² = 2	2.39, df = 1	(P = 0.1	12); l² = 5	8%			
	Test for overall effect: 2	Z = 0.57 (P	= 0.57)					
		Z = 0.57 (P			005	400.09/	0.05 10 40 0 891	
	Total (95% CI)	·	= 0.57) 777		805	100.0%	0.65 [0.49, 0.88]	•
	Total (95% CI) Total events	85	777	134		100.0%	0.65 [0.49, 0.88]	→
	Total (95% CI) Total events Heterogeneity: Chi ² = 9	85 9.47, df = 5	777 (P = 0.0	134)9); I² = 4		100.0%	0.65 [0.49, 0.88]	◆ 0.005 0.1 1 10 200
	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 2	85 9.47, df = 5 Z = 2.80 (P	777 (P = 0.0 = 0.005	134 09); I² = 4 ⁻ 5)	7%			0.005 0.1 1 10 200 Favours [experimental] Favours [control]
	Total (95% CI) Total events Heterogeneity: Chi ² = 9	85 9.47, df = 5 Z = 2.80 (P	777 (P = 0.0 = 0.005	134 09); I² = 4 ⁻ 5)	7%			
	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 3	85 9.47, df = 5 Z = 2.80 (P rences: Ch	777 (P = 0.0 = 0.005 j ² = 5.22	134 09); I² = 4 ⁻ 5)	7% P = 0.0			
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 3	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime	777 (P = 0.0 = 0.005 i ² = 5.22	134 09); I ² = 4 5) 2, df = 1 (F Contr	7% P = 0.0 ol	2), I² = 80	8%	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime	777 (P = 0.0 = 0.005 i ² = 5.22	134 09); I ² = 4 5) 2, df = 1 (F Contr	7% P = 0.0 ol	2), I² = 80	.8% Odds Ratio	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = S Test for overall effect: Test for subgroup diffe Study or Subgroup	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime	777 (P = 0.0 = 0.005 i ² = 5.22	134 09); I ² = 4 5) 2, df = 1 (F Contr	7% P = 0.0 ol	2), I² = 80	.8% Odds Ratio	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = S Test for overall effect: Test for subgroup diffe Study or Subgroup 4.1.1 >5 days	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events	777 (P = 0.0 = 0.005 $j^2 = 5.22$ ental Total	134 09); I ² = 4 5) 2, df = 1 (F Contro Events	7% P = 0.0 ol <u>Total</u>	2), I² = 80 Weight	.8% Odds Ratio M-H, Fixed, 95% Cl	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005	85 9.47, df = 5 Z = 2.80 (P rrences: Ch Experime Events 0	777 (P = 0.0 = 0.005 $i^2 = 5.22$ ental Total 23	134 09); I ² = 4 0) 2, df = 1 (F <u>Contro</u> <u>Events</u> 7	7% P = 0.0 ol <u>Total</u> 23	2), I ² = 80 <u>Weight</u> 6.7% 40.5%	.8% Odds Ratio <u>M-H, Fixed, 95% Cl</u> 0.05 [0.00, 0.88]	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023	85 9.47, df = 5 Z = 2.80 (P rrences: Ch Experime Events 0 25	777 (P = 0.0 = 0.005 $j^2 = 5.22$ ental Total 23 400	134 09); I ² = 4 5) 2, df = 1 (F <u>Events</u> 7 47	7% P = 0.0 ol <u>Total</u> 23 395	2), I ² = 80 <u>Weight</u> 6.7% 40.5%	.8% Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.49 [0.30, 0.82]	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3	777 (P = 0.0) = 0.005 $i^2 = 5.22$ ental Total 23 400 13	134 09); I ² = 4 2, df = 1 (F <u>Events</u> 7 47 4	7% P = 0.0 ol <u>Total</u> 23 395 13	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8%	.8% Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87]	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50	777 (P = 0.0) = 0.005 $i^2 = 5.22$ ental Total 23 400 13 297	134 09); I ² = 4 ;) 2, df = 1 (F <u>Events</u> 7 47 4 47	7% P = 0.0 ol <u>Total</u> 23 395 13 287	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3%	.8% Odds Ratio <u>M-H. Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60]	Favours [experimental] Favours [control] Odds Ratio
:	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50	777 (P = 0.0) = 0.005 $i^2 = 5.22$ ental Total 23 400 13 297 30	134 09); I ² = 4 ;) 2, df = 1 (F <u>Events</u> 7 47 4 47	7% P = 0.0 ol <u>Total</u> 23 395 13 287 71	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3%	.8% Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20]	Favours [experimental] Favours [control] Odds Ratio
	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI)	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84	777 (P = 0.05) P = 0.005 P = 5.22 ental Total 23 400 13 297 30 763	134 (09); ² = 4 (0) 2, df = 1 (F Contr Events 7 47 47 47 47 26 131	7% P = 0.0 ol Total 23 395 13 287 71 789	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3%	.8% Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20]	Favours [experimental] Favours [control] Odds Ratio
	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 7 Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4	$(P = 0.0)$ $= 0.005$ $i^{2} = 5.22$ ental Total 23 400 13 297 30 763 $(P = 0.0)$	134)9); ² = 4' ;) , df = 1 (F <u>Contre</u> <u>Events</u> 7 4 7 26 17 17 17 17 17 17 17 17 17 17	7% P = 0.0 ol Total 23 395 13 287 71 789	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3%	.8% Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20]	Favours [experimental] Favours [control] Odds Ratio
	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 3 Test for subgroup diffe Study or Subgroup 4.1.1 > 5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: 3	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4	$(P = 0.0)$ $= 0.005$ $i^{2} = 5.22$ ental Total 23 400 13 297 30 763 $(P = 0.0)$	134)9); ² = 4' ;) , df = 1 (F <u>Contre</u> <u>Events</u> 7 4 7 26 17 17 17 17 17 17 17 17 17 17	7% P = 0.0 ol Total 23 395 13 287 71 789	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3%	.8% Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20]	Favours [experimental] Favours [control] Odds Ratio
:	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore Test for subgroup diffe Study or Subgroup 4.1.1 > 5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore 4.1.2 \leq 5 days	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P	777 (P = 0.0) = 0.005 $i^2 = 5.22$ ental Total 23 400 13 297 30 763 (P = 0.0) = 0.007	134 ()); ² = 4 () 2, df = 1 (F Contri- Events 7 47 47 47 26 131 () ()	7% ol Total 23 395 13 287 71 789 6%	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3% 97.6%	.8% Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89]	Favours [experimental] Favours [control] Odds Ratio
:	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore 4.1.2 \leq 5 days Marik 1993	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4	777 (P = 0.0] = 0.005 $i^2 = 5.22$ ental Total 23 400 13 297 30 763 (P = 0.0] = 0.007 14	134)9); ² = 4' ;) , df = 1 (F <u>Contre</u> <u>Events</u> 7 4 7 26 17 17 17 17 17 17 17 17 17 17	7% P = 0.0 ol <u>Total</u> 23 395 13 287 71 789 56% 16	2), l ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3% 97.6% 2.4%	.8% Odds Ratio M-H. Fixed, 95% Cl 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control] Odds Ratio
	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI)	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P	777 (P = 0.0) = 0.005 $i^2 = 5.22$ ental Total 23 400 13 297 30 763 (P = 0.0) = 0.007	134 (a)(b); $ ^2 = 4^{\circ};$ (b)(c)(c)(c)(c)(c)(c)(c)(c)(c)(c)(c)(c)(c)	7% ol Total 23 395 13 287 71 789 6%	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3% 97.6%	.8% Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89]	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI) Total events	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P 1 1	777 (P = 0.0] = 0.005 $i^2 = 5.22$ ental Total 23 400 13 297 30 763 (P = 0.0] = 0.007 14	134 ()); ² = 4 () 2, df = 1 (F Contri- Events 7 47 47 47 26 131 () ()	7% P = 0.0 ol <u>Total</u> 23 395 13 287 71 789 56% 16	2), l ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3% 97.6% 2.4%	.8% Odds Ratio M-H. Fixed, 95% Cl 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control] Odds Ratio
; _	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI) Total events Heterogeneity: Not app	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P 1 1 1 blicable	777 (P = 0.05) P = 0.005 P = 5.22 Pental Total 23 400 13 297 30 763 (P = 0.07) 14 14	134 (09); $ ^2 = 4^\circ$ (1) (2, df = 1 (F Events 7 47 47 47 26 131 (26); $ ^2 = 5(7)$ (3) 3	7% P = 0.0 ol <u>Total</u> 23 395 13 287 71 789 56% 16	2), l ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3% 97.6% 2.4%	.8% Odds Ratio M-H. Fixed, 95% Cl 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control] Odds Ratio
; _	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI) Total events	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P 1 1 1 blicable	777 (P = 0.05) P = 0.005 P = 5.22 Pental Total 23 400 13 297 30 763 (P = 0.07) 14 14	134 (09); $ ^2 = 4^\circ$ (1) (2, df = 1 (F Events 7 47 47 47 26 131 (26); $ ^2 = 5(7)$ (3) 3	7% P = 0.0 ol <u>Total</u> 23 395 13 287 71 789 56% 16	2), l ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3% 97.6% 2.4%	.8% Odds Ratio M-H. Fixed, 95% Cl 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: $:$	85 9.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P 1 1 1 blicable	$(P = 0.0)$ $= 0.005$ $i^{2} = 5.22$ ental $Total$ 23 400 13 297 30 763 $(P = 0.0)$ 14 14 $= 0.37)$	134 (09); $ ^2 = 4^\circ$ (1) (2, df = 1 (F Events 7 47 47 47 26 131 (26); $ ^2 = 5(7)$ (3) 3	7% ol Total 23 395 13 287 71 789 6% 16 16	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 97.6% 2.4% 2.4%	.8% Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control] Odds Ratio
	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: $:$	85 2.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P 1 1 blicable Z = 0.90 (P	777 (P = 0.05) P = 0.005 P = 5.22 Pental Total 23 400 13 297 30 763 (P = 0.07) 14 14	134 (a) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c	7% ol Total 23 395 13 287 71 789 6% 16 16	2), l ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 11.3% 97.6% 2.4%	.8% Odds Ratio M-H. Fixed, 95% Cl 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control] Odds Ratio
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore Test for subgroup diffe Study or Subgroup 4.1.1 > 5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: \therefore 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: \therefore Total (95% CI) Total events	85 2.47, df = 5 Z = 2.80 (P rences: Ch Experime Events 0 25 3 50 6 84 9.11, df = 4 Z = 2.70 (P 1 1 blicable Z = 0.90 (P 85	$(P = 0.0)$ $= 0.005$ $i^{2} = 5.22$ ental $Total$ 23 400 13 297 30 763 $(P = 0.0)$ 14 14 $= 0.37)$ 777	134 (a) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c	7% P = 0.0 ol Total 23 395 13 287 71 789 6% 16 16 805	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 97.6% 2.4% 2.4%	.8% Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control]
;	Total (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ Test for subgroup diffe Study or Subgroup 4.1.1 >5 days Confalonieri 2005 Dequin 2023 Kim 2006 Meduri 2022 Ugajin 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 9 Test for overall effect: $:$ 4.1.2 \leq 5 days Marik 1993 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: $:$	85 $2 = 2.80 (P)$ rences: Ch Experime 0 25 3 50 6 84 $9.11, df = 4$ $Z = 2.70 (P)$ 1 1 $blicable$ $Z = 0.90 (P)$ 85 $9.47, df = 5$	$(P = 0.0)$ $= 0.005$ $i^{2} = 5.22$ ental 23 400 13 297 30 763 (P = 0.0) 14 14 = 0.37) 777 (P = 0.0)	134 (a) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c	7% P = 0.0 ol Total 23 395 13 287 71 789 6% 16 16 805	2), I ² = 80 <u>Weight</u> 6.7% 40.5% 2.8% 36.3% 97.6% 2.4% 2.4%	.8% Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.49 [0.30, 0.82] 0.68 [0.12, 3.87] 1.03 [0.67, 1.60] 0.43 [0.16, 1.20] 0.66 [0.49, 0.89] 0.33 [0.03, 3.64] 0.33 [0.03, 3.64]	Favours [experimental] Favours [control] Odds Ratio

FIGURE 2

Meta-analysis of duration of hospital stay in individuals taking corticosteroid treatment versus control group (A), subgroup analysis of corticosteroid type (B), and subgroup analysis of duration (C).

		Experime	ental	Contro	ol		Odds Ratio	Odds Ratio
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	Confalonieri 2005	0	23	7	23	11.9%	0.05 [0.00, 0.88]	
	Nafae 2013	4	60	6	20	13.7%	0.17 [0.04, 0.67]	
	El Ghamrawy 2006	3	17	6	17	8.0%	0.39 [0.08, 1.94]	
	Kim 2006	2	13	4	13	5.5%	0.41 [0.06, 2.77]	
	Torres 2015	3	55	7	57	10.6%	0.41 [0.10, 1.68]	
	Ceccato 2016	5	56	5	50	7.8%	0.88 [0.24, 3.25]	
	Serrano 2011	1	23	1	22	1.6%	0.95 [0.06, 16.27]	
	Meduri 2022	34	291	28	281	40.9%	1.20 [0.70, 2.03]	
	Total (95% CI)		538		483	100.0%	0.70 [0.47, 1.03]	•
	Total events	52		64				
	Heterogeneity: Chi ² = 1	12.79, df =	7 (P = 0	.08); ² = 4	45%			
	Test for overall effect: 2		·					0.005 0.1 1 10 200
		,						Favours [experimental] Favours [control]
		Experim		Contro			Odds Ratio	Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	3.2.1 Hydrocortisone							
	Confalonieri 2005	0	23	7	23	11.9%	0.05 [0.00, 0.88]	
	El Ghamrawy 2006	3	17	6	17	8.0%	0.39 [0.08, 1.94]	
	Kim 2006	2	13	4	13	5.5%	0.41 [0.06, 2.77]	
	Nafae 2013	4	60	6	20	13.7%	0.17 [0.04, 0.67]	
	Subtotal (95% CI)		113		73	39.1%	0.21 [0.09, 0.50]	
	Total events	9		23				
	Heterogeneity: Chi ² = 2 Test for overall effect: 2		•		%			
	3.2.2 Not Hydrocortis	one						
	Ceccato 2016	5	56	5	50	7.8%	0.88 [0.24, 3.25]	
	Meduri 2022	34	291	28	281	40.9%	1.20 [0.70, 2.03]	-
	Serrano 2011	1	23	1	22	1.6%	0.95 [0.06, 16.27]	
	Torres 2015	3	55	7	57	10.6%	0.41 [0.10, 1.68]	
	Subtotal (95% CI)		425		410	60.9%	1.01 [0.64, 1.59]	◆
	Total events							
		43	(D - 0	41	24			
	Heterogeneity: Chi ² = 1 Test for overall effect: 2	1.99, df = 3	= 0.96)	57); l ² = 0 ⁴				
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI)	1.99, df = 3 Z = 0.06 (P		57); I ² = 0 ⁴		100.0%	0.70 [0.47, 1.03]	•
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events	1.99, df = 3 Z = 0.06 (P 52	= 0.96) 538	57); l ² = 0 ⁴	483	100.0%	0.70 [0.47, 1.03]	•
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI)	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P	= 0.96) 538 7 (P = 0 = 0.07)	64 (0.08); ² = 4	483 45%			0.005 0.1 1 10 200 Favours [experimental] Favours [control]
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch	538 7 (P = 0 = 0.07) i ² = 10. ⁻	64 0.08); l ² = 0 13, df = 1	483 45% (P = 0.		90.1%	Favours [experimental] Favours [control]
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime	= 0.96) 538 7 (P = 0 = 0.07) i ² = 10. ² ental	64 0.08); l ² = 0 13, df = 1 Contr	483 45% (P = 0. ol	001), l² = s	90.1% Odds Ratio	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch	= 0.96) 538 7 (P = 0 = 0.07) i ² = 10. ² ental	64 0.08); l ² = 0 13, df = 1 Contr	483 45% (P = 0. ol	001), l² = s	90.1%	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 > 5 days	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events	= 0.96; 538 7 (P = C = 0.07); i ² = 10. ⁻¹ ental <u>Total</u>	64 .08); ² = 0 .08); ² = 4 .13, df = 1 <u>Contro</u> <u>Events</u>	483 45% (P = 0. ol <u>Total</u>	001), I² = 9 Weight	90.1% Odds Ratio <u>M-H, Fixed, 95% CI</u>	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ <u>Study or Subgroup</u> 4.2.1 >5 days Confalonieri 2005	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events 0	= 0.96; 538 7 (P = C = 0.07); i ² = 10.7 ental Total 23	64 0.08); l ² = 0 0.3, df = 1 Contru <u>Events</u> 7	483 45% (P = 0. ol <u>Total</u> 23	001), I ² = 9 <u>Weight</u> 11.9%	0.1% Odds Ratio <u>M-H. Fixed. 95% CI</u> 0.05 [0.00, 0.88]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experim Events 0 3	= 0.96; 538 7 (P = C = 0.07); i ² = 10. ² ental Total 23 17	64 0.08); l ² = 0 13, df = 1 Contro Events 7 6	483 45% (P = 0. ol <u>Total</u> 23 17	001), I ² = 9 <u>Weight</u> 11.9% 8.0%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.05 [0.00, 0.88] 0.39 [0.08, 1.94]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ <u>Study or Subgroup</u> 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events 0 3 2	= 0.96; 538 7 (P = C = 0.07) i ² = 10. ⁻¹ ental <u>Total</u> 23 17 13	64 1.08); ² = 0 13, df = 1 Contru Events 7 6 4	483 45% (P = 0. ol <u>Total</u> 23 17 13	001), I ² = 9 <u>Weight</u> 11.9% 8.0% 5.5%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events 0 3 2 34	= 0.96; 538 7 (P = C = 0.07); i ² = 10. ⁻ ental Total 23 17 13 297	64 (.08); ² = 0 (.08); ² = 4 (.08); ² = 0 (.08); ² = 4 (.08); ²	483 45% (P = 0. ol <u>Total</u> 23 17 13 281	001), I ² = 9 <u>Weight</u> 11.9% 8.0% 5.5% 41.2%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ <u>Study or Subgroup</u> 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013	1.99, df = 3 Z = 0.06 (P 2279, df = Z = 1.82 (P rences: Ch Experim Events 0 3 2 34 4	= 0.96 538 7 (P = C = 0.07) i ² = 10. ental Total 17 13 297 60	64 .08); l ² = 0 l3, df = 1 Contru Events 7 6 4 28 6	483 45% (P = 0. ol Total 13 281 20	001), I ² = 1 Weight 11.9% 8.0% 5.5% 41.2% 13.6%	Odds Ratio M-H. Fixed. 95% Cl 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events 0 3 2 34	= 0.96 538 7 (P = 0 = 0.07) i ² = 10. ⁻¹ ental Total 17 13 297 60 23	64 (.08); ² = 0 (.08); ² = 4 (.08); ² = 0 (.08); ² = 4 (.08); ²	483 45% (P = 0. ol Total 13 281 20 22	001), l ² = 1 <u>Weight</u> 11.9% 8.0% 5.5% 41.2% 13.6% 1.6%	Odds Ratio M-H. Fixed, 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI)	1.99, df = 3 Z = 0.06 (P 2.279, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1	= 0.96 538 7 (P = C = 0.07) i ² = 10. ental Total 17 13 297 60	64 0.08); ² = 0 13, df = 1 Contri <u>Events</u> 7 6 4 8 6 1	483 45% (P = 0. ol Total 13 281 20	001), I ² = 1 Weight 11.9% 8.0% 5.5% 41.2% 13.6%	Odds Ratio M-H. Fixed. 95% Cl 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1 1 4 11.76, df =	= 0.96 538 7 (P = 0 = 0.07) i ² = 10. ⁻ ental Total 23 17 13 297 60 23 433 5 (P = 0	64 1.08); ² = 0 13, df = 1 Contr Events 7 6 4 28 6 1 52 1.04); ² = 4	483 45% (P = 0. 01 Total 23 17 13 281 20 22 376	001), l ² = 1 <u>Weight</u> 11.9% 8.0% 5.5% 41.2% 13.6% 1.6%	Odds Ratio M-H. Fixed, 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1 1 4 11.76, df =	= 0.96 538 7 (P = 0 = 0.07) i ² = 10. ⁻ ental Total 23 17 13 297 60 23 433 5 (P = 0	64 1.08); ² = 0 13, df = 1 Contr Events 7 6 4 28 6 1 52 1.04); ² = 4	483 45% (P = 0. 01 Total 23 17 13 281 20 22 376	001), l ² = 1 <u>Weight</u> 11.9% 8.0% 5.5% 41.2% 13.6% 1.6%	Odds Ratio M-H. Fixed, 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ <u>Study or Subgroup</u> 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 4.2.2 ≤5 days	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1 1 76, df = Z = 1.60 (P	= 0.96) 538 7 (P = C = 0.07) i ² = 10. ⁻ ental Total 13 297 60 23 433 5 (P = C = 0.11)	64 .08); ² = 0 13, df = 1 Contro Events 7 6 4 28 6 1 52 .004); ² = 4 .004); ² = 4 .004); ² = 4 .004); ² = 4 .005); ² = 4 .00	483 45% (P = 0. ol Total 23 17 13 281 20 22 376 57%	001), I ² = 1 <u>Weight</u> 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for overall effect: 2 Test for subgroup differ <u>Study or Subgroup</u> 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 4.2.2 ≤5 days Ceccato 2016	1.99, df = 3 Z = 0.06 (P 2.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1 1.76, df = Z = 1.60 (P 5	= 0.96) 538 7 (P = 0 = 0.07) i ² = 10. ⁻ ental Total 13 297 60 23 433 5 (P = 0 = 0.11) 56	57); ² = 0 64 108); ² = 4 13, df = 1 Contru- Events 7 6 4 28 6 1 52 9.04); ² = 4 5	483 45% (P = 0. ol Total 23 17 281 20 22 376 57%	001), l ² = 1 Weight 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 4.2.2 \leq 5 days Ceccato 2016 Torres 2015	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1 1 76, df = Z = 1.60 (P	= 0.96) 538 7 (P = 0 = 0.07) i ² = 10. ⁻¹ ental Total 23 17 13 297 60 23 433 5 (P = 0 = 0.11) 56 55	64 .08); ² = 0 13, df = 1 Contro Events 7 6 4 28 6 1 52 .004); ² = 4 .004); ² = 4 .004); ² = 4 .004); ² = 4 .005); ² = 4 .00	483 45% (P = 0. ol Total 23 17 13 281 20 22 376 57% 50 57	001), I ² = 1 Weight 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8% 10.5%	Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25] 0.41 [0.10, 1.68]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 4.2.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI)	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1 1.76, df = Z = 1.60 (P 5 3	= 0.96) 538 7 (P = 0 = 0.07) i ² = 10. ⁻ ental Total 13 297 60 23 433 5 (P = 0 = 0.11) 56	57); ² = 0 64 1.08); ² = 4 13, df = 1 Contri- Events 7 6 4 28 6 1 52 9.04); ² = 5 7	483 45% (P = 0. ol Total 23 17 281 20 22 376 57%	001), l ² = 1 Weight 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 4.2.2 \leq 5 days Ceccato 2016 Torres 2015	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events 0 3 2 34 4 1 1.76, df = Z = 1.60 (P 5 3 8 0.61, df = 1		57); $ ^2 = 0^{(2)}$ 64 (0.08); $ ^2 = 4^{(2)}$ 13, df = 1 Control Events 7 6 4 28 6 1 52 9.04); $ ^2 = 5^{(2)}$ 7 12 44); $ ^2 = 0^{(2)}$	483 45% (P = 0. 01 Total 23 17 13 281 20 22 376 57% 50 57%	001), I ² = 1 Weight 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8% 10.5%	Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25] 0.41 [0.10, 1.68]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 4.2.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0$ Total events Heterogeneity: $Chi^2 = 0$ Total events Heterogeneity: $Chi^2 = 0$ Total events Heterogeneity: $Chi^2 = 0$ Test for overall effect: 2	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events 0 3 2 34 4 1 1.76, df = Z = 1.60 (P 5 3 8 0.61, df = 1	= 0.96) 538 7 (P = C = 0.07) i ² = 10. ⁻ ental Total Total 23 17 13 297 60 23 433 5 (P = C = 0.11) 56 55 111 (P = 031)	57); $ ^2 = 0^{(2)}$ 64 (0.08); $ ^2 = 4^{(2)}$ 13, df = 1 Control Events 7 6 4 28 6 1 52 9.04); $ ^2 = 5^{(2)}$ 7 12 44); $ ^2 = 0^{(2)}$	483 45% (P = 0. ol Total 23 17 13 28 20 22 376 57% 50 577 107 %	001), I ² = 1 <u>Weight</u> 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8% 10.5% 18.3%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25] 0.41 [0.10, 1.68] 0.61 [0.24, 1.57]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 EI Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 4.2.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0$ Test for overall effect: 2	1.99, df = 3 Z = 0.06 (P 2.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 2 34 4 1 1.76, df = Z = 1.60 (P 5 3 0.61, df = 1 Z = 1.02 (P		57); ² = 0 64 10.08); ² = 4 13, df = 1 Contru- Events 7 6 4 28 6 1 52 9.04); ² = 4 5 7 12 44); ² = 0	483 45% (P = 0. ol Total 23 17 13 28 20 22 376 57% 50 577 107 %	001), I ² = 1 Weight 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8% 10.5%	Odds Ratio M-H, Fixed, 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25] 0.41 [0.10, 1.68]	Favours [experimental] Favours [control] Odds Ratio
	Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Test for overall effect: 2 Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 > 5 days Confalonieri 2005 El Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 4.2.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0 Total (95% CI) Total events	1.99, df = 3 Z = 0.06 (P 2.79, df = Z = 1.82 (P rences: Ch Experim: Events 0 3 4 4 1 1.76, df = Z = 1.60 (P 5 3 0.61, df = 1 Z = 1.02 (P 52	= 0.96) 538 7 (P = C = 0.07) i ² = 10. ⁻ ental Total 23 17 13 297 60 23 433 5 (P = C 23 433 5 (P = C 55 111 (P = 0 = 0.31) 544	57); $ ^2 = 0^{(2)}$ 64 $.08)$; $ ^2 = 4^{(2)}$ $ 13, df = 1^{(2)}$ $13, df = 1^{(2)}$ $10, 000$; $ ^2 = 4^{(2)}$ 52 $10, 000$; $ ^2 = 5^{(2)}$ 57 12 12 144); $ ^2 = 0^{(2)}$ 64	483 45% (P = 0. ol Total 23 17 13 281 20 22 376 57% 50 57 50 57 107 % 483	001), I ² = 1 <u>Weight</u> 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8% 10.5% 18.3%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25] 0.41 [0.10, 1.68] 0.61 [0.24, 1.57]	Favours [experimental] Favours [control]
	Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 Test for subgroup differ Study or Subgroup 4.2.1 >5 days Confalonieri 2005 EI Ghamrawy 2006 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 1$ Test for overall effect: 2 4.2.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0$ Test for overall effect: 2	1.99, df = 3 Z = 0.06 (P 52 12.79, df = Z = 1.82 (P rences: Ch Experime Events 0 3 2 34 4 1 1.76, df = Z = 1.60 (P 5 3 0 0 3 2 34 4 1 1.25 (P 2 2 1.60 (P 5 3 0 0 3 2 34 4 1 1.25 (P 1.25 (P) 1.25	= 0.96) 538 7 (P = C = 0.07) i ² = 10. ⁻ ental Total 23 17 13 297 60 23 433 5 (P = C = 0.11) 56 55 111 (P = 0) 544 7 (P = C	57); $ ^2 = 0'$ 64 $(.08)$; $ ^2 = 4$ 13, df = 1 Control Events 7 6 4 28 6 1 52 104); $ ^2 = 4$ 52 104); $ ^2 = 5$ 7 12 144); $ ^2 = 0'$ 64 102 12	483 45% (P = 0. ol Total 23 17 13 281 20 22 376 57% 50 57 50 57 107 % 483	001), I ² = 1 <u>Weight</u> 11.9% 8.0% 5.5% 41.2% 13.6% 1.6% 81.7% 7.8% 10.5% 18.3%	Odds Ratio M-H. Fixed. 95% CI 0.05 [0.00, 0.88] 0.39 [0.08, 1.94] 0.41 [0.06, 2.77] 1.17 [0.69, 1.98] 0.17 [0.04, 0.67] 0.95 [0.06, 16.27] 0.71 [0.46, 1.08] 0.88 [0.24, 3.25] 0.41 [0.10, 1.68] 0.61 [0.24, 1.57]	Favours [experimental] Favours [control] Odds Ratio

Meta-analysis comparing the risk of gastrointestinal hemorrhage (A), frequency of hyperglycemia requiring treatment (B), and incidence of hospitalacquired infection (C) between the study group treated with corticosteroids and the control group.

		erimenta			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean			Mean			Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Ceccato 2016		10.06	56	7.67	8.49	50	3.0%	0.18 [-3.35, 3.71]	
Confalonieri 2005	12.34	7.52	23	19.65	10.89	23		-7.31 [-12.72, -1.90]	
Kim 2006	12.5	6.6	13	13.2	8.4	13	1.1%	-0.70 [-6.51, 5.11]	
Marik 1993	4.3	3.8	14	4.6	5.9	16	3.1%	-0.30 [-3.81, 3.21]	
Meduri 2022	4.4	4.47	297	4.7	4.47	287	71.9%	-0.30 [-1.03, 0.43]	
Nafae 2013	3.1	4.9	60	6.3	8.2	20	2.6%	-3.20 [-7.00, 0.60]	
Serrano 2011	7.04	2.77	23	14	14.46	22		-6.96 [-13.11, -0.81]	
Torres 2015	5.36	3.86	37	6	3.07	44	16.0%	-0.64 [-2.18, 0.90]	
Total (95% CI)			523			475	100.0%	-0.58 [-1.19, 0.04]	•
Heterogeneity: Chi ² =	12.69, df	i = 7 (P =	= 0.08)	; l² = 45	%			-	
Test for overall effect:	Z = 1.84	(P = 0.0)7)						-10 -5 0 5 10 Favours [experimental] Favours [control]
	Exp	erimenta	al	c	ontrol			Mean Difference	Mean Difference
Study or Subgroup				Mean		Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.3.1 Hydrocortisone	•						-		
Confalonieri 2005	12.34	7.52	23	19.65	10.89	23	1.3%	-7.31 [-12.72, -1.90]	·
Kim 2006	12.5	6.6	13	13.2	8.4	13	1.1%	-0.70 [-6.51, 5.11]	
Marik 1993	4.3	3.8	14	4.6	5.9	16	3.1%	-0.30 [-3.81, 3.21]	
Nafae 2013	3.1	4.9	60	6.3	8.2	20	2.6%	-3.20 [-7.00, 0.60]	
Subtotal (95% CI)			110			72	8.1%	-2.41 [-4.57, -0.25]	\bullet
Heterogeneity: Chi ² =	5.04, df =	= 3 (P =	0.17);	l² = 40%	6				
Test for overall effect:	Z = 2.19	(P = 0.0)3)						
3.3.2 Not Hydrocortis	sone								
Ceccato 2016		10.06	56	7.67	8.49	50	3.0%	0.18 [-3.35, 3.71]	
Meduri 2022	4.4	4.47	297	4.7	4.47	287	71.9%	-0.30 [-1.03, 0.43]	-
Serrano 2011	7.04	2.77	237		14.46	207		-6.96 [-13.11, -0.81]	T
Torres 2015	5.36	3.86	37	6	3.07	44	16.0%	-0.64 [-2.18, 0.90]	
Subtotal (95% CI)	0.00	0.00	413	0	0.07	403	91.9%	-0.42 [-1.06, 0.23]	•
Heterogeneity: $Chi^2 = 4$ Test for overall effect:			1.	l² = 35%	6			. / .	
		(1 0.4							
Total (95% CI)		(1 0.1	523			475	100.0%	-0.58 [-1.19, 0.04]	•
Total (95% CI) Heterogeneity: Chi ² =			523	: l² = 45	i%	475	100.0%	-0.58 [-1.19, 0.04]	→ <u></u>
Heterogeneity: Chi ² =	12.69, df	f = 7 (P =	523 = 0.08)	; I² = 45	9%	475	100.0%	-0.58 [-1.19, 0.04] _	-10 -5 0 5 10
	12.69, df Z = 1.84	f = 7 (P = · (P = 0.0	523 = 0.08) 07)					-0.58 [-1.19, 0.04] _	-10 -5 0 5 10 Favours [experimental] Favours [control]
Heterogeneity: Chi ² = Test for overall effect:	12.69, df Z = 1.84	f = 7 (P = · (P = 0.0	523 = 0.08) 07)					-0.58 [-1.19, 0.04] –	
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe	12.69, df Z = 1.84 erences: (Expe	f = 7 (P = (P = 0.0 Chi ² = 3. erimenta	523 = 0.08))7) .01, df al	= 1 (P =	= 0.08), Control	I² = 66.	8%	Mean Difference	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup	12.69, df Z = 1.84 erences: (Expe	f = 7 (P = (P = 0.0 Chi ² = 3. erimenta	523 = 0.08))7) .01, df al	= 1 (P :	= 0.08), Control	I² = 66.		Mean Difference	Favours [experimental] Favours [control]
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.3.1 >5 days	12.69, df Z = 1.84 erences: (Expe Mean	f = 7 (P = . (P = 0.0 Chi ² = 3 erimenta SD	523 = 0.08) 07) .01, df al <u>Total</u>	= 1 (P = C <u>Mean</u>	= 0.08), Control SD	² = 66. Total	8% Weight	Mean Difference IV, Fixed, 95% Cl	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe <u>Study or Subgroup</u> 4.3.1 >5 days Confalonieri 2005	12.69, df Z = 1.84 erences: 0 <u>Expe</u> <u>Mean</u> 12.34	f = 7 (P = (P = 0.0 Chi ² = 3. eriment: <u>SD</u> 7.52	523 = 0.08) 07) .01, df al <u>Total</u> 23	= 1 (P = 0 <u>Mean</u> 19.65	= 0.08), Control SD 10.89	² = 66. <u>Total</u> 23	8% <u>Weight</u> 1.3%	Mean Difference IV, Fixed, 95% CI -7.31 [-12.72, -1.90]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.3.1 >5 days Confalonieri 2005 Kim 2006	12.69, df Z = 1.84 erences: 0 Expe <u>Mean</u> 12.34 12.5	f = 7 (P = (P = 0.0 Chi ² = 3. eriment: <u>SD</u> 7.52 6.6	523 = 0.08))7) .01, df al <u>Total</u> 23 13	= 1 (P = 0 <u>Mean</u> 19.65 13.2	= 0.08), Control SD 10.89 8.4	l ² = 66. <u>Total</u> 23 13	8% <u>Weight</u> 1.3% 1.1%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different 4.3.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4	f = 7 (P = 0.0) (Chi ² = 3.) erimenta SD 7.52 6.6 4.47	523 = 0.08) 07) .01, df al <u>Total</u> 23 13 297	= 1 (P = 0 <u>Mean</u> 19.65 13.2 4.7	= 0.08), Control SD 10.89 8.4 4.47	l ² = 66. Total 23 13 287	8% Weight 1.3% 1.1% 71.9%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe <u>Study or Subgroup</u> 4.3.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1	$f = 7 (P = 0.0)$ $Chi^{2} = 3.0$ erimenta SD 7.52 6.6 4.47 4.9	523 = 0.08) 07) .01, df al Total 23 13 297 60	= 1 (P = C <u>Mean</u> 19.65 13.2 4.7 6.3	= 0.08), Control SD 10.89 8.4 4.47 8.2	l ² = 66. <u>Total</u> 23 13 287 20	8% Weight 1.3% 1.1% 71.9% 2.6%	Mean Difference IV. Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe 4.3.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4	f = 7 (P = 0.0) (Chi ² = 3.) erimenta SD 7.52 6.6 4.47	523 = 0.08) 07) .01, df al Total 23 13 297 60 23	= 1 (P = C <u>Mean</u> 19.65 13.2 4.7 6.3	= 0.08), Control SD 10.89 8.4 4.47	l ² = 66. <u>Total</u> 23 13 287 20 22	8% <u>Weight</u> 1.3% 1.1% 71.9% 2.6% 1.0%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different 4.3.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: Chi ² =	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df	f = 7 (P = 0.0) $(P = 0.0)$	523 = 0.08) 07) .01, df al Total 23 13 297 60 23 416 = 0.01)	= 1 (P = C Mean 19.65 13.2 4.7 6.3 14	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46	l ² = 66. <u>Total</u> 23 13 287 20	8% Weight 1.3% 1.1% 71.9% 2.6%	Mean Difference IV. Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different for subgroup	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df	f = 7 (P = 0.0) $(P = 0.0)$	523 = 0.08) 07) .01, df al Total 23 13 297 60 23 416 = 0.01)	= 1 (P = C Mean 19.65 13.2 4.7 6.3 14	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46	l ² = 66. <u>Total</u> 23 13 287 20 22	8% <u>Weight</u> 1.3% 1.1% 71.9% 2.6% 1.0%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different di	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70	f = 7 (P = 0.0) (P = 0.0) Chi ² = 3. erimenta SD 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) f = 0.0	523 = 0.08) 07) .01, df al Total 23 13 297 60 23 416 = 0.01)	= 1 (P = C Mean 19.65 13.2 4.7 6.3 14	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 %	l ² = 66. <u>Total</u> 23 13 287 20 22	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9%	Mean Difference IV. Fixed. 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different 4.3.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: 4.3.2 \leq 5 days Ceccato 2016	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85	f = 7 (P = 0.0) (P = 0.0) Chi ² = 3. erimenta 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06	523 = 0.08) 07) .01, df al Total 23 13 297 60 23 416 = 0.01)	= 1 (P = C Mean 19.65 13.2 4.7 6.3 14	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 % 8.49	l ² = 66. <u>Total</u> 23 13 287 20 22	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different 4.3.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: 4.3.2 \leq 5 days Ceccato 2016 Marik 1993	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 12.48, df Z = 1.70 7.85 4.3	f = 7 (P = 0.0) Chi ² = 3. erimenta 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06 3.8	523 = 0.08))7) 0.01, df al Total 23 13 297 60 23 416 = 0.01))9) 56 14	= 1 (P = <u>Mean</u> 19.65 13.2 4.7 6.3 14 ; l ² = 68 7.67 4.6	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 19% 8.49 5.9	l ² = 66. Total 23 13 287 20 22 365 50 16	8% <u>Weight</u> 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1%	Mean Difference IV. Fixed, 95% CI -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different for subgroup	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85	f = 7 (P = 0.0) (P = 0.0) Chi ² = 3. erimenta 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06	523 = 0.08))7) .01, df al Total 23 13 297 60 23 416 = 0.01))9) 566 14 37	= 1 (P = <u>0</u> 19.65 13.2 4.7 6.3 14 ; l ² = 68 7.67	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 % 8.49	² = 66. Total 23 13 287 20 22 365 50 16 44	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1% 16.0%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21] -0.64 [-2.18, 0.90]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different 4.3.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: Chi ² = Test for overall effect: 4.3.2 \leq 5 days Ceccato 2016 Marik 1993 Torres 2015 Subtotal (95% CI)	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85 4.3 5.36	f = 7 (P = 0.0) (P = 0.0) Chi ² = 3.0 erimentation 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06 3.8 3.86	523 = 0.08))7) 0.01, df al Total 23 13 297 60 23 2416 = 0.01))9) 56 14 37 107	= 1 (P : <u>Mean</u> 19.65 13.2 4.7 6.3 14 ; l ² = 68 7.67 4.6 6	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 19% 8.49 5.9 3.07	l ² = 66. <u>Total</u> 23 13 287 20 22 365 50 16	8% <u>Weight</u> 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1%	Mean Difference IV. Fixed, 95% CI -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different for subgroup	12.69, dff Z = 1.84 erences: (Mean 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85 4.3 5.36 0.19, df =	f = 7 (P = 0.0) (P = 0.0) Chi ² = 3. erimenta 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06 3.8 3.86 = 2 (P = 0.0)	523 = 0.08))7) .01, df al Total 23 13 297 60 23 4 297 60 23 4 60 23 4 90 23 4 90 23 4 37 60 23 4 37 60 23 4 37 7 00 23 4 37 7 00 8 9 7 10 8 10 8 10 8 10 8 10 8 10 8 10 8 10	= 1 (P : <u>Mean</u> 19.65 13.2 4.7 6.3 14 ; l ² = 68 7.67 4.6 6	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 19% 8.49 5.9 3.07	² = 66. Total 23 13 287 20 22 365 50 16 44	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1% 16.0%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21] -0.64 [-2.18, 0.90]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different 4.3.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: 4.3.2 \leq 5 days Ceccato 2016 Marik 1993 Torres 2015 Subtotal (95% Cl) Heterogeneity: Chi ² = 1 Test for overall effect:	12.69, dff Z = 1.84 erences: (Mean 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85 4.3 5.36 0.19, df =	f = 7 (P = 0.0) (P = 0.0) Chi ² = 3. erimenta 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06 3.8 3.86 = 2 (P = 0.0)	523 523 50.01, 77) .01, df al Total 23 13 297 60 23 416 50.01) 99) 56 14 37 107 0.91); 17)	= 1 (P : <u>Mean</u> 19.65 13.2 4.7 6.3 14 ; l ² = 68 7.67 4.6 6	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 19% 8.49 5.9 3.07	Total 23 13 287 20 22 365 50 16 44 110	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1% 16.0% 22.1%	Mean Difference IV. Fixed, 95% CI -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21] -0.64 [-2.18, 0.90] -0.48 [-1.79, 0.83]	Favours [experimental] Favours [control] Mean Difference
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different A.3.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: 4.3.2 \leq 5 days Ceccato 2016 Marik 1993 Torres 2015 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: Test for overall effect:	12.69, df Z = 1.84 erences: (Mean 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85 4.3 5.36 0.19, df = Z = 0.72	f = 7 (P = 0.0) Chi ² = 3. erimenta 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06 3.8 3.86 = 2 (P = 0.4)	523 523 500 507 507 60 23 416 500 23 416 500 14 37 107 00.91); 57 523	= 1 (P * <u>Nean</u> 19.65 13.2 4.7 6.3 14 ; I ² = 68 7.67 4.6 6 1 ² = 0%	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 ¹ % 8.49 5.9 3.07	Total 23 13 287 20 22 365 50 16 44 110	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1% 16.0%	Mean Difference IV, Fixed, 95% Cl -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21] -0.64 [-2.18, 0.90]	Favours [experimental] Favours [control]
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe 4.3.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: 4.3.2 \leq 5 days Ceccato 2016 Marik 1993 Torres 2015 Subtotal (95% Cl) Heterogeneity: Chi ² = 1 Test for overall effect: Total (95% Cl) Heterogeneity: Chi ² = 1	12.69, df Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85 4.3 5.36 0.19, df = Z = 0.72 12.69, df	f = 7 (P = 0.0) (P = 0.0) Chi ² = 3. erimenta: SD 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06 3.8 3.86 = 2 (P = 0.4) (P = 0.4) f = 7 (P = 0.4)	523 523 57 001, df al Total 7 23 3 3 297 60 23 416 = 0.01) 99 566 14 37 107 0.91); 77 523 = 0.08)	= 1 (P * <u>Nean</u> 19.65 13.2 4.7 6.3 14 ; I ² = 68 7.67 4.6 6 1 ² = 0%	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 ¹ % 8.49 5.9 3.07	Total 23 13 287 20 22 365 50 16 44 110	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1% 16.0% 22.1%	Mean Difference IV. Fixed, 95% CI -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21] -0.64 [-2.18, 0.90] -0.48 [-1.79, 0.83]	Favours [experimental] Favours [control]
Heterogeneity: Chi ² = Test for overall effect: Test for subgroup different A.3.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: 4.3.2 \leq 5 days Ceccato 2016 Marik 1993 Torres 2015 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: Test for overall effect:	12.69, dff Z = 1.84 erences: (<u>Expe</u> <u>Mean</u> 12.34 12.5 4.4 3.1 7.04 12.48, df Z = 1.70 7.85 4.3 5.36 0.19, df = Z = 0.72 12.69, df Z = 1.84	$f = 7 (P = 0.0)$ $(P = 0.0)$ $Chi^{2} = 3.$ eriment: SD 7.52 6.6 4.47 4.9 2.77 f = 4 (P = 0.0) 10.06 3.88 3.86 = 2 (P = 0.4) f = 7 (P = 0.0)	523 523 57) 001, df al Total 23 13 297 60 23 416 = 0.01) 09) 566 14 37 107 0.91); 47) 523 = 0.08)	= 1 (P = 1) $(P = 1)$	= 0.08), Control SD 10.89 8.4 4.47 8.2 14.46 % 8.49 5.9 3.07 %	I² = 66. Total 23 13 287 20 22 365 50 16 44 110 475	8% Weight 1.3% 1.1% 71.9% 2.6% 1.0% 77.9% 3.0% 3.1% 16.0% 22.1%	Mean Difference IV. Fixed, 95% CI -7.31 [-12.72, -1.90] -0.70 [-6.51, 5.11] -0.30 [-1.03, 0.43] -3.20 [-7.00, 0.60] -6.96 [-13.11, -0.81] -0.60 [-1.30, 0.09] 0.18 [-3.35, 3.71] -0.30 [-3.81, 3.21] -0.64 [-2.18, 0.90] -0.48 [-1.79, 0.83]	Favours [experimental] Favours [control]

type (B), and subgroup analysis of duration (C).

and mineralocorticoid actions, may offer distinct therapeutic benefits, especially in the context of sCAP. Additionally, hydrocortisone is a low-potency and short-acting glucocorticoid, while prednisolone, and methylprednisolone are long-acting corticosteroids that exhibit higher potency than hydrocortisone (43). Hydrocortisone regulates the

immune response and reducing inflammation without inducing excessive immune dysregulation, unlike other corticosteroids that can lead to prolonged immunosuppression (46). Therefore, these characteristics of hydrocortisone may contribute to the observed mortality benefits in sCAP (47).

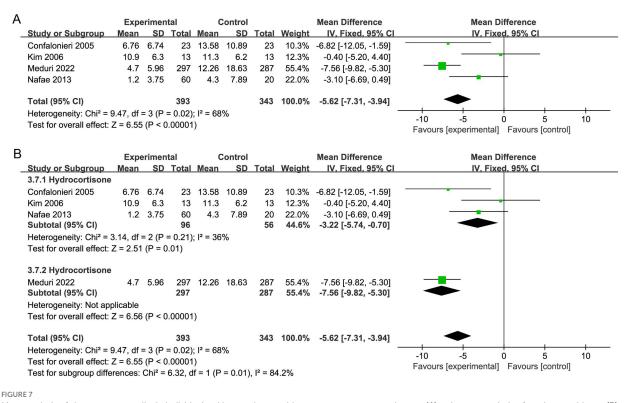
		eriment			ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean			Mean			Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Ceccato 2016		15.11		15.49		50	1.2%	-0.53 [-7.06, 6.00]	
Confalonieri 2005	18.1	11.15	23	25.55	17.89	23	0.7%	-7.45 [-16.07, 1.17]	
Kim 2006	19.5	11.3	13	17.9	7.9	13	0.9%	1.60 [-5.89, 9.09]	
Meduri 2022	7.7	5.96	297	9.05	8.2	287	38.1%	-1.35 [-2.52, -0.18]	
Nafae 2013	9.27	2.4	60	16.5	2.24	20	38.8%	-7.23 [-8.38, -6.08]	
Serrano 2011	10.71	3.16	23	13.08	7.13	22	4.9%	-2.37 [-5.62, 0.88]	
Torres 2015	11	4.57	55	11.5	5.32	57	15.4%	-0.50 [-2.33, 1.33]	
Total (95% CI)			527			472	100.0%	-3.56 [-4.28, -2.84]	•
Heterogeneity: Chi ² =	67.26, d	f = 6 (P	< 0.00	001); l ² :	= 91%			-	
Test for overall effect:	Z = 9.69) (P < 0.	00001)						-10 -5 0 5 10 Favours [experimental] Favours [control]
	_								
	-	eriment			ontrol			Mean Difference	Mean Difference
Study or Subgroup 3.4.1 Hydrocortisone	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Confalonieri 2005		11.15	23	25.55	17.89	23	0.7%	-7.45 [-16.07, 1.17]	+
Kim 2006	19.5		13	17.9	7.9	13	0.9%	1.60 [-5.89, 9.09]	
Nafae 2013	9.27	2.4	60	16.5	2.24	20		-7.23 [-8.38, -6.08]	-
Subtotal (95% CI)	5.21	2.4	96	10.0	2.24	56		-7.03 [-8.16, -5.90]	•
Heterogeneity: Chi ² =	5 22 df	- 2 (P -		12 - 620	/	00	40.470	-1.00 [-0.10, -0.00]	•
Test for overall effect:					0				
3.4.2 Not Hydrocortis	sone								
Ceccato 2016		15.11	56	15.49	18.76	50	1.2%	-0.53 [-7.06, 6.00]	
Meduri 2022	7.7		297	9.05	8.2	287	38.1%		
Serrano 2011	10.71	3.16		13.08	7.13	22	4.9%	-2.37 [-5.62, 0.88]	
Torres 2015	11	4.57	55	11.5	5.32	57	15.4%	-0.50 [-2.33, 1.33]	
Subtotal (95% CI)			431	1110	0.02	416		-1.20 [-2.13, -0.27]	\bullet
Heterogeneity: Chi ² = Test for overall effect:				l² = 0%					
root for overall endet.	Z = 2.52	2 (P = 0.)	01)						
	Z = 2.52	2 (P = 0.)	01) 527			472	100.0%	-3.56 [-4.28, -2.84]	•
Total (95% CI)			527)01): l² :	= 91%	472	100.0%	-3.56 [-4.28, -2.84]	• • •
	67.26, d	f = 6 (P	527 < 0.00		= 91%	472	100.0%	-3.56 [-4.28, -2.84] _	
Total (95% CI) Heterogeneity: Chi ² =	67.26, d Z = 9.69	f = 6 (P 9 (P < 0.	527 < 0.000 00001)					-3.56 [-4.28, -2.84] _	-10 -5 0 5 10 Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect:	67.26, d Z = 9.69 erences:	f = 6 (P 9 (P < 0. Chi² = 6	527 < 0.000 00001) 0.88, c	if = 1 (P	< 0.00			_	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe	67.26, d Z = 9.69 erences: Exp	f = 6 (P 9 (P < 0.1 Chi ² = 6 periment	527 < 0.000 00001) 0.88, c	if = 1 (P	< 0.00	001), I²	= 98.4%	Mean Difference	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup	67.26, d Z = 9.69 erences: Exp	f = 6 (P 9 (P < 0.1 Chi ² = 6 periment	527 < 0.000 00001) 0.88, c	if = 1 (P	< 0.00	001), I²		Mean Difference	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days	67.26, d Z = 9.69 erences: Exp Mean	f = 6 (P 9 (P < 0. Chi ² = 6 eeriment SD	527 < 0.000 00001) 0.88, c al <u>Total</u>	lf = 1 (P C Mean	< 0.00 Control	001), I² <u>Total</u>	= 98.4% Weight	Mean Difference IV. Fixed, 95% Cl	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005	67.26, d Z = 9.69 erences: Exp <u>Mean</u> 18.1	f = 6 (P) O(P < 0.1) $Chi^2 = 6$ $Chi^2 = 6$ SD 11.15	527 < 0.000 00001) 0.88, c al <u>Total</u> 23	lf = 1 (P C <u>Mean</u> 25.55	< 0.00 Control SD 17.89	001), I² <u>Total</u> 23	= 98.4% <u>Weight</u> 0.7%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006	67.26, d Z = 9.69 erences: <u>Exp</u> <u>Mean</u> 18.1 19.5	f = 6 (P < 0.) $Chi^2 = 6$ periment <u>SD</u> 11.15 11.3	527 < 0.000 00001) 00.88, c tal <u>Total</u> 23 13	if = 1 (P <u>Mean</u> 25.55 17.9	 < 0.000 Control SD 17.89 7.9 	001), I ² <u>Total</u> 23 13	= 98.4% <u>Weight</u> 0.7% 0.9%	Mean Difference IV, Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7	f = 6 (P eriment <u>SD</u> 11.15 11.3 5.96	527 < 0.000 00001) 0.88, o tal <u>Total</u> 23 13 297	ff = 1 (P Mean 25.55 17.9 9.05	control SD 17.89 7.9 8.2	001), I ² Total 23 13 287	= 98.4% Weight 0.7% 0.9% 38.1%	Mean Difference IV. Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7 9.27	$f = 6 (P < 0.)$ $Chi^{2} = 6$ eriment SD 11.15 11.3 5.96 2.4	527 < 0.000 00001) 0.88, o al Total 23 13 297 60	ff = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5	 < 0.000 Control SD 17.89 7.9 8.2 2.24 	001), I ² Total 23 13 287 20	= 98.4% Weight 0.7% 0.9% 38.1% 38.8%	Mean Difference IV. Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Međuri 2022 Nafae 2013 Serrano 2011	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7	$f = 6 (P < 0.)$ $Chi^{2} = 6$ eriment SD 11.15 11.3 5.96 2.4	527 < 0.000 00001) 0.88, c al <u>Total</u> 23 13 297 60 23	ff = 1 (P Mean 25.55 17.9 9.05	control SD 17.89 7.9 8.2	001), I ² Total 23 13 287 20 22	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI)	67.26, d Z = 9.69 erences: <u>Exp</u> <u>Mean</u> 18.1 19.5 7.7 9.27 10.71	f = 6 (P 0 (P < 0.) Chi2 = 6 eriment 11.15 11.3 5.96 2.4 3.16	527 < 0.000 00001) 0.88, c al Total 23 13 297 60 23 416	lf = 1 (P C 25.55 17.9 9.05 16.5 13.08	< 0.000 control SD 17.89 7.9 8.2 2.24 7.13	001), I ² Total 23 13 287 20	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9%	Mean Difference IV. Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Međuri 2022 Nafae 2013 Serrano 2011	67.26, d Z = 9.65 erences: Exp <u>Mean</u> 18.1 19.5 7.7 9.27 10.71 53.48, d	f = 6 (P < 0.) Chi ² = 6 eriment SD 11.15 11.3 5.96 2.4 3.16 f = 4 (P	527 < 0.000 00001) 0.88, c al Total 23 13 297 60 23 416 < 0.000	lf = 1 (P C 25.55 17.9 9.05 16.5 13.08	< 0.000 control SD 17.89 7.9 8.2 2.24 7.13	001), I ² Total 23 13 287 20 22	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect:	67.26, d Z = 9.65 erences: Exp <u>Mean</u> 18.1 19.5 7.7 9.27 10.71 53.48, d	f = 6 (P < 0.) Chi ² = 6 eriment SD 11.15 11.3 5.96 2.4 3.16 f = 4 (P	527 < 0.000 00001) 0.88, c al Total 23 13 297 60 23 416 < 0.000	lf = 1 (P C 25.55 17.9 9.05 16.5 13.08	< 0.000 control SD 17.89 7.9 8.2 2.24 7.13	001), I ² Total 23 13 287 20 22	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: Chi ² = Test for overall effect: 4.4.2 \leq 5 days	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3	$f = 6 (P)$ $(P < 0.)$ $Chi^{2} = 6$ $eriment$ 11.15 11.3 5.96 2.4 3.16 $f = 4 (P)$ $F < 0$	527 < 0.000 00001) 00.88, c al Total 23 3 3 297 60 23 416 < 0.000	if = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5 13.08 001); I ²	control SD 17.89 7.9 8.2 2.24 7.13 = 93%	001), I ² Total 23 13 287 20 22 365	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4%	Mean Difference IV. Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016	67.26, d Z = 9.65 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3	f = 6 (P 0 (P < 0.) Chi2 = 6 eriment 11.15 11.3 5.96 2.4 3.16 f = 4 (P 07 (P < 0 15.11	527 < 0.000 00001) 0.88, c tal Total 23 13 297 60 23 416 < 0.000 0.0000 56	lif = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5 13.08 (001); I ²	control SD 17.89 7.9 8.2 2.24 7.13 = 93% 18.76	001), I ² Total 23 13 287 20 22 365 50	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016 Torres 2015	67.26, d Z = 9.65 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3	$f = 6 (P)$ $(P < 0)$ $Chi^{2} = 6$ $Periment$ SD 11.15 11.3 5.96 2.4 3.16 $f = 4 (P)$ $F < C$	527 < 0.000 00001) 00.88, c tal Total 23 13 297 60 23 416 < 0.000 0.0000 56 55	lif = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5 13.08 (001); I ²	control SD 17.89 7.9 8.2 2.24 7.13 = 93%	001), I ² 23 13 287 20 22 365 50 57	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2% 15.4%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00] -0.50 [-2.33, 1.33]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI)	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3 14.96 11	f = 6 (P < 0.) Chi ² = 6 eriment 11.15 11.3 5.96 2.4 3.16 f = 4 (P 87 (P < 0) 15.11 4.57	527 < 0.000 00001) 00.88 c al Total 23 13 297 60 23 416 < 0.000 0.00000 566 555 111	If = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5 13.08 001); I ² 1) 15.49 11.5	control SD 17.89 7.9 8.2 2.24 7.13 = 93% 18.76	001), I ² Total 23 13 287 20 22 365 50	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00] -0.50 [-2.33, 1.33]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016 Torres 2015	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3 14.96 11 0.00, df	f = 6 (P < 0.) Chi ² = 6 eriment 11.15 11.3 5.96 2.4 3.16 f = 4 (P 37 (P < 0) 15.11 4.57 = 1 (P = 1)	527 < 0.000 00001) 00.88, c al Total 23 13 297 60 0 23 416 < 0.000 0.00000 566 55 111 0.99);	If = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5 13.08 001); I ² 1) 15.49 11.5	control SD 17.89 7.9 8.2 2.24 7.13 = 93% 18.76	001), I ² 23 13 287 20 22 365 50 57	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2% 15.4%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00] -0.50 [-2.33, 1.33]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect:	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3 14.96 11 0.00, df	f = 6 (P < 0.) Chi ² = 6 eriment 11.15 11.3 5.96 2.4 3.16 f = 4 (P 37 (P < 0) 15.11 4.57 = 1 (P = 1)	527 < 0.000 000001) 00.88, c al 23 13 297 23 416 < 0.000 0.0000 56 55 111 0.99); 58)	If = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5 13.08 001); I ² 1) 15.49 11.5	control SD 17.89 7.9 8.2 2.24 7.13 = 93% 18.76	001), I ² Total 23 3 287 20 22 365 50 57 107	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2% 15.4% 16.6%	Mean Difference IV. Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00] -0.50 [-2.33, 1.33] -0.50 [-2.27, 1.26]	Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Total (95% CI)	67.26, d Z = 9.65 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3 14.96 11 0.00, df Z = 0.56	$f = 6 (P)$ $(P < 0.)$ $Chi^{2} = 6$ F F SD 11.15 11.3 5.96 2.4 3.16 $f = 4 (P)$ 15.11 4.57 $f = 1 (P) = 0$ $(P = 0.1)$	527 < 0.000 000001) 0.88, c al 23 13 297 60 23 297 60 23 416 < 0.000 23 2416 < 0.0000 56 55 111 0.99); 58) 527	lf = 1 (P (<u>Mean</u> 25.55 17.9 9.05 16.5 13.08 001); l ² 1) 15.49 11.5 l ² = 0%	< 0.000 Sontrol 5D 7.9 8.2 2.24 7.13 = 93% 18.76 5.32	001), I ² Total 23 3 287 20 22 365 50 57 107	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2% 15.4% 16.6%	Mean Difference IV. Fixed, 95% CI -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00] -0.50 [-2.33, 1.33]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 > 5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Total (95% CI) Heterogeneity: $Chi^2 =$	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3 14.96 11 0.00, df Z = 0.56 67.26, d	f = 6 (P 0 (P < 0.) Chi2 = 6 eriment 11.15 11.3 5.96 2.4 3.16 f = 4 (P 37 (P < C 15.11 4.57 = 1 (P = 6 (P = 0.) f = 6 (P	527 < 0.000 000001) 0.88, c aal 23 13 297 60 23 2416 < 2.000 0.0000 556 55111 0.99); 558) 527 < 0.000	lf = 1 (P (Mean 25.55 17.9 9.05 16.5 13.08 001); I ² 15.49 11.5 I ² = 0% 001); I ²	< 0.000 Sontrol 5D 7.9 8.2 2.24 7.13 = 93% 18.76 5.32	001), I ² Total 23 3 287 20 22 365 50 57 107	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2% 15.4% 16.6%	Mean Difference IV. Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00] -0.50 [-2.33, 1.33] -0.50 [-2.27, 1.26]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Test for subgroup diffe Study or Subgroup 4.4.1 >5 days Confalonieri 2005 Kim 2006 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: 4.4.2 \leq 5 days Ceccato 2016 Torres 2015 Subtotal (95% CI) Heterogeneity: $Chi^2 =$ Test for overall effect: Total (95% CI)	67.26, d Z = 9.69 erences: Exp Mean 18.1 19.5 7.7 9.27 10.71 53.48, d Z = 10.3 14.96 11 0.00, df Z = 0.56 67.26, d Z = 9.69	f = 6 (P 0 (P < 0.) Chi2 = 6 eriment 11.15 11.3 5.96 2.4 3.16 f = 4 (P 0 (P < 0.) 15.11 4.57 = 1 (P = 6 (P = 0.) f = 6 (P < 0.) f = 6 (P < 0.) (P < 0.)	527 < 0.000 000001) 00.88, c aal 70tal 23 13 297 60 023 416 < 20.000 0.0000 556 55111 0.99); 58) 527 < 0.000	lf = 1 (P <u>Mean</u> 25.55 17.9 9.05 16.5 13.08 001); l ² 15.49 11.5 l ² = 0% 001); l ²	< 0.000 control SD 17.89 7.9 8.2 2.24 7.13 = 93% 18.76 5.32 = 91%	0001), I ² Total 23 13 287 20 22 365 50 57 107 472	= 98.4% Weight 0.7% 0.9% 38.1% 38.8% 4.9% 83.4% 1.2% 15.4% 16.6% 100.0%	Mean Difference IV. Fixed, 95% Cl -7.45 [-16.07, 1.17] 1.60 [-5.89, 9.09] -1.35 [-2.52, -0.18] -7.23 [-8.38, -6.08] -2.37 [-5.62, 0.88] -4.17 [-4.95, -3.38] -0.53 [-7.06, 6.00] -0.50 [-2.33, 1.33] -0.50 [-2.27, 1.26]	Favours [experimental] Favours [control]

and subgroup analysis of duration (C).

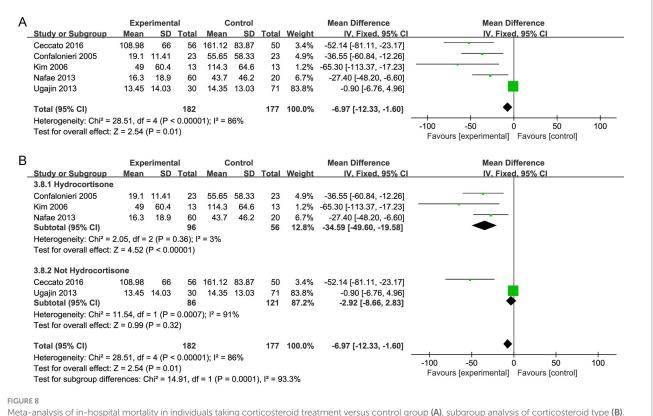
In conclusion, our meta-analysis included the largest sample size according to current international sCAP inclusion standards. In light of the disparate results of two recent RCTs, we performed subgroup analyses in accordance with corticosteroid type. From the perspective of pathophysiology, although different types of corticosteroids are dose-equivalent, the choice of corticosteroids can vary due to differences in terms of efficacy and pharmacokinetic characteristics. In fact, these corticosteroids are not exactly the same in terms of efficacy and pharmacokinetic characteristics. Our meta-analysis demonstrated the benefits of hydrocortisone treatment compared with other types of corticosteroids. This discovery has significant implications for informing the design of RCTs.

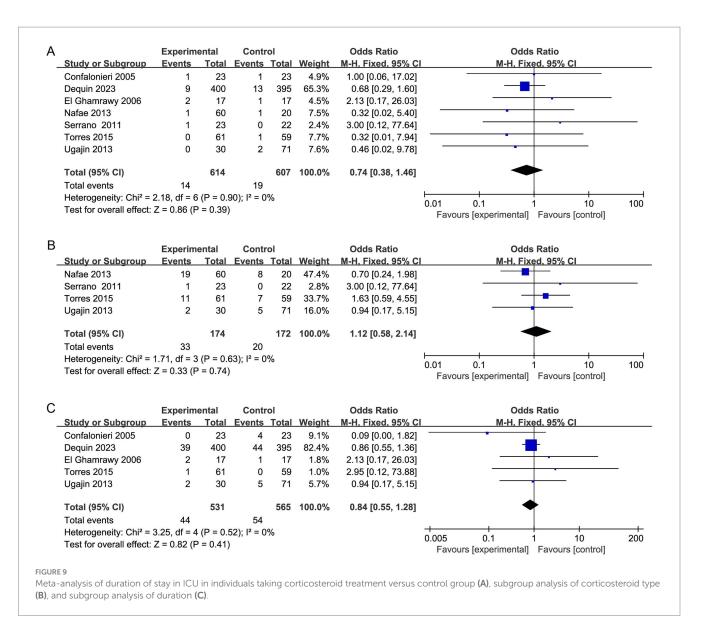
	Study or Subgroup	Experime Events		Contro Events		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl
	Ceccato 2016	5	56	6	50	4.6%	0.72 [0.21, 2.52]	
	Deguin 2023	55	308	89	310	58.2%	0.54 [0.37, 0.79]	
	Marik 1993	2	14	4	16	2.6%	0.50 [0.08, 3.27]	
	Meduri 2022	28	200	29	191	20.4%	0.91 [0.52, 1.60]	_ _
	Nafae 2013	8	60	5	20	5.2%	0.46 [0.13, 1.62]	
	Serrano 2011	1	23	5	20	3.9%	0.40 [0.13, 1.02]	
	Torres 2015	3	23 55	5	22 57			
	Tones 2015	3	55	'	57	5.2%	0.41 [0.10, 1.68]	
	Total (95% CI)		716		666	100.0%	0.60 [0.45, 0.79]	◆
	Total events	102		145				
	Heterogeneity: Chi ² = 4 Test for overall effect:				%			0.02 0.1 1 10 50 Favours [experimental] Favours [control]
3		Experime		Contr			Odds Ratio	Odds Ratio
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	3.6.1 Hydrocortisone							_
	Dequin 2023	55	308	89	310	58.2%	0.54 [0.37, 0.79]	
	Marik 1993	2	14	4	16	2.6%	0.50 [0.08, 3.27]	
	Nafae 2013	8	60	5	20	5.2%	0.46 [0.13, 1.62]	
	Subtotal (95% CI)	-	382	-	346	65.9%	0.53 [0.37, 0.76]	\bullet
	Total events	65		98				
	Heterogeneity: $Chi^2 = 0$ Test for overall effect:	0.06, df = 2		97); l² = 0	%			
	3.6.2 Not Hydrocortis	one						
	Ceccato 2016	5	56	6	50	4.6%	0.72 [0.21, 2.52]	
	Meduri 2022	28	200	29	191	20.4%	0.91 [0.52, 1.60]	
	Serrano 2011	1	23	5	22	3.9%	0.15 [0.02, 1.45]	
	Torres 2015	3	55	7	57	5.2%	0.41 [0.10, 1.68]	
	Subtotal (95% CI)	Ū	334	,	320	34.1%	0.72 [0.45, 1.14]	•
	Total events	37		47				
	Heterogeneity: $Chi^2 = 3$ Test for overall effect:	3.08, df = 3		38); l² = 3	%			
	Total (95% CI)		716		666	100.0%	0.60 [0.45, 0.79]	•
	Total events	102		145				
	Heterogeneity: Chi ² = 4	4.37, df = 6	(P = 0.6	53); l ² = 0 ⁴	%			0.01 0.1 1 10 100
	Test for overall effect: Test for subaroup diffe			,	P = 0.3	1). I² = 4.0	1%	Favours [experimental] Favours [control]
		Experime	ental	Contr	al		Odds Ratio	Odds Ratio
)						Weight	M-H, Fixed, 95% CI	
-	Study or Subgroup		Total	Events	Total	weight	MI-11, 1 1XCG, 33/0 OI	INI-II, FIXEU, 35% CI
_	4.5.1 >5 days	Events						
;	4.5.1 >5 days Dequin 2023	Events 55	308	89	310	58.2%	0.54 [0.37, 0.79]	
;	4.5.1 >5 days Dequin 2023 Meduri 2022	Events 55 28	308 200	89 29	310 191	58.2% 20.4%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60]	
; _	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013	Events 55 28 8	308 200 60	89 29 5	310 191 20	58.2% 20.4% 5.2%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62]	
; _	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011	Events 55 28	308 200 60 23	89 29	310 191 20 22	58.2% 20.4% 5.2% 3.9%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45]	
) _	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI)	55 28 8 1	308 200 60	89 29 5 5	310 191 20	58.2% 20.4% 5.2%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62]	
)	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events	Events 55 28 8 1 92	308 200 60 23 591	89 29 5 5 128	310 191 20 22 543	58.2% 20.4% 5.2% 3.9%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45]	
) _	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI)	<u>Events</u> 55 28 8 1 92 3.97, df = 3	308 200 60 23 591 (P = 0.2	89 29 5 5 128 26); I ² = 2	310 191 20 22 543	58.2% 20.4% 5.2% 3.9%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45]	
	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect:	<u>Events</u> 55 28 8 1 92 3.97, df = 3	308 200 60 23 591 (P = 0.2	89 29 5 5 128 26); I ² = 2	310 191 20 22 543	58.2% 20.4% 5.2% 3.9%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45]	
-	4.5.1 > 5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: $4.5.2 \leq 5$ days	<u>Events</u> 55 28 8 1 92 3.97, df = 3 Z = 3.28 (P	308 200 60 23 591 (P = 0.2 = 0.001	89 29 5 5 128 26); ² = 2-	310 191 20 22 543	58.2% 20.4% 5.2% 3.9% 87.6%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45] 0.60 [0.45, 0.82]	
	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 4.5.2 \leq 5 days Ceccato 2016	<u>Events</u> 55 28 8 1 92 3.97, df = 3 Z = 3.28 (P 5	308 200 60 23 591 (P = 0.2 = 0.001	89 29 5 128 26); I ² = 24	310 191 20 22 543 4%	58.2% 20.4% 5.2% 3.9% 87.6%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45] 0.60 [0.45, 0.82]	• • • • • • • • • • • • • • • • • • •
>_	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 4.5.2 \leq 5 days Ceccato 2016 Marik 1993	<u>Events</u> 55 28 8 1 92 3.97, df = 3 Z = 3.28 (P 5 2	308 200 60 23 591 (P = 0.2 = 0.001 56 14	89 29 5 5 26); ² = 2) 6 4	310 191 20 22 543 4% 50 16	58.2% 20.4% 5.2% 3.9% 87.6% 4.6% 2.6%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45] 0.60 [0.45, 0.82] 0.72 [0.21, 2.52] 0.50 [0.08, 3.27]	• • • • • • • • • • • • • • • • • • •
;	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 4.5.2 \leq 5 days Ceccato 2016 Marik 1993 Torres 2015	<u>Events</u> 55 28 8 1 92 3.97, df = 3 Z = 3.28 (P 5	308 200 60 23 591 (P = 0.2 = 0.001 56 14 55	89 29 5 128 26); I ² = 24	310 191 20 22 543 4% 50 16 57	58.2% 20.4% 5.2% 3.9% 87.6% 4.6% 2.6% 5.2%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45] 0.60 [0.45, 0.82] 0.72 [0.21, 2.52] 0.50 [0.08, 3.27] 0.41 [0.10, 1.68]	• • • • • • • • • • • • • • • • • • •
>	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = $(5, 2, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3,$	Events 55 28 8 1 92 3.97, df = 3 Z = 3.28 (P 5 2 3	308 200 60 23 591 (P = 0.2 = 0.001 56 14	89 29 5 5 128 26); ² = 2:) 6 4 7	310 191 20 22 543 4% 50 16	58.2% 20.4% 5.2% 3.9% 87.6% 4.6% 2.6%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45] 0.60 [0.45, 0.82] 0.72 [0.21, 2.52] 0.50 [0.08, 3.27]	• • • • • • • • • • • • • • • • • • •
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>_	4.5.1 >5 days Dequin 2023 Meduri 2022 Nafae 2013 Serrano 2011 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = $(5, 2, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3,$	Events 55 28 8 1 92 3.97, df = 3 Z = 3.28 (P 5 2 3 0.35, df = 2	308 200 60 23 591 (P = 0.2 = 0.001 56 14 55 125 (P = 0.8	89 29 5 5 128 26); I ² = 2: 1) 6 4 7 17 34); I ² = 0'	310 191 20 543 4% 50 16 57 123	58.2% 20.4% 5.2% 3.9% 87.6% 4.6% 2.6% 5.2%	0.54 [0.37, 0.79] 0.91 [0.52, 1.60] 0.46 [0.13, 1.62] 0.15 [0.02, 1.45] 0.60 [0.45, 0.82] 0.72 [0.21, 2.52] 0.50 [0.08, 3.27] 0.41 [0.10, 1.68]	
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Meta-analysis of the CRP level in patients receiving corticosteroid therapy versus the control group (A), subgroup analysis of corticosteroid type (B), and subgroup analysis of duration (C).



Meta-analysis of short-term mortality in individuals taking corticosteroid treatment versus control group (A), subgroup analysis of corticosteroid type (B).





With regard to treatment duration, we implemented a subgroup analysis based on the most recent sCAP management guidelines (1). However, there is no unified standard for the dosage and start time of corticosteroid use, and further research is needed. As sCAP is a clinically common syndrome with high heterogeneity, and the patients included in the present study represented a heterogeneous population. Furthermore, treatment protocols and guideline recommendations varied among studies. Hence, there are great challenges in standardizing treatment regimens of corticosteroid use. In our meta-analysis, we found that in terms of reduced need for MV and shorter hospital stays, a treatment duration of more than 5 days is more beneficial than a duration of less than or equal to 5 days. Further RCT studies with regards to the standard dosing and timing of corticosteroids in sCAP are needed.

Though our meta-analysis showed that corticosteroids might be clinical beneficial for sCAP, there were still some aspects unresolved. Firstly, based on our analysis, future RCTs investigating which type of corticosteroids is more effective in treating sCAP are expected. Secondly, future RCTs investigating the effect of corticosteroids in sCAP with different types of pathogens (bacterial, viral, influenza) are meaningful. Thirdly, further studies exploring biomarkers that could assist in personalized treatment of corticosteroids in sCAP are clinical useful.

Our meta-analysis has several strengths. Firstly, only sCAP studies were included in our studies, which avoided the confounding effects, such as severe hospital acquired pneumonia and disease severity. Secondly, 11 studies were included in our meta-analysis, as our known, this is the largest sample size so far. Thirdly, TSA analyses were used to robust our results.

There exist some limitations to this meta-analysis. First of all, the patients in this research represented a heterogeneous sample because sCAP is a clinically frequent condition with considerable heterogeneity. For instance, some studies used the ATS standard, other studies used the BTS standard, some studies included patients with immune deficiencies, and other studies included patients with COVID-19 (19, 20, 29–37). Second, there is no unified standard for the start time of corticosteroid use, and we lacked data to perform subgroup analysis with regard to this aspect. Third, the sample sizes of the studies included were small, and those included were predominantly single-center trials, which may have produced bias.

Conclusion

Our meta-analysis demonstrated that corticosteroids, especially hydrocortisone, can reduce the mortality of sCAP patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

YC: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. HK: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. YZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. XL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was

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supported by Guangzhou Municipal Science and Technology Bureau (2024A03J0667) and Research-oriented Hospital Program of Guangzhou (RHPG05). The funding body was not involved in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Acknowledgments

We acknowledge all staffs who helped us in performing this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1457469/ full#supplementary-material

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