SYSTEMATIC REVIEW



Efficacy and safety of glucocorticoids therapy of severe community-acquired pneumonia in older adults: a systematic review and meta-analysis

Mure Ali^{1,2†}, Jiaqi Liu^{2,3†}, Yixiong Zheng^{1,2}, Jing Chen^{1,2}, Ziyi He^{2,4}, Xiamin Jiang^{2,4}, Yao Luo^{2,3}, Xin Zheng^{2,3} and Huaicong Long^{5*}

Abstract

Background The use of corticosteroids in older adult patients with severe community-acquired pneumonia (sCAP) remains controversial. This meta-analysis aimed to thoroughly assess the efficacy and safety of corticosteroids in the treatment of older adult patients with sCAP.

Methods We performed a comprehensive search in Public Medline, Excerpta Medica Database, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang Database, and SinoMed, covering records from the earliest available to September 15, 2024. Randomized controlled trials (RCTs) were conducted. The primary outcome was 30-day all-cause mortality, with safety outcomes including gastrointestinal bleeding, secondary infections, and acute kidney injury.

Results This meta-analysis included data from nine RCTs with 2,034 patients, showing that corticosteroid therapy was associated with lower 30-day all-cause mortality (risk ratio (RR) = 0.67; 95% confidence interval [CI], 0.52–0.86; P=0.002). Corticosteroid use also shortens hospital and intensive care unit stays, reduces mechanical ventilation requirements, lowers vasopressor dependence, and decreases C-reactive protein levels. Regarding safety, corticosteroid s did not significantly increase risks of superinfection (RR=0.78; 95% CI, 0.54–1.13; P=0.19), upper gastrointestinal bleeding (RR=0.71; 95% CI, 0.35–1.44; P=0.34), or acute kidney injury (RR=0.71; 95% CI, 0.23–2.21; P=0.56).

Conclusions This meta-analysis demonstrated that glucocorticoid use is associated with higher survival in older patients with sCAP; however, the safety outcomes remain uncertain due to variability in study definitions.

Trial Registration PROSPERO CRD 42024591076 was successfully registered on September 30, 2024.

Keywords Corticosteroids, Severe community-acquired pneumonia, Older adult, Meta-analysis

[†]Mure Ali and Jiaqi Liu have equally contributed to this work.

*Correspondence: Huaicong Long longhc69@163.com Full list of author information is available at the end of the article



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Background

Community-acquired pneumonia (CAP) is a primary contributor to lower respiratory tract infections (LRTIs) among hospitalized patients, especially in individuals aged 65 years and older [1]. In 2019, the global mortality rate of LRTI was 6.46 per 100,000 individuals. Over the past 30 years (1990–2019), the mortality rate showed a decreasing trend among individuals aged \geq 55 years; however, it increased by 85.84% in absolute terms, with the highest rates observed in patients aged ≥ 85 years [2]. Additionally, patients with clinical failure (CF) after CAP treatment are generally older than those with clinical success, with a reported CF incidence of 13.1% in older adult patients with CAP [3]. Severe community-acquired pneumonia (sCAP), characterized by the requirement of intensive care unit (ICU) admission, mechanical ventilation, or hemodynamic support, has a mortality rate of 16–36% [4]. sCAP is prevalent among older adults who often have immunosuppression and age-related comorbidities, leading to poor clinical outcomes despite timely and adequate antibiotic therapy. Corticosteroid therapy, which attenuates local and systemic inflammatory responses [5], has been proposed as an adjunctive treatment to improve the outcomes of patients with sCAP. However, glucocorticoids are associated with numerous adverse effects, necessitating caution when prescribing them to older adults in distinct patient populations. Evaluation of the effectiveness and safety of glucocorticoid treatment in older adult patients with sCAP is essential. Currently, international guidelines lack specific treatment recommendations for older adult patients with sCAP, and conflicting guidelines on corticosteroid use in patients with severe CAP are available [6, 7]. Over the past decade, several randomized controlled trials (RCTs) with a mean patient age>60 years have examined the efficacy of glucocorticoids for sCAP. Some studies have indicated beneficial outcomes; however, the overall conclusions remain inconclusive [8-16]. A 2023 meta-analysis incorporating recent studies reported that corticosteroid use in adult patients with sCAP was associated with reduced all-cause mortality, shorter hospital stays, and favorable safety profiles [17]. However, it remains unclear whether these effects extend to older patients with sCAP. To investigate this, we performed a meta-analysis of both domestic and international RCTs involving patients with a mean age>60 years to assess the effectiveness and safety of glucocorticoid treatment in older individuals with sCAP.

Methods

Study protocol search strategy

The meta-analysis protocol was registered in PROSPERO (CRD 42024591076). The literature search followed the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, encompassing both Chinese and English databases, including Public Medline, Excerpta Medica Database, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang, and SinoMed, with coverage from the inception of each database through September 15, 2024. The supplementary material provides a full search strategy.

Study selection

This study incorporated domestic and international RCTs to evaluate the effectiveness and safety of glucocorticoid therapy in patients with sCAP with an average age of 60 years or older. The following studies were excluded from the analysis: (1) trials with unclear efficacy and safety data; (2) reviews, conference abstracts, survey reports, animal studies, and other low-quality articles; (3) studies using data from the same patient cohort in multiple publications, with only the most recent article considered for data extraction; and (4) trials involving patients with coronavirus disease in 2019.

Literature screening and data extraction

Two researchers independently screened the titles and abstracts of the selected articles to determine their eligibility based on inclusion criteria. Any disagreements were resolved by consensus with a third reviewer. The two researchers also independently extracted data including author names, publication date, country, study center and design, participant count, mean age, corticosteroid treatment protocol, and primary and secondary outcomes. For studies reporting all-cause mortality at multiple time points, we selected data closest to 30 days. Data were extracted using Microsoft Excel.

Primary and secondary outcomes

The primary outcome assessed was 30-day all-cause mortality, while secondary outcomes included length of hospital stay, length of ICU stay, mechanical ventilation requirement, incidence of acute respiratory distress syndrome (ARDS), vasopressor use, and post-treatment C-reactive protein (CRP) levels. The safety outcomes were defined as the incidence of secondary infections, gastrointestinal bleeding, and adverse events of renal injury during the study period. Subgroup analysis of the primary outcome was performed, incorporating the criteria for evaluating severe pneumonia and variations in steroid type, dosage, loading-dose administration, and treatment duration. For dosage subgroup analysis, the cumulative dose over the entire treatment course was assessed. Corticosteroid dosages were standardized to equivalent hydrocortisone doses and the median value was used as the cutoff.

Statistical analysis

Heterogeneity across studies was evaluated using the I² test, with the I² values interpreted as follows: 0% (none), 0-25% (low), 25-50% (moderate), 50-75% (high), and $\geq 75\%$ (very high) [18]. For I² $\geq 50\%$ and P < 0.1, a random-effects model was employed; otherwise, a random-effects model was applied and a fixed-effects model was utilized. Subgroup analyses were conducted to identify the sources of significant heterogeneity. The inverse variance method provided the mean difference (MD) with a 95% confidence interval (CI) for continuous data, while the Mantel–Haenszel method provided pooled risk ratios (RR) with 95% CI for binary data.

Each outcome's evidence certainty was independently evaluated following the five criteria of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system [19]. Trial Sequential Analysis (TSA) [20] was conducted to control for type I and II errors in both primary and secondary outcomes. The reliability of the outcomes was evaluated by analyzing the relationship between the cumulative Z-curve, conventional boundaries (defined by setting a Type I error rate of 5%), TSA boundaries, and required information size (RIS) (determined by setting the incidence rates in the intervention and control groups, assuming a Type I error rate of 5% and a power of 80%). Additionally, a sensitivity analysis using the leave-one-out method was conducted on the primary outcome to evaluate the stability of the overall results. Publication bias was assessed using Egger's test and funnel plots [21].

Differences were considered statistically significant at p < 0.05, except for the heterogeneity test threshold set at 0.1. All *P*-values were calculated using two-tailed tests. Statistical analyses were performed using Review Manager 5.4, StataMP 17 (64-bit), TSA 0.9.5.10 Beta, and RStudio.

Results

Search strategy and study description

An initial search yielded 1,103 articles, of which nine studies (totaling 2,034 cases) were included in the final analysis following screening via the PRISMA flowchart (Fig. 1). Among these studies, seven were doubleblind RCTs, and six were multicenter trials. Two studies were conducted in the Netherlands [10, 15], two in China [12, 14], and one each in the United States [16], France [8], Egypt [11], Spain [13], and Italy [9]. These studies varied in terms of the corticosteroid type, timing of administration, and dosage. Table 1 presents the additional details of the basic characteristics of these studies.

Evaluation of bias risk in the included studies

In this study, the methodological quality was assessed by two researches independently using the Cochrane Collaboration's Risk of Bias 2 tool [22]. Of the nine included studies, selection bias was identified due to an inadequate randomization process in one study [11] and allocation concealment deficiencies in four studies [10–12, 16]. Performance bias and detection bias were observed in two studies due to unclear blinding methods [12, 14]. Additionally, four studies provided limited descriptions of other bias sources, contributing to some risk of bias [9–12]. The remaining three studies demonstrated a low risk of bias through all domains. The results of Cochrane risk-of-bias assessment are presented in Fig. 2. The quality of evidence for each outcome, as assessed by the GRADE system, is shown in Table 2.

Primary outcome: total mortality by 30 days

Seven studies involving 1,853 patients evaluated differences in 30-day all-cause mortality. The 30-day all-cause mortality rate was 14.05% (129/918) in the control group compared to 9.41% (88/935) in the glucocorticoid group (RR=0.67; 95% CI, 0.52–0.86; P=0.002; I²=21%; moderate evidence; Fig. 3a).

Subgroup analysis consistently demonstrated an association between corticosteroid use and lower mortality; however, statistical significance was achieved only in specific subgroups (Pneumonia Severity Index [PSI] diagnostic criterion, hydrocortisone use, total dose \leq 1,750 mg, treatment duration \leq 7 days, without loading dose; Fig. 3b).

Secondary outcomes Length of ICU stay

Four studies involving 1,513 patients evaluated the differences in ICU length of stay. The results showed a significantly shorter ICU stay in the corticosteroid-treated group than in the control group (MD = -0.9 days, 95% CI: -1.36 to -0.43, P=0.0002; I² = 37%; moderate certainty; Fig. 4a).

Length of hospital stay

Seven studies evaluated the differences in hospital length of stay, including 1,159 patients. The findings indicated a statistically significant inverse association between corticosteroid use and hospital stay duration (MD = -1.32 days, 95% CI: -2.23 to -0.40, P = 0.005; I² = 51%; low-quality evidence; Fig. 4b). Subgroup analysis performed to examine the sources of heterogeneity revealed no significant within-group heterogeneity for either single-center or multicenter studies (I² = 0%),

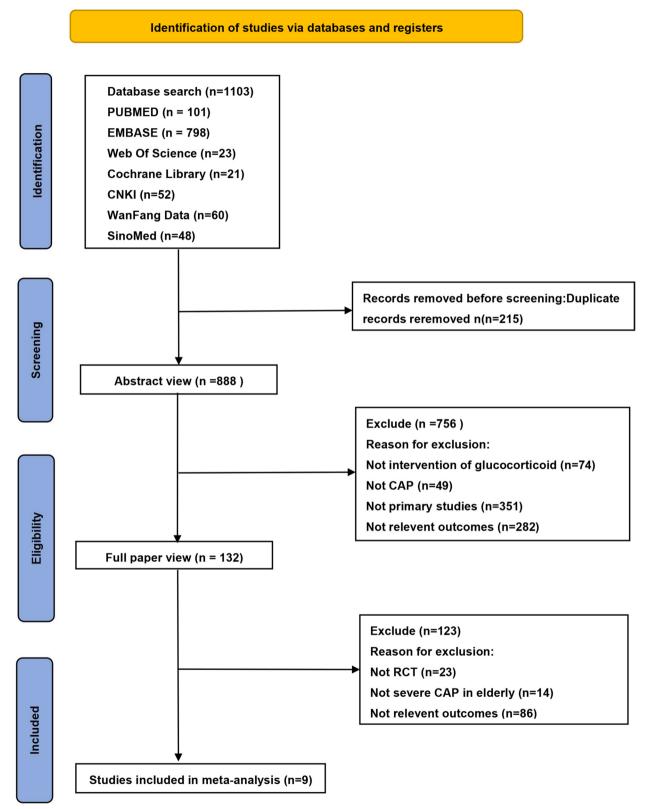


Fig. 1 The flowchart for study screening and selection process according to the PRISMA guidelines

Study	Country	Severe	Study	Number	Sample			Corticosteroid	Corticosteriod Dosage	Cumulative	Corticosteroid
		criterion	criterion Design	of Sites		g Z	age(y) T	lype		Hydrocortisone Dose (mg)*	duration(d)
Confalonier 2005 [9]	ltaly	ATS	DB RCT	9	23 2	23 63	63.5 H	Hydrocortisone	Intravenous 200 mg IV bolus; followed 10 mg/hour IV	1880	7
Snijders 2010 [10]	Netherlands	s PSI	DB RCT	-	48	45 63	63.51 F	Prednisolone	40 mg oral or IV daily	1120	7
Sabry 2011 [11]	Egypt	ATS	DB RCT	2	40	40 62	62.22 H	Hydrocortisone	200 mg IV bolus then maintenance dose of 12.5 mg/h	2300	2
Sui,DongJiang 2013 [12]	China	BTS	RCT		30 3	30 62	62.71 N	Methylprednisolone	40 mg IV twice daily on days 1–3 and 8 mg oral twice daily on days 4–7	1440	7
Torres 2015 [13]	Spain	ATS	DB RCT	¢,	61 5	59 65	65.29 N	Methylprednisolone	Methylprednisolone 0.5 mg/kg IV twice daily	1750	L)
Chu,ZiDong 2018 [14]	China	NR	RCT		50 5	50 70	70.5 N	Methylprednisolone	Methylprednisolone 40 mg IV twice daily on days 1–3 and 8 mg oral twice daily on days 4–7	1440	7
Wittermans 2021 [15]	Netherlands	s PSI	DB RCT	4	77 7	79 76	76.51 D	Dexamethason	6 mg oral daily	638.4	4
Meduri 2022 [16]	USA	ATS	DB RCT	42	297 2	287 68	68.8 N	Methylprednisolone	40 mg bolus followed by 40 mg daily on days $1-7$, 20 mg daily on days $8-14$, 12 mg daily on days $15-17$ and 4 mg daily on days $18-20$	2540	20
Dequin 2023 [8]	France	PSI	DB RCT	31	400 3	395 67		Hydrocortisone	IV 200 mg daily for either 4 or 8 days, fol- lowed by tapering for 8 or 14 days	1000	8/14
ATS = American Thoracic Society, BTS = British Thoracic Society,PSI = patients in the corticosteroids group,NR = Not reported, IV = intraver were satisfied; BTS \ge 3;	society, BTS = Br oids group,NR =	ritish Thoracic = Not reportec	: Society,PSI d, IV = intrav	= Pneumon /enous, Sever	ia Sever e comn	ity Inde nunity-a	x,DB = d acquired	louble-blind, RCT=ran pneumonia is defined	ATS = American Thoracic Society, BTS = British Thoracic Society, PSI = Pneumonia Severity Index, DB = double-blind, RCT = randomized controlled trial, N = the number of patients in the control group, n = the number of patients in the control group, n = the number of patients in the control group, N = N = intravenous, Severe community-acquired pneumonia is defined as PSI of IV or V, CURB-65 \geq 2;Meeting ATS-IDSA 2007 rule where 1 major or 3 minor criteria were satisfied; BTS \geq 3;	s in the control group, n)7 rule where 1 major or	= the number of 3 minor criteria

 Table 1
 Characteristics of the included studies

* The total steroid dose administered during the treatment course was reported as the cumulative dose, with all corticosteroids standardized to hydrocortisone-equivalent doses. For studies that reported dosages per kilogram of body weight, calculations were based on a 70 kg elderly individual

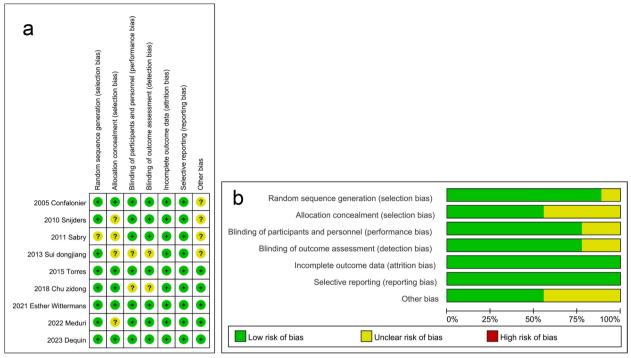


Fig. 2 (a) Risk of bias summary (b) Risk of bias graph

suggesting that the number of study centers may have contributed to the observed heterogeneity.

CRP level

Four studies (n=286) investigated post-treatment CRP level variations between the groups receiving glucocorticoid treatment and the control groups. Findings indicated a significant reduction in CRP levels in the glucocorticoid group than in control (MD=-25.92, 95% CI: -33.90 to -17.94, P < 0.00001; $I^2 = 70\%$; very low certainty; Fig. 5a). Subgroup analysis based on the glucocorticoid type (hydrocortisone vs. methylprednisolone) showed minimal heterogeneity within each subgroup ($I^2=0\%$ and $I^2=4\%$), suggesting that the glucocorticoid type may partly explain the observed heterogeneity.

Vasopressor dependent shock

Five studies (n=1494) evaluated the requirement for vasopressors, showing that corticosteroid use was significantly linked to reduced vasopressor needs (RR=0.39; 95% CI, 0.18–0.87; P=0.02; $I^2=68\%$; moderate certainty; Fig. 5b). Subgroup analysis to explore heterogeneity sources found minimal heterogeneity in patients treated with corticosteroids for ≤ 7 days ($I^2=0\%$) and moderate heterogeneity for those treated >7 days ($I^2=43\%$). This suggests that treatment duration may have contributed to the observed heterogeneity.

Mechanical ventilation

Four studies comprising 688 patients, evaluated the cumulative incidence of mechanical ventilation among those not receiving mechanical ventilation at baseline. The findings demonstrated a significantly lower requirement for mechanical ventilation in the glucocorticoid group (68 of 346, 19.65%) compared to the control group (119 of 342, 34.79%), with a statistically significant difference (RR=0.57; 95% CI, 0.44–0.73; P<0.00001; I²=0%; moderate evidence; Fig. 6a).

ARDS

Three studies (n=632) evaluated the incidence of ARDS using the consensus criteria [23]The results indicated no significant advantage of corticosteroid therapy over the control group in reducing ARDS risk (RR=0.64; 95% CI, 0.31–1.29; P=0.21; I²=45%; low-quality evidence; Fig. 6b).

Adverse events

Adverse events included secondary infections, gastrointestinal bleeding, and acute kidney injury.

1 Four studies reported on the incidence of secondary infections. The findings showed no statistically significant difference in secondary infection rates between the glucocorticoid group (44/534, 8.23%)

Outcomes	No of participants (studies)	Glucocorticoid Group	Control Group	Relative effect (95% Cl)	Absolute effect	Overall Effect	l ² (%)	Certainty of the evidence (GRADE)
Total mortality	1853 (7)	88/935 (9.41%)	129/918 (14.05%)	RR 0.67 (0.52 to 0.86)	46 fewer per 1000 (67 fewer to 20 fewer)	Z=3.12,P=.002	21	⊕⊕⊕⊖Mod- erate
Gastrointestinal bleeding	1041 (4)	12/524 (2.29%)	17/517 (3.3%)	RR 0.71 (0.35 to 1.44)	10 fewer per 1000 (21fewer to 14 more)	Z=0.95,P=.34	0	⊕⊕ ⊖OLow
Superinfection	1061(4)	44/534 (8.24%)	56/527 (10.63%)	RR 0.78 (0.54 to 1.13)	23 fewer per 1000 (49 fewer to 14 more)	Z=1.31,P=.19	10	⊕⊕⊕⊖Mod- erate
Acute kidney injury	830 (4)	19/421 (4.51%)	23/409 (5.62%)	RR 0.71 (0.23 to 2.21)	16 fewer per 1000 (43 fewer to 68 more)	Z=0.59,P=.56	54	⊕OOOVery low
Mechanical ventilation	688 (4)	68/346 (19.65%)	119/342 (34.80%)	RR 0.57 (0.44 to 0.73)	150 fewer per 1000 (195 fewer to 94 fewer)	Z=4.44,P<.00001	0	⊕⊕⊕⊖Mod- erate
Vasopressor dependent shock	1494 (5)	72/757 (9.51%)	135/737 (18.32%)	RR 0.38 (0.17 to 0.88)	114 fewer per 1000 (152 fewer to 22 fewer)	Z=2.28,P=.02	70	⊕⊕⊕⊖Mod- erate
ARDS	632 (3)	12/328 (3.66%)	18/304 (5.9%)	RR 0.64 (0.31 to 1.29)	21 fewer per 1000 (41 fewer to 17 more)	Z=1.25,P=.21	45	⊕⊕ ⊖OLow
CRP(mean±SD)	286 (4)	17.23±11.56	41.12±35.99	-	MD 25.92 lower (33.90 lower to 17.94 lower)	Z=6.37,P<.00001	70	⊕⊖⊖OVery low
The length of ICU stay(d) (mean±SD)	1513 (4)	5.39±6.11	6.51±7.92	-	MD 0.9 lower (1.36 lower to 0.43 lower)	Z=3.79,P=.0002	37	⊕⊕⊕ ⊖Mod- erate
The length of hosp- tial stay(d) (mean ± SD)	1159 (7)	9.77±10.49	11.08±14.64	-	MD 1.32lower (2.23 lower to 0.4 lower)	Z=2.82,P=.005	51	⊕⊕ ⊖OLow

Table 2 GRADE quality assessment of glucocorticoid treatment outcomes

and control group (56/527, 10.62%) (RR=0.78; 95% CI, 0.54–1.13; P=0.19; I²=10%; moderate certainty; supplementary material Fig. S 1).

- 2 Four studies provided data regarding the risk of gastrointestinal bleeding. The results indicated that, compared with the control group (12/517, 3.28%), the glucocorticoid group (12/524, 2.29%) showed no increased risk of upper gastrointestinal bleeding (RR=0.71; 95% CI, 0.35–1.44; P=0.34; I²=0%; lowquality evidence; supplementary material Fig. S2).
- 3 Four studies reported on the incidence of acute kidney injury. The results showed no statistically significant difference between the glucocorticoid group (19/421, 4.51%) and control group (23/409, 5.62%)

 $(RR = 0.73, 95\% CI: 0.25 - 2.18, P = 0.58, I^2 = 51\%; very low certainty; supplementary material Fig. S3).$

Publication bias

For publication bias in 30-day all-cause mortality, visual assessment of the funnel plot showed a slight asymmetry (supplementary material Fig. S4); however, the Egger test (supplementary material Fig. S5) indicated no significant effect (P=0.2). Furthermore, the Trim-and-Fill analysis (supplementary material Fig. S6) demonstrated that the effect size remained essentially unchanged after adjusting for potential missing studies, indicating the absence of publication bias.

	Glucocor	ticoid	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I M-H, Fixed, 95% CI
2005 Confalonieri	0	23	7	23	5.7%	0.07 [0.00, 1.10]	
2010 Snijders	5	48	5	45	3.9%	0.94 [0.29, 3.02]	— <u> </u>
2011 Sabry	2	40	6	40	4.6%	0.33 [0.07, 1.55]	
2015 Torres	6	61	9	59	7.0%	0.64 [0.24, 1.70]	
2021 Esther Wittermans	3	77	5	79	3.8%	0.62 [0.15, 2.49]	
2022 Meduri	47	286	50	277	38.8%	0.91 [0.63, 1.31]	+
2023 Dequin	25	400	47	395	36.1%	0.53 [0.33, 0.84]	-#-
Total (95% CI)		935		918	100.0%	0.67 [0.52, 0.86]	◆
Total events	88		129				
Heterogeneity: Chi ² = 7.55	5, df = 6 (P =	0.27); P	² = 21%				
Test for overall effect: Z =	3.12 (P = 0.	002)					0.005 0.1 1 10 200 Favours [glucocorticoid] Favours [control]

b

Subgroup	Glucocorticoid Event/Total	Control Event/Total		Risk Ratio(95%CI)	Absolute Risk Reduction(95%CI)	P value
Loading dose						
YES	49/349	63/340		0.45(0.13-1.60)	4.49%(-1.24%-10.22%)	0.22
NO	39/586	66/578	┝┳╌┥	0.58(0.40-0.85)	4.76%(1.35%-8.23%)	0.005
Severe criterion						
ATS	55/410	72/399	⊢∎→	0.74(0.54-1.03)	4.63%(-0.57%-9.84%)	0.07
PSI	33/525	57/519	┝╼╌┥	0.57(0.38-0.86)	4.70%(1.15%-8.30%)	0.007
Corticosteroid type						
Hydrocortisone	27/463	60/458	⊢∎→↓	0.45(0.29-0.69)	7.27%(3.36%-11.26%)	0.0003
Not Hydrocortisone	61/472	69/460	┝╼┼┥	0.86(0.62-1.18)	2.08%(-2.54%-6.71%)	0.34
Corticosteroid doseage						
>1750mg	49/349	63/340		0.45(0.13-1.60)	4.49%(-1.24%-10.22%)	0.22
<=1750mg	39/586	66/578	┝╼╌┥	0.58(0.40-0.85)	4.76%(1.35%-8.23%)	0.005
Corticosteroid duration						
>7d	72/686	97/672	┝╼┼┥	0.71(0.41-1.21)	3.94%(0.32%-7.58%)	0.2
<=7d	16/249	32/249	0 0.5 1 2 Glucocorticoid Control	0.50(0.28-0.88)	6.43%(0.93%-12.01%)	0.02

Fig. 3 Forest Plot and Subgroup Analysis Results of 30-day all-cause mortality (a) Forest Plot Results (b) Subgroup Analysis Results

Sensitivity analysis

Sensitivity analysis confirmed the robustness of the 30-day all-cause mortality findings, showing that the overall outcome remained consistent even after excluding studies with significant deviations (supplementary material Figs. S7-S8).

Trial sequence analysis

The TSA for 30-day all-cause mortality (supplementary material Fig. S9) indicated that while the cumulative Z-curve did not reach the RIS of 2,635 cases, it crossed the conventional and TSA monitoring boundaries, providing strong evidence supporting a true-positive effect associated with lower mortality. Similarly, TSA confirmed true-positive results for ICU and hospital length of stay, CRP levels, and mechanical ventilation (supplementary material Figs. S10-S13). In contrast, vasopressor outcomes (supplementary material Fig. S14). Although the cumulative Z-curve crossed the conventional boundary, it neither crossed the TSA boundary nor reached

the RIS, which suggests the need for additional trials. TSA results for ARDS and adverse events (supplementary material Figs. S15-S18) showed that the cumulative Z-curve stayed within the futility area, aligning with the lack of statistically significant differences between the corticosteroid and control groups.

Discussion

This meta-analysis, which encompassed nine RCTs and 2,034 cases, assessed the effectiveness and safety of glucocorticoids in older adults with sCAP. The results showed that Corticosteroid therapy was associated with lower 30-day all-cause mortality. Subgroup analyses revealed significant benefits when PSI was used, with hydrocortisone administration, at total doses \leq 1,750 mg and for treatment periods \leq 7 days. Additionally, corticosteroid therapy was linked to reduced mechanical ventilation needs, shorter hospitalizations, shorter ICU length of stay, lower vasopressor use, and a more pronounced CRP level reduction. Despite the high heterogeneity of the h

а	(Apple)		10.00						
	Gluc	ocortic	oid	0	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2005 Confalonieri	15.67	22.76	23	22	32.97	23	0.1%	-6.33 [-22.70, 10.04]	←
2015 Torres	5.33	3.84	42	6	3.06	46	10.1%	-0.67 [-2.13, 0.79]	
2022 Meduri	4.3	4.4	297	4.67	4.4	287	42.2%	-0.37 [-1.08, 0.34]	
2023 Dequin	5.6	4.44	400	7	5.19	395	47.6%	-1.40 [-2.07, -0.73]	
Total (95% CI)			762			751	100.0%	-0.90 [-1.36, -0.43]	
Heterogeneity: Chi ² =	4.76, df	= 3 (P =	: 0.19);	$ ^2 = 379$	6				-4 -2 0 2 4
Test for overall effect:	Z = 3.79	(P = 0.	0002)						Favours [glucocorticoid] Favours [control]

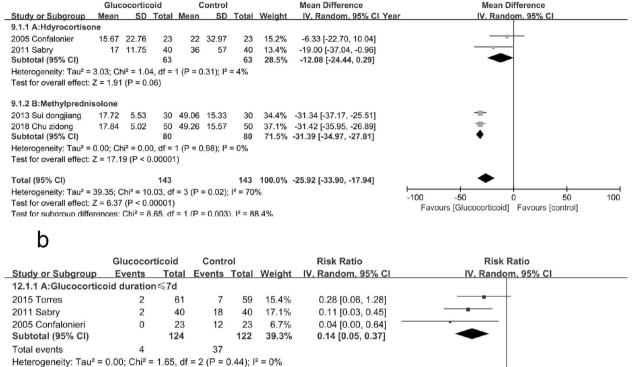
D									
		ocortic			ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
7.1.1 A:single center									
2010 Snijders	15	16.4	48	16.4	18.4	45	1.6%	-1.40 [-8.50, 5.70]	
2013 Sui dongjiang	15.23	4.76	30	18.32	5.73	30	8.9%	-3.09 [-5.76, -0.42]	
2018 Chu zidong	15.87	3.86	50	18.75	4.39	50	17.0%	-2.88 [-4.50, -1.26]	
Subtotal (95% CI)			128			125	27.6%	-2.88 [-4.24, -1.52]	•
Heterogeneity: Tau ² = 0.00	0; Chi ² =	0.19, d	f = 2 (F	= 0.91	; l ² = 0%	6			
Test for overall effect: Z =	4.15 (P	< 0.000	1)						
7.1.2 B:multicenter									
2005 Confalonieri	25.33	33.75	23	32	54.16	23	0.1%	-6.67 [-32.75, 19.41]	• • • • • • • • • • • • • • • • • • • •
2015 Torres	10.83	4.81	61	11.17	5.18	59	15.3%	-0.34 [-2.13, 1.45]	
2021 Esther Wittermans	5.5	1.33	77	6	1.33	79	34.0%	-0.50 [-0.92, -0.08]	
2022 Meduri	7.7	5.92	297	9	8.15	287	23.1%	-1.30 [-2.46, -0.14]	
Subtotal (95% CI)			458			448	72.4%	-0.58 [-0.97, -0.20]	•
Heterogeneity: Tau ² = 0.00	0; Chi² =	1.90, d	f = 3 (F	= 0.59	; l ² = 0%	6			
Test for overall effect: Z =	2.97 (P	= 0.003)						
									•
Total (95% CI)			586			573	100.0%	-1.32 [-2.23, -0.40]	•
Heterogeneity: Tau ² = 0.60	0; Chi² =	12.27,	df = 6 (P = 0.00	5); ² = 5	51%			-20 -10 0 10 20
Test for overall effect: Z =	2.82 (P	= 0.005)						Favours [Glucocorticoid] Favours [control]
Test for subaroup differen	ces: Chi2	² = 10.1	8. df =	1 (P = 0)	.001). 1	2 = 90.2	%		

Fig. 4 Results of the Forest Plot (a) Length of ICU stay (b) Length of hospital stay

studies, sources of variability were identified. However, further analysis indicated no significant impact of corticosteroids on the risk of ARDS or incidence of adverse events.

Before this study, only one early meta-analysis was conducted internationally, which included five studies with 295 cases [24]. This analysis showed a more favorable reduction in mortality (RR = 0.42; 95% CI: 0.18–0.96; P=0.04), a shorter average hospital stay, and a reduced risk of upper gastrointestinal bleeding, findings that align with ours. Building on these results, we integrated recent studies, expanded our assessment criteria, conducted subgroup analyses, and updated our conclusions. Recent meta-analyses have assessed the efficacy and safety of corticosteroids in adults with sCAP. However, our analysis excluded studies with a mean patient age of < 60 years and included only RCTs. Consistent with previous adult-focused meta-analyses [25-28], our findings indicated that corticosteroid use was associated with lower mortality, supported by moderate-quality evidence. The TSA results further enhanced the reliability of this association. Additionally, our findings regarding reductions in mechanical ventilation, shorter hospital stays, and decreased vasopressor requirements align with those of previous adult meta-analyses [25–28], with evidence quality ranging from moderate to very low. However, we observed no significant association between corticosteroid treatment and a reduced risk of ARDS, in contrast to findings from adult studies. This discrepancy may be attributed to differences in age groups included in the studies [25, 26].

Currently, an optimal treatment approach for patients with sCAP has not yet been fully established. Subgroup analysis in this study showed that a single maintenance dose notably reduced mortality among older adult patients with sCAP. In contrast, meta-analyses in adults suggested the benefit of a loading dose followed by maintenance therapy [27]. Previous meta-analyses revealed no significant differences in outcomes based on daily corticosteroid doses when 200 mg/day was used as the threshold [27]. Comparing the daily doses because of the variability in hormone types and dosages was challenging. Therefore, we analyzed the differences between various corticosteroids by normalizing their total doses to hydrocortisone-equivalent values. Furthermore, our findings indicate that a lower total corticosteroid dose $(\leq 1,750 \text{ mg})$ is significantly associated with reduced mortality. Additionally, the duration of corticosteroid use а



Test for overall effect: Z = 3.98 (P < 0.0001)

12.1.2 B:Glucocorticoid duration>7d

2023 Dequin

2022 Meduri

Total events

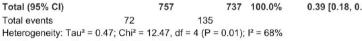
Subtotal (95% CI)

55

13

68

135 Total events 72 Heterogeneity: Tau² = 0.47; Chi² = 12.47, df = 4 (P = 0.01); I² = 68% Test for overall effect: Z = 2.30 (P = 0.02)

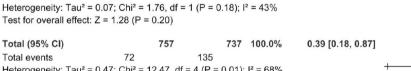


86 344

12 271

98

615



33.9%

26.8%

60.7%

0.61 [0.45, 0.83]

1.07 [0.50, 2.31]

0.72 [0.44, 1.19]

0.002 10 0.1 Favours [experimental] Favours [control]

Test for subaroup differences: $Chi^2 = 8.67$. df = 1 (P = 0.003). $I^2 = 88.5\%$

Fig. 5 Results of the Forest Plot (a) CRP level (b) Vasopressor dependent shock

359

274

633

appeared to be a critical factor affecting efficacy, which is consistent with previous findings in adult meta-analyses. The timing of drug administration has also emerged as a key determinant of drug efficacy. Unlike previous metaanalyses in adults, which used a 5-day threshold, we discovered that short-term corticosteroid use (≤ 7 days) was associated with reduced mortality [27]. These discrepancies may reflect differences between the older adult and adult patient populations. Moreover, subgroup analysis showed that hydrocortisone treatment was associated with improved survival, which is consistent with the findings of an adult meta-analysis [25]. Owing to data limitations, the optimal dose and duration of treatment remain unclear.

The safety of corticosteroids in older adult patients remains a critical concern in the clinical practice. Given the limited data on adverse events associated with corticosteroid use in older adult patients with sCAP, we conducted a meta-analysis that focused on secondary infections, upper gastrointestinal bleeding, and renal injury. Our findings demonstrated no significant increase in the risk of these adverse events. The supporting evidence ranged from moderate to very low quality; Our findings align with previous studies in adult sCAP cohorts [17, 25-28]. However, due to data constraints, this study did not assess the incidence of hyperglycemia in older adult patients with sCAP. While previous metaanalyses have suggested that corticosteroid use does not

500

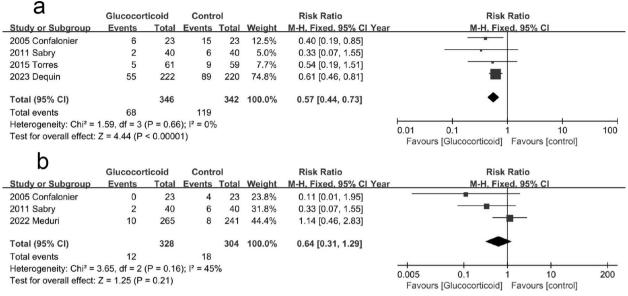


Fig. 6 Results of the Forest Plot (a) Mechanical ventilation (b) ARDS

increase the incidence of hyperglycemia in adult populations [25–28], further research is necessary to evaluate this effect, specifically in older adult patients. Although this study confirmed that the risk of adverse events investigated did not show a significant increase, the statistical power may be insufficient due to the heterogeneity in the definitions of adverse events across studies, limited sample size, and low-quality evidence. As a result, rare adverse events may not be reliably detected, and the safety outcomes remain uncertain.

The results of this meta-analysis suggest that corticosteroid use is associated with a lower mortality rate; however, its safety remains uncertain. Therefore, in clinical practice, a comprehensive assessment of individualized benefits and risks is essential. Special caution should be exercised in patients with underlying conditions such as diabetes, osteoporosis, immunodeficiency, fungal infections, or gastrointestinal bleeding. This study provides evidence-based support for the use of corticosteroids in older patients with sCAP and may serve as a reference for clinical decision-making. Given the uncertainty regarding safety outcomes and the necessity of individualized corticosteroid therapy, future guidelines may consider a conditional recommendation for corticosteroid use in older adult patients with sCAP without high-risk comorbidities, while ensuring close monitoring of potential adverse effects to maintain clinical safety.

This meta-analysis has some limitations. First, in the absence of RCTs that focused specifically on corticosteroid treatment in older adult patients with sCAP, studies with a mean age ≥ 60 years were included. Second, for studies reporting mortality across different time intervals, data closest to 30 days were used. Third, variations in the definition of sCAP across studies introduced heterogeneity that could not be entirely resolved. Fourth, older patients often present with multiple underlying comorbidities, and the effectiveness of glucocorticoid therapy may be influenced by these baseline conditions. Due to the lack of relevant data, this study did not explore this aspect. Finally, the secondary outcome means were estimated from the median values.

Conclusion

Corticosteroid therapy in older adult patients with sCAP was associated with lower mortality, particularly when hydrocortisone is administered. The benefits are more notable with lower total doses (\leq 1,750 mg), extended treatment durations (\leq 7 days), and single-maintenance dosing. Additionally, corticosteroids are associated with shorter hospital and ICU stays, decreased need for vaso-pressors and mechanical ventilation, and reduced CRP levels. However, due to the heterogeneity in the definitions of adverse events across studies, the safety outcomes remain uncertain.

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Authors' contributions

Mure Ali and Jiaqi Liu participated in literature screening, literature retrieval, and data extraction. Mure Ali, Jiaqi Liu, Yixiong Zheng, and Jing Chen were involved in data analysis and figure preparation. Mure Ali, Jiaqi Liu, and Ziyi He drafted the manuscript. Huaicong Long, Xiamin Jiang, Yao Luo, and Xin Zheng revised the manuscript. Huaicong Long conceptualized and designed the study. All authors reviewed and approved the final manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹School of Medical and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, China. ²Department of Geriatric ICU, Sichuan Provincial People's Hospital, Chengdu, China. ³School of Medicine, University of Electronic Science and Technology of China, Chengdu, China. ⁴Department of Clinical Medicine, North Sichuan Medical College, Chengdu, China. ⁵Department of Geriatric ICU, Sichuan Provincial People'S Hospital, University of Electronic Science and Technology of China, Chengdu, China.

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