Corticosteroids Had no Effect on 28-Days Mortality in Adult Patients with sepsis: A Systematic Review and Meta-Analysis

Huoyan Liang

Zhengzhou University First Affiliated Hospital

Heng Song

Zhengzhou University First Affiliated Hospital

Gaofei Song

Zhengzhou University First Affiliated Hospital

Hongyi Li

Zhengzhou University First Affiliated Hospital

Xianfei Ding

Zhengzhou University First Affiliated Hospital

Quancheng Kan

Zhengzhou University First Affiliated Hospital

Tongwen Sun (✉ suntongwen@163.com)

Zhengzhou University First Affiliated Hospital <https://orcid.org/0000-0001-6536-3222>

Research

Keywords: Randomized controlled trials (RCTs), relative risk (RR)

Posted Date: May 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-508536/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective: Corticosteroids are a common option used in the treatment of sepsis. However, the efficacy and potential risk of corticosteroids in septic patients have not been well assessed. We performed this review to assess the efficacy and safety of corticosteroids in sepsis patients.

Methods: We searched the PubMed, Embase, and Cochrane library databases from inception to March 2021. Randomized controlled trials (RCTs) that evaluated the effect of corticosteroids on septic patients were included. The quality of outcomes in the included articles was evaluated using the Grading of Recommendations Assessment, Development and Evaluation methodology. The data were pooled by using relative risk (RR) and mean difference (MD). The random-effects model were used to evaluate the pooled MD or RR and 95% CI.

Results: Fifty-three RCTs that included 12,310 patients with sepsis were identified. Corticosteroids were not associated with the mortality in 28-day (RR, 0.94; 95% CI, 0.87–1.02; evidence rank, moderate), and long-term mortality (>60 d) (RR, 0.96; 95% CI, 0.88–1.05) in septic patients (evidence rank, low). However, corticosteroids may exert a significant effect on the mortality in ICU (RR, 0.89; 95% CI, 0.80–0.98), in-hospital (RR, 0.93; 95% CI, 0.88–0.99; evidence rank, moderate) in patients with sepsis or septic shock (evidence rank, low). Furthermore, corticosteroids probably achieved a very small reductions in the length of hospital stay and ICU. Corticosteroids were associated with an higher risk of hypernatremia and hyperglycemia; further, they appear to have no significant effect on superinfection and gastroduodenal bleeding.

Conclusions: Corticosteroids had no significant effect on the 28 and long-term mortality; however, they decreased the ICU and hospital mortality. Further, corticosteroids could increase the risk of the hypernatremia and hyperglycemia in sepsis patients.

Introduction

Sepsis is a life-threatening organ dysfunction, which is caused by a dysregulated host response to infection[1, 2] that culminates in systematic hypoperfusion and considerable organ dysfunction. The therapy mainly are antibiotic administration and perfusion restoration in the early phase[3]. Early and aggressive treatment is associated with a mortality rate of 30–50% in critical ill patients admitted to the ICU and induces more than 5 million deaths each year across the world[3, 4]. Therefore, further investigation for the treatment of sepsis is crucial.

The pathology of sepsis is marked by a dysregulated host response to infection; therefore, immunomodulatory therapies have been used in sepsis treatment that may provide effective[5]. In fact, since the middle of the 20th century, the doctors start to use the corticosteroids as adjuvant therapy for sepsis[3]. With corticosteroids were used in sepsis, especially septic shock therapy, numerous randomized clinical trials (RCTs) were performed to evaluate the safety and efficacy of corticosteroids. However, the results of these RCTs varied. Thus, many systematic reviews have been performed to assess the safety and efficacy of corticosteroids in septic patients. However, the results of the most recent reviews remain controversial[6, 7]. Subsequently, several studies have further assessed whether the combination of corticosteroids, vitamin C, and thiamine as compared with corticosteroids or placebo, improved the survival duration, increased the vasopressor-free time over 7 d, and reduced organ injury[8, 9]. These results suggest that the use of corticosteroids in combination with other drugs did not affect the safety and efficacy of corticosteroids on septic patients. Hence, resolution of this controversy regarding the latest reviews that have assessed the efficacy of corticosteroids on septic patients is currently the primary problem in the treatment of sepsis. Therefore, this systematic review and meta-analysis were performed based on the latest reviews to re-integrate the relevant data to evaluate the effects and safety of corticosteroids in septic patients.

Methods

The protocol of this systematic review and meta-analysis was registered on INPLASY (ID: INPLASY2020110122). The methodology of this study was according to items of the Cochrane Collaboration, and each outcome was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines[10].

Study Searches

We performed this meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, and we showed the PRISMA 2020 checklist in **eTable 1**. We searched the PubMed, Embase, and Cochrane library databases for relevant data from inception to November 2020, March 2021 to identify RCTs that have evaluated the effect of corticosteroids on septic patients. The MeSH/Emtree and title/abstract keywords combination was used to identify the eligible articles; the keyword search terms used for the English literature included the words corticosteroids and sepsis (the detailed search strategy in **eTable 2** in the Supplement). It is noteworthy that we also conducted a manual search for the references of the relevant articles (the study search flowchart in **Figure 1**).

Study Selection

Before the potential articles were searched and screened, the eligibility criteria and excluded criteria were identified. Articles may be eligible according to the criteria of inclusion in this study, if they meet all of the following conditions: (1) the adult patients diagnosed with sepsis, severe sepsis, or septic shock, as per the accepted criteria during the study[11–13]. We included studies reported the adult patients with acute respiratory distress syndrome (ARDS), and of which reported the adult septic patients; (2) the study compared the use of corticosteroids (including hydrocortisone, methylprednisolone, betamethasone, fludrocortisone, and dexamethasone) with no use of corticosteroids; (3) the study measured and reported the outcomes in terms of 28-day and long-term mortality (> 90 d), ICU mortality, in-hospital mortality, short-time mortality, length of stay in hospital and ICU, vasopressor-free days, ventilation-free time, shock reversal at day 7 and day 28, time to resolution of shock, hypernatremia, hyperglycemia, superinfection, and gastroduodenal bleeding. (4) the study was a RCT and was published in English. Furthermore, the study design including case reports, case series, and observational studies were excluded. All the available

articles were searched by two searchers respectively, and when the disagreements occurred during the proceed, the third investigator should be resolved these disagreements. Reviewers performed reviews in pairs to screen all relevant citations and references as per the search strategy, and the screening process included the following two stages: initial evaluation of the titles and abstracts and skimming of the full text to identify the eligible studies.

Data Extraction

Researchers conducted data extraction respectively and in duplicate based on the eligibility criteria and excluded criteria. In case of disagreements, the third reviewer resolved the issue. Relevant data, including the study title, first author, study type, study period, the therapy in treatment group and control group, reported outcomes, sepsis definition and so on were collected. The data only for the studies we searched including the previous review[6] was abstracted. We assessed the risk of bias for this meta-analysis by two investigators independently for every abstracted data of each articles based on the Cochrane Collaboration[14], and domains were including allocation concealment, blinding of participants and staff, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other biases. Additionally, the GRADE framework was used to evaluate the overall evidence rank for every outcome[15]. The studies with more than six, four to six, and fewer than six items were considered high, fair, and poor quality, respectively. Importantly, we used the GRADE to assess the evidence rank of mortality and adverse events. According to the risk of bias, inconsistency, indirectness, imprecision, and publication bias to evaluated the studies as low, moderate, or high quality.

Statistical Analyses

M-H or DL methods with random-effects meta-analyses were conducted for the eligible RCTs. All the relevant data were assessed using the Review Manager (RevMan), version 5.3 (Cochrane Collaboration), STATA 16.0 (StataCorp, College Station, TX). Risk Ratio (RR) and mean difference (MD) were used to present the dichotomous outcomes and continuous outcomes, with 95% CI. Moreover, a funnel plot was used to examine the potential for some small effects if the outcome included more than 10 trials, and the possibility of publication bias was assessed using funnel plot and regression test of the Egger test[16]. The chi-square test, I^2 , and visual inspection of the forest plots were used to evaluate heterogeneity among the eligible studies; when I^2 was $> 50\%$, the heterogeneity was considered substantial. In addition, we performed the subgroup analyses based on the following variables: sepsis subtype [sepsis, septic shock, sepsis and ARDS, sepsis and community-acquired pneumonia, severe COVID-19]; type of corticosteroids (hydrocortisone or hydrocortisone plus fludrocortisone or methylprednisolone or prednisone or betamethasone or dexamethasone), searching the source of heterogeneity.

Results

Characteristics of Eligible Studies

We initially identified 9,363 records, and 8971 citations remained after the duplicate trials were removed; 145 RCTs were eligible after preliminary screening by title and abstract. Finally, Fifty-three RCTs [17–69] that included 12,310 patients with sepsis were included in this meta-analysis (Fig. 1). The characteristics of the included RCTs are listed in Table 1. Twenty-eight RCTs[18, 20–23, 25–29, 35, 36, 38, 40–42, 45, 46, 48, 52, 54, 57, 59–63, 67] on 8,503 patients with septic shock, 8 RCTs[37, 39, 43, 44, 50, 55, 68, 69] on 936 patients with sepsis, 4 RCTs[17, 47, 49, 65] on 390 patients with sepsis and ARDS, 9 RCTs[24, 30, 33, 34, 51, 53, 56, 58, 66] on 1,733 patients with sepsis and community-acquired pneumonia, and 4 RCTs[19, 31, 32, 64] on 748 patients with severe COVID-19 were included. Additionally, 30 RCTs[19, 23, 25, 27, 28, 30, 31, 33, 35, 36, 38–43, 46, 48, 50, 52–56, 59, 61–63, 65, 67] (7,115 patients) of which were treated with hydrocortisone, 4 RCTs[18, 20–22] (2,082 patients) with hydrocortisone plus fludrocortisone, 10 RCTs[17, 26, 32, 33, 37, 47, 49, 57, 60, 66] (1,245 patients) with methylprednisolone, 4 RCTs[34, 58, 68, 69] (364 patients) with prednisolone, 3 RCTs[29, 51, 64] (408 patients) with dexamethasone, and only one RCTs with betamethasone (85 patients) [44]and corticosteroid (21 patients)[45], respectively.

Table 1

Characteristics of the Included Studies in the Meta-analysis of Corticosteroids Vs Placebo or Standard Supportive Care in Adults With Sepsis or Septic Shock

Study	Study type	Single/Multi Center	Study period	Total Patients / Patients in Corticosteroids No.	Mean Age, y	Female/ Male of Patients No.	Type of Patients Population	Sepsis or Septic Shock Definition	Experimental Intervention	Reported Outcome
Annane et al (2018)	RCT	M	NA	1241/614	CS:66 PC:66	415/826	Septic shock	Sepsis-3.0	Hydrocortisone (50mg) intravenously every 6 hours plus fludrocortisone(50ug tablet) nasogastric tube for 7d	28d,90d, discharge hospital discharge cause mortality; Vasopressor days; Ventilator days; Organ-failure free days
Venkatesh et al (2018)	RCT	M	03/2013-04/2017	3658/1832	CS:62.3 PC:62.7	1399/2259	Septic shock	Sepsis-3.0	Hydrocortisone (200mg) intravenous infusion per day for 7d	90d and mortality discharge hospital discharge Ventilator days
Annane et al (2002)	RCT	M	10/1995-02/1999	300/151	CS: 62 PC: 60	200/100	Septic shock	Sepsis-2	Hydrocortisone bolus (50mg) every 6 h and fludrocortisone (50 µg) taken orally every 24 h for 7 d	28d mortality
Li et al (2017)	RCT	S	09/2015-09/2016	118/58	CS: 68.8 PC: 64.8	70/68	Septic shock	NA	Hydrocortisone (200 mg) daily as a continuous infusion for 6 d	28d mortality the reverse shock; in hospital mortality duration hospital
Klastersky et al (1971)	RCT	S	NA	85/46	NA	47/38	Severe sepsis	NA	Betamethasone 0.5 mg/kg every 12 h for 3 d	30d mortality

Table 1
(Continued)

Study	Study type	Single/Multi Center	Study period	Patients / Patients in Corticosteroids No.	Mean Age, y	Female/Male of Patients No.	Type of Patient Population	Sepsis or Septic Shock Definition	Experimental Intervention	Reported Outcomes
Bone et al (1987)	RCT	M	11/1982-12/1985	382/191	CS: 53.0 PC: 53.6	147/235	septic shock	NA	Methylprednisolone bolus (30mg/kg) repeated every 6 h for 24 h	Shock incidence; shock reversal; overall mortality; 14d mortality
Schumer et al (1976)	RCT	S	1967-1975	172/86	50	5/167	Septic shock	NA	Group 1: methylprednisolone (30 mg/kg); Group 2: dexamethasone (3 mg/kg); dose was repeated once in both groups after 4 h and had to be initiated at the time of diagnosis	Mortality; age-associated mortality; severity of shock associated mortality; underlying condition; associated mortality; organ injury-associated mortality; complications
Sprung et al (1984)	RCT	M	8/1979-2/1982	59/43	CS: 58 PC: 55	13/46	Septic shock	NA	Group 1: methylprednisolone (30 mg/kg); Group 2: dexamethasone (6 mg/kg); dose was repeated once in both groups after 4 h if shock persisted	Shock reversal; hospital mortality; blood cultures; adverse events
Vasscs et al (1987)	RCT	M	10/1983-04/1986	223/112	CS: 60.9 PC: 60.6	NA	Sepsis	NA	Methylprednisolone bolus (30mg/kg) repeated every 6 h for 24h	14d mortality; adverse occurrences

Primary Outcome

Forty trials[17, 18, 21–30, 35–39, 42–44, 47–51, 54–62, 64–69] (10,612 patients), 24 trials[21–23, 25, 27, 28, 30, 33–36, 43, 47–49, 51, 53, 55, 59, 62, 66–68] (11,613 patients), and 17 trials[21–23, 27, 28, 30, 35, 36, 38, 43, 49, 55, 56, 59, 66, 67] (7,175 patients) were included in this meta-analysis for assessing the 28-day mortality, in-hospital mortality, and ICU mortality, respectively. We used the random-effects model with RRs to assess the pooled results. Corticosteroid therapy showed a no small reduction in the 28-day mortality (RR, 0.94; 95% CI, 0.87–1.02; evidence rank, moderate; Fig. 2), with low heterogeneity among the trials ($I^2 = 24\%$). However, corticosteroids treatment resulted in a significant decreased in the in-hospital mortality (RR, 0.93; 95% CI, 0.88–0.99; evidence rank, moderate; Fig. 3) and ICU mortality (RR, 0.89; 95% CI, 0.80–0.98; evidence rank, high; Fig. 4) with low heterogeneity ($I^2 = 11\%$ and $I^2 = 22\%$, respectively). The Funnel plot and Egger test showed no publication bias in the 28-day mortality ($P = 0.15$), in-hospital mortality ($P = 0.01$), and ICU mortality ($P = 0.02$) (Supplemental Fig. 1–3 in the Supplement). The results of sensitivity analysis showed that the models of the 28-day mortality, in-hospital mortality, and ICU mortality were credible (Supplemental Fig. 4–6 in the Supplement). Furthermore, L'Abbé plot reported that the mortality in the placebo group increased significantly than the corticosteroid group, suggesting the potential effects of corticosteroids in septic patients (Supplemental Fig. 7–9 in the Supplement).

Secondary Outcomes

Supplemental Fig. 10–23 in the Supplement present the assessment of the secondary outcomes. Corticosteroids achieved a small reduction in length of stay in hospital (MD, -1.54; 95% CI, -2.68 to -0.41; $I^2 = 20\%$; evidence rank, high), SOFA scores at day 7 (MD, -0.90; 95% CI, -1.72 to -0.08; $I^2 = 93\%$; evidence rank, low) and time to resolution of shock (MD, -1.36; 95% CI, -1.79 to -0.93; $I^2 = 68\%$; evidence rank, low) for patients with sepsis. Conversely, corticosteroids resulted in

higher risk of hypernatremia (RR, 1.51; 95% CI, 1.11–2.00; $I^2 = 0\%$; evidence rank, moderate) and hyperglycemia (RR, 1.18; 95% CI, 1.09–1.28; $I^2 = 56\%$; evidence rank, high). Furthermore, corticosteroids increased the vasopressor-free days (MD, 1.93; 95% CI, 0.76–3.09; $I^2 = 0\%$; evidence rank, moderate), ventilation-free time (MD, 1.46; 95% CI, 0.27–2.65; $I^2 = 21\%$; evidence rank, moderate), shock reversal at day 7 (RR, 1.18; 95% CI, 1.08–1.29; $I^2 = 71\%$; evidence rank, moderate) and day 28 (RR, 1.07; 95% CI, 1.02–1.11; $I^2 = 6\%$; evidence rank, moderate). Additionally, corticosteroids achieve no reduction in the long-term mortality (> 60 d) (RR, 0.94; 95% CI, 0.84–1.04; $I^2 = 62\%$; evidence rank, low), length of stay in ICU (MD, -0.89; 95% CI, -1.80–0.03; $I^2 = 47\%$; evidence rank, moderate), superinfection (RR, 1.05; 95% CI, 0.92–1.19; $I^2 = 11\%$; evidence rank, moderate) and gastroduodenal bleeding (RR, 1.18; 95% CI, 1.09–1.28; $I^2 = 0\%$; evidence rank, high).

The Funnel plot and Egger test showed no publication bias in the length of stay in hospital ($P = 0.53$), SOFA scores at day 7 ($P = 0.82$), hyperglycemia ($P = 0.14$), the shock reversal at day 7 ($P = 0.05$), length of stay in ICU ($P = 0.15$), superinfection ($P = 0.03$), and gastroduodenal bleeding ($P = 0.97$) (Supplemental Fig. 24–30 in the Supplement). Shock reversal at day 28 showed a significant publication bias in the Funnel plot and Egger test ($P = 0.046$) (Supplemental Fig. 31 in the Supplement). The results of the sensitivity analysis showed that the models of the above mentioned outcomes, including length of stay in hospital, SOFA scores at day 7, hyperglycemia, shock reversal at day 7, length of stay in ICU, superinfection, gastroduodenal bleeding, and shock reversal at day 28 were credible (Supplemental Fig. 32–38 in the Supplement).

Importantly, risk of bias were reported in the forest plot of each outcome, and the evidence rank was showed in Table 2.

Table 2
The findings and evidence rank of the included studies with corticosteroids vs placebo treatment in patients with sepsis.

Pooled results	No. of Patients (No. of Studies)	Relative Effect, RR, or MD (95% CI)	Heterogeneity $I^2, \%$	Absolute effect (95%CI)	Evidence rank
Primary outcomes					
28d mortality	10,612 (40)	0.94 (0.87, 1.02)	24	17 fewer per 1000 (from 37 fewer to 6 more)	Moderate ¹
In-hospital mortality	11,613 (24)	0.93 (0.88, 0.99)	11	22 fewer per 1000 (from 3 fewer to 37 fewer)	Moderate ¹
ICU mortality	7,199 (17)	0.89 (0.8, 0.98)	22	31 fewer per 1000 (from 6 fewer to 56 fewer)	High
Secondary outcomes					
Long-term mortality	6,254 (9)	0.94 (0.84, 1.04)	62	24 fewer per 1000 (from 64 fewer to 16 more)	Low ^{2,3}
Shock reversal at 7d	6,651 (16)	1.18 (1.08, 1.29)	71	211 more per 1000 (from 54 more to 195 more)	Moderate ²
Shock reversal at 28d	2,997 (12)	1.07 (1.02, 1.11)	6	49 more per 1000 (from 14 fewer to 77 more)	Moderate ²
Gastroduodenal bleeding	5,157 (24)	1.18 (1.09, 1.28)	0	3 more per 1000 (from 7 fewer to 16 more)	High
Superinfection	5,490 (25)	1.05 (0.92, 1.19)	11	9 more per 1000 (from 14 fewer to 33 more)	Moderate ²
Hypernatremia	4,554 (3)	1.51 (1.11, 2)	0	12 more per 1000 (from 3 more to 24 more)	Moderate ²
Hyperglycemia	8,787 (20)	1.18 (1.09, 1.28)	56	49 more per 1000 (from 24 more to 76 more)	High
Vasopressor-free days	1,316 (2)	1.93 (0.76, 3.09)	0	1.93 more per 1000 (from 0.76 more to 3.09 more)	Moderate ²
Ventilation-free days	1,812 (4)	1.46 (0.27, 2.65)	21	1.46 more per 1000 (from 0.27 more to 2.65 more)	Moderate ²
length of stay in hospital	8,539 (19)	-1.54 (-2.68, -0.41)	20	1.54 fewer per 1000 (from 2.68 fewer to 0.41 fewer)	High
length of stay in ICU	8,166 (22)	-0.89 (-1.80, 0.03)	47	0.89 fewer per 1000 (from 1.8 fewer to 0.03 more)	High
time to resolution of shock	4,134 (5)	-1.36 (-1.79, -0.93)	68	1.36 fewer per 1000 (from 1.79 fewer to 0.93 fewer)	Low ^{2,3}
SOFA score at day 7	3,076 (13)	-0.90 (-1.72, -0.08)	93	0.9 fewer per 1000 (from 1.72 fewer to 0.08 fewer)	Low ^{2,3}

Subgroup Analysis

We performed subgroup analysis based on the sepsis subtype or type of corticosteroids used for the primary outcomes or $I^2 > 75\%$ in the secondary outcomes with more than 10 trials for each outcome. The results of the subgroup analysis showed no effect on the 28-day mortality; however, the in-hospital and ICU

mortality were significantly improved in the hydrocortisone plus fludrocortisone treatment and in the patients with septic shock, sepsis, and community-acquired pneumonia (**Supplemental Fig. 39–44** in the Supplement). Moreover, the result of subgroup in SOFA scores at day 7 represented that the main original heterogeneity may be from the trials with smaller samples who were given hydrocortisone treatment or trials on patients with sepsis shock (**Supplemental Fig. 45–46** in the Supplement).

Discussion

This meta-analysis included 53 RCTs (12,310 patients) and demonstrated that corticosteroids failed to improve the 28-day mortality and long-time mortality; however, there was a small reduction in the in-hospital mortality and ICU mortality. To our knowledge, this systematic review and meta-analysis is the most comprehensive review on many new RCTs, the precision of the pooled effect estimates on sepsis would be increased substantially.

We found that corticosteroids therapy for sepsis increased the incidence of the vasopressor-free days, ventilation-free time, shock reversal at day 7 and day 28, and adverse events, such as hyperglycemia and hypernatremia. Corticosteroids was associated with a decreased risk of the time shock resolution and length of stay in hospital. However, our study failed to report an decreased risk of corticosteroids on the length of ICU stay and adverse events, such as superinfection and gastroduodenal bleeding. Ascertainment of the adverse events in the eligible trials was also vulnerable, which may induce the evidence rank was low.

Subgroup analyses in this review showed that the results did not identify any credible effect modification in sepsis subtype and type of corticosteroids used. Many evidence comes from the trials with hydrocortisone or methylprednisolone treatment. Our results of the subgroup analyses showed that the efficacy of corticosteroids on in-hospital, ICU, and short-time mortality was mainly due to the hydrocortisone plus fludrocortisone.

Mechanistically, Corticosteroids could inhibit the NF- κ B activation and the extensive inflammatory factors release, finally, improving the inflammatory response of sepsis or pneumonia. Our previous studies reported that corticosteroids was associated with a decreased risk of ARDS and length of the disease in CAP patients [70]. Previous reviews have assessed the efficacy and safety of corticosteroids in septic patients. Unfortunately, the conclusions were contradictory and were in cretinal owing to the small number of trials included. One meta-analysis included 20 RCTs and showed no reduction in the 28-day, hospital, and ICU mortality in patients with severe sepsis and sepsis shock on corticosteroids treatment[71]. Subsequently, a Cochrane systematic review further to search the effect of corticosteroids on mortality of patients with sepsis, including a total of 33 RCTs, which found a small reduction in 28 d mortality under the corticosteroids treatment[72]. Simultaneously, another study included 35 RCTs and showed a converse result that corticosteroids failed to decrease the mortality[73]. In 2018, Rochwerg et al.[7] examined 42 RCTs including 10,194 patients, wherein corticosteroids achieved no reduction in the short-term (28–31 d) mortality, and may achieve a little effect on the long-term mortality. In 2019, Fang et al.[74] included 37 RCTs; this trial suggested that corticosteroids use was associated with a decrease in the 28-day mortality, ICU mortality, and in-hospital mortality. In parallel, Annane et al.[6] published a Cochrane systematic review on 40 RCTs and achieved a reduction in the 28-day mortality in patients with sepsis on corticosteroids therapy.

The results of this meta-analysis showed that corticosteroids treatment failed to improve the 28-day mortality, in contrast with results from previous meta-analysis. The difference in part maybe due to the result reported by Annane et al.[6] as per which corticosteroids therapy showed an increased risk of 28-day mortality, while the CI contained the null effect line, suggesting corticosteroids had no effect on sepsis based on the statistics in fact. More importantly, we included 4 RCTs about the sever COVID-19 and showed there was no significant difference in 28-day mortality with corticosteroids use. The data were extracted from the latest RCTs and may have helped in reinforcing the conclusions, decreasing the heterogeneity among the studies, and improving precision with more comprehensive assess for the therapy effects of corticosteroids treatment.

This meta-analysis has several strengths. First, this study is the most comprehensive trial to assess the efficacy of corticosteroids treatment on patients with sepsis to date. Second, we performed a thorough literature search including unpublished sources, using the GRADE methodology to evaluate the evidence rank in overall RR, a predefined illustration of potential effect variables including direction of effect and subsequent subgroup analysis to search the effect variables, and illustration include the relative and absolute effects. Third, the primary outcomes showed low or no heterogeneity among the studies, suggesting that the results were not variable. Furthermore, the heterogeneity of the SOFA scores on day 7 was high, and the subgroup analysis showed that the source of heterogeneity may be the inclusion of trials with small size on patients who were given hydrocortisone treatment. Finally, the results of the sensitivity analysis for this study suggested that this conclusions were robust and reliable.

However, this meta-analysis also has certain shortcomings, including the significant methodological or clinical heterogeneity among the included studies, especially with respect to the SOFA score on day 7. All the included RCTs enrolled patients with sepsis as per the previous sepsis definition criteria; however, we do not know the efficacy and safety of corticosteroids whether change using the Sepsis-3 definition criteria. Hence, the defined mortality may be essential, but the certainty is limited due to the imprecision of the included studies.

Conclusions

This is the most comprehensive systematic review and meta-analysis to describe the efficacy and safety of corticosteroids for sepsis patients. The findings demonstrate that corticosteroids failed to reduce the 28-day mortality and long-term mortality; however, they could reduce the in-hospital mortality and ICU mortality. Importantly, our subgroup analyses results indicated that this efficacy of corticosteroids in sepsis patients may be associated with the hydrocortisone plus fludrocortisone treatment. Therefore, the results suggest that corticosteroids could not improve the 28-day mortality in adult patient with sepsis.

Abbreviations

RR, relative risk; CI, confidence interval; randomized controlled trials, RCTs; mean difference, MD; community-acquired pneumonia, CAP; ICU, intensive care unite; SOFA, acute respiratory distress syndrome, ARDS; Grading of Recommendations Assessment, Development and Evaluation, GRADE; SOFA, Sequential organ failure.

Declarations

Consent for publication

Not applicable.

Author Contributions

All the authors contributed importantly to the work presented in this article. TWS, HYL(Huoyan Liang) conceived the study. XFD, HYL(Hongyi Li) and GFS contributed to the data extraction. SH and XFD computed and evaluated the pooled outcomes. HYL and SH contributed to the study protocol and wrote the article. QCK and TWS revised the article. The QCK and TWS had full access to all of the data and the final responsibility for the decision to submit this article for publication.

Funding

This study was supported by the United Fund of National Natural Science Foundation of China (Grant No. U2004110), Leading Talents Fund in Science and Technology Innovation in Henan Province (Grant No.194200510017).

Availability of Data and Materials

The datasets used and analysed in the available RCTs are from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

References

1. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, et al: **Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *Jama* 2016, **315**(8):762–774.
2. DeMerle KM, Angus DC, Baillie JK, Brant E, Calfee CS, Carcillo J, Chang CH, Dickson R, Evans I, Gordon AC, et al: **Sepsis Subclasses: A Framework for Development and Interpretation**. *Critical care medicine* 2021.
3. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive care medicine*. 2017;**43**(3):304–77.
4. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, Kadri SS, Angus DC, Danner RL, Fiore AE, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009–2014. *Jama*. 2017;**318**(13):1241–9.
5. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive care medicine*. 2017;**43**(12):1781–92.
6. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y, Pirracchio R, Rochweg B. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev*. 2019;**12**(12):Cd002243.
7. Rochweg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, Duan E, English S, Gossack-Keenan K, Alghuroba M, et al. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. *Critical care medicine*. 2018;**46**(9):1411–20.
8. Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, Deane AM, Shehabi Y, Hajjar LA, Oliveira G, et al. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *Jama*. 2020;**323**(5):423–31.
9. Sevransky JE, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, Busse LW, Coopersmith CM, DeWilde C, Ely EW, et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. *Jama*. 2021;**325**(8):742–50.
10. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008;**336**(7651):995–8.
11. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: **Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine**. *Chest* 1992, **101**(6):1644–1655.

12. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: **2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference**. *Critical care medicine* 2003, **31**(4):1250–1256.
13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *Jama* 2016, **315**(8):801–810.
14. Higgins JPTGS. **Cochrane handbook for systematic reviews of interventions, version 5.1.0 [updated March 2011]**. *Cochrane Collaboration* 2011.
15. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–6.
16. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
17. Abdelsalam Rezk N, Mohamed Ibrahim A. Effects of methyl prednisolone in early ARDS. *Egyptian Journal of Chest Diseases Tuberculosis*. 2013;62(1):167–72.
18. Aboab J, Polito A, Orlikowski D, Sharshar T, Castel M, Annane D. Hydrocortisone effects on cardiovascular variability in septic shock: a spectral analysis approach. *Critical care medicine*. 2008;36(5):1481–6.
19. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, van Bentum-Puijk W, Berry L, Bhimani Z, Bonten M, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *Jama*. 2020;324(13):1317–29.
20. Annane D, Cariou A, Maxime V, Azoulay E, D'Honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *Jama*. 2010;303(4):341–8.
21. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med*. 2018;378(9):809–18.
22. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *Jama*. 2002;288(7):862–71.
23. Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, Knawy BA, Hajeer AH, Tamimi W, Cherfan A. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *Cmaj*. 2010;182(18):1971–7.
24. Blum CA, Nigro N, Briel M, Schuetz P, Ullmer E, Suter-Widmer I, Winzeler B, Bingisser R, Elsaesser H, Drozdov D, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet*. 2015;385(9977):1511–8.
25. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Critical care medicine*. 1998;26(4):645–50.
26. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med*. 1987;317(11):653–8.
27. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Critical care medicine*. 1999;27(4):723–32.
28. Chawla K, Kupfer Y, Goldman I, Tessler S. HYDROCORTISONE REVERSES REFRACTORY SEPTIC SHOCK. *Critical care medicine*. 1999;27(1):33A.
29. Cicarelli DD, Benseñor FE, Vieira JE. Effects of single dose of dexamethasone on patients with systemic inflammatory response. *Sao Paulo Med J*. 2007;124(2):90–5.
30. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med*. 2005;171(3):242–8.
31. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, François B, Aubron C, Ricard JD, Ehrmann S, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. *Jama*. 2020;324(13):1298–306.
32. Edalatfard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, Najafizadeh SR, Farhadi E, Jalili N, Esfahani M, et al: **Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial**. *Eur Respir J* 2020, 56(6).
33. El-Ghamrawy AHSM, Esmat AA. **Effects of low dose hydrocortisone in ICU patients with severe community acquired pneumonia**. *Egyptian Journal of Chest* 2006(55):91–99.
34. Fernández-Serrano S, Dorca J, García-Vidal C, Fernández-Sabé N, Carratalà J, Fernández-Agüera A, Corominas M, Padrones S, Gudiol F, Manresa F. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. *Crit Care*. 2011;15(2):R96.
35. Gordon AC, Mason AJ, Perkins GD, Stotz M, Terblanche M, Ashby D, Brett SJ. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. *Critical care medicine*. 2014;42(6):1325–33.
36. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, Pogson DG, Aya HD, Anjum A, Frazier GJ, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *Jama*. 2016;316(5):509–18.
37. Group VASSCS. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. *N Engl J Med*. 1987;317(11):659–65.
38. Hu B, Li JG, Liang H, Zhou Q, Yu Z, Li L, Luo Y, Liu C, Gan Q. [The effect of low-dose hydrocortisone on requirement of norepinephrine and lactate clearance in patients with refractory septic shock]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*. 2009;21(9):529–31.
39. Huang R, Zhang Z, Xu M, Chang X, Qiao Q, Wang L, Meng X. [Effect of Sini decoction on function of hypothalamic-pituitary-adrenal axis in patients with sepsis]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2014;26(3):184–7.

40. Huh JW, Lim C-M, Koh Y, Hong S-B. EFFECT OF LOW DOSES OF HYDROCORTISONE IN PATIENT WITH SEPTIC SHOCK AND RELATIVE ADRENAL INSUFFICIENCY: 3 DAYS VERSUS 7 DAYS TREATMENT.: 369. *Critical care medicine*. 2006;34(12):A101.
41. Hyvernath H, Barel R, Gentilhomme A, Césari-Giordani JF, Freche A, Kaidomar M, Goubaux B, Pradier C, Dellamonica J, Bernardin G. Effects of Increasing Hydrocortisone to 300+ mg Per Day in the Treatment of Septic Shock: a Pilot Study. *Shock*. 2016;46(5):498–505.
42. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, Volk HD, Doecke WD, Falke KJ, Gerlach H. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med*. 2003;167(4):512–20.
43. Keh D, Trips E, Marx G, Wirtz SP, Abduljawwad E, Bercker S, Bogatsch H, Briegel J, Engel C, Gerlach H, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. *Jama*. 2016;316(17):1775–85.
44. Klastersky J, Cappel R, Debusscher L. Effectiveness of betamethasone in management of severe infections. A double-blind study. *N Engl J Med*. 1971;284(22):1248–50.
45. Kurugundla NIL, Kilari D, Amchentsev A, Devakonda A, George L, et al.: **Effect of steroids in septic shock patients without relative adrenal insufficiency**. *American Thoracic Society* 2008.
46. Loisa P, Parviainen I, Tenhunen J, Hovilehto S, Ruokonen E. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. *Crit Care*. 2007;11(1):R21.
47. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Respir Dis*. 1988;138(1):62–8.
48. Lv QQ, Gu XH, Chen QH, Yu JQ, Zheng RQ. Early initiation of low-dose hydrocortisone treatment for septic shock in adults: A randomized clinical trial. *Am J Emerg Med*. 2017;35(12):1810–4.
49. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007;131(4):954–63.
50. Meduri GU, Golden E, Umberger R. PROSPECTIVE DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL ON THE EFFECTS OF LOW-DOSE HYDROCORTISONE INFUSION IN PATIENTS WITH SEVERE SEPSIS. *Chest*. 2009;136(4):45S.
51. Meijvis SC, Hardeman H, Remmelts HH, Heijligenberg R, Rijkers GT, van Velzen-Blad H, Voorn GP, van de Garde EM, Endeman H, Grutters JC, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9782):2023–30.
52. Mirea L, Ungureanu R, Pavelescu D, Grintescu IC, Dumitrache C, Grintescu I, Mirea D. Continuous administration of corticosteroids in septic shock can reduce risk of hypernatremia. *Crit Care*. 2014;18(1):P239.
53. Nafae RMRM, Amany FM, Rashed SB. **Adjuvant role of corticosteroids in the treatment of community acquired pneumonia**. *Egyptian Journal of Chest Diseases and Tuberculosis* 2013(62):439–445.
54. Oppert M, Schindler R, Husung C, Offermann K, Gräf KJ, Boenisch O, Barckow D, Frei U, Eckardt KU. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Critical care medicine*. 2005;33(11):2457–64.
55. Rinaldi S, Adembi C, Grechi S, De Gaudio AR. Low-dose hydrocortisone during severe sepsis: effects on microalbuminuria. *Critical care medicine*. 2006;34(9):2334–9.
56. Sabry NAE-DOE. Corticosteroids and ICU course of community acquired pneumonia in Egyptian settings. *Pharmacology Pharmacy*. 2011;2:73–81.
57. Schumer W. Steroids in the treatment of clinical septic shock. *Ann Surg*. 1976;184(3):333–41.
58. Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. *Am J Respir Crit Care Med*. 2010;181(9):975–82.
59. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111–24.
60. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, Duncan RC, Tendler MD, Karpf M. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *N Engl J Med*. 1984;311(18):1137–43.
61. Talebi Doluee M, Salehi M, Mahmoudi Gharaee A, Jalalyazdi M, Reihani H. The effect of physiologic dose of intravenous hydrocortisone in patients with refractory septic shock: a randomized control trial. *Journal of Emergency Practice Trauma*. 2018;4(1):29–33.
62. Tandan SMGR, Gupta N: **Low dose steroids and adrenocortical insufficiency in septic shock: a double-blind randomised controlled trial from India**. *Proceedings of the American Thoracic Society Meeting* 2005, **A24**.
63. Tilouche N, Jaoued O, Ali HBS, Gharbi R, Fekih Hassen M, Elatrous S. Comparison Between Continuous and Intermittent Administration of Hydrocortisone During Septic Shock: A Randomized Controlled Clinical Trial. *Shock*. 2019;52(5):481–6.
64. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, Avezum A, Lopes RD, Bueno FR, Silva M, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *Jama*. 2020;324(13):1307–16.
65. Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, Meduri GU. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care*. 2016;20(1):329.
66. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, Gabarrús A, Sellarés J, Restrepo MI, Anzueto A, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *Jama*. 2015;313(7):677–86.

67. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med*. 2018;378(9):797–808.
68. Yildiz O, Doganay M, Aygen B, Güven M, Keleştimur F, Tutu A. Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. *Crit Care*. 2002;6(3):251–9.
69. Yildiz O, Tanriverdi F, Simsek S, Aygen B, Keleştimur F. The effects of moderate-dose steroid therapy in sepsis: A placebo-controlled, randomized study. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2011;16(11):1410–21.
70. Wan YD, Sun TW, Liu ZQ, Zhang SG, Wang LX, Kan QC. Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis. *Chest*. 2016;149(1):209–19.
71. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *Jama*. 2009;301(22):2362–75.
72. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev*. 2015;2015(12):Cd002243.
73. Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. *Intensive care medicine*. 2015;41(7):1220–34.
74. Fang F, Zhang Y, Tang J, Lunsford LD, Li T, Tang R, He J, Xu P, Faramand A, Xu J, et al: **Association of Corticosteroid Treatment With Outcomes in Adult Patients With Sepsis: A Systematic Review and Meta-analysis**. *JAMA internal medicine* 2019, **179**(2):213–223.

Figures

Figure 1

Flowchart of the search strategy in this meta-analysis.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 2

28-day mortality of patients with sepsis based on the corticosteroids treatment. The pooled effects in the forest plot was calculated by the M-H method with random-effects model.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 3

In-hospital mortality of patients with sepsis based on the corticosteroids treatment. The pooled effects in the forest plot was calculated by the M-H method with random-effects model.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 4

ICU mortality of patients with sepsis based on the corticosteroids treatment. The pooled effects in the forest plot was calculated by the M-H method with random-effects model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalTable1.docx](#)
- [SupplementalTable2.docx](#)
- [SupplementalFigure1.tif](#)
- [SupplementalFigure2.tif](#)
- [SupplementalFigure3.tif](#)
- [SupplementalFigure4.tif](#)
- [SupplementalFigure5.tif](#)
- [SupplementalFigure6.tif](#)
- [SupplementalFigure7.tif](#)
- [SupplementalFigure8.tif](#)
- [SupplementalFigure9.tif](#)
- [SupplementalFigure10.tif](#)
- [SupplementalFigure11.tif](#)
- [SupplementalFigure12.tif](#)
- [SupplementalFigure13.tif](#)
- [SupplementalFigure14.tif](#)
- [SupplementalFigure15.tif](#)
- [SupplementalFigure16.tif](#)

- [SupplementalFigure17.tif](#)
- [SupplementalFigure18.tif](#)
- [SupplementalFigure19.tif](#)
- [SupplementalFigure20.tif](#)
- [SupplementalFigure21.tif](#)
- [SupplementalFigure22.tif](#)
- [SupplementalFigure23.tif](#)
- [SupplementalFigure24.tif](#)
- [SupplementalFigure25.tif](#)
- [SupplementalFigure26.tif](#)
- [SupplementalFigure27.tif](#)
- [SupplementalFigure28.tif](#)
- [SupplementalFigure29.tif](#)
- [SupplementalFigure30.tif](#)
- [SupplementalFigure31.tif](#)
- [SupplementalFigure32.tif](#)
- [SupplementalFigure33.tif](#)
- [SupplementalFigure34.tif](#)
- [SupplementalFigure35.tif](#)
- [SupplementalFigure36.tif](#)
- [SupplementalFigure37.tif](#)
- [SupplementalFigure38.tif](#)
- [SupplementalFigure39.tif](#)
- [SupplementalFigure40.tif](#)
- [SupplementalFigure41.tif](#)
- [SupplementalFigure42.tif](#)
- [SupplementalFigure43.tif](#)
- [SupplementalFigure44.tif](#)
- [SupplementalFigure45.tif](#)
- [SupplementalFigure46.tif](#)