Original Article

Efficacy and safety of corticosteroids in immunocompetent patients with septic shock

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BACKGROUND: The use of corticosteroids in septic shock has been studied for many decades but yielded conflicting results. We conducted a systematic review to evaluate the efficacy and the safety of corticosteroids in immunocompetent patients with septic shock.

METHODS: Medline via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and EMBASE were searched from inception to March 2020. Two reviewers independently identified randomized controlled trials (RCTs) comparing corticosteroids with a control group for immunocompetent patients with septic shock. Data were abstracted and reported following the *Cochrane Handbook for Systematic Review of Intervention* and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The efficacy outcome included mortality and shock reversal. The safety outcomes were infection, gastrointestinal bleeding, and hyperglycemia.

RESULTS: Nine RCTs with a total of 1,298 patients were included. Compared with the control group, corticosteroid group did not lower the short-term (28 or 30 days) mortality (risk ratio [*RR*] 0.95, 95% confidence interval (*CI*) 0.85 to 1.06, inconsistency [I^2]=0%, trial sequential analysis [TSA]-adjusted *CI* 0.83 to 1.09, moderate-certainty evidence). Corticosteroids significantly shortened the time to shock reversal compared with the control group (mean difference [*MD*] –21.56 hours; 95% *CI* –32.95 to –10.16, I^2=0%; TSA-adjusted *CI* –33.33 to –9.78, moderate-certainty evidence). The corticosteroid treatment was associated with an increased risk of hyperglycemia but not the infection or gastrointestinal bleeding.

CONCLUSIONS: The corticosteroid treatment is not associated with lower short- or long-term mortality compared with placebo in immunocompetent patients with septic shock. However, corticosteroids significantly shorten the time to shock reversal without increasing the risk of infection. The patient's immune status should also be considered during clinical treatment and clinical trials in future.

KEYWORDS: Corticosteroids; Septic shock; Immunocompetent patients; Systematic review; Meta-analysis

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INTRODUCTION

Septic shock, a life-threatening organ dysfunction caused by the dysregulated host response to infection, is characterized by severe circulatory, cellular, and metabolic abnormalities.[1] It has been regarded as a formidable clinical challenge associated with mortality 30% to 40%.[2,3] Septic shock is a common clinical syndrome, but has pronounced heterogeneity such as variable infection sites and sources, pathogen species, and host comorbidities.[4] There has been an increasing

emphasis on evidence-based adjunct therapy beyond hemodynamic support and antimicrobial therapy.[5,6]

Corticosteroids have been used in the treatment of patients with septic shock for more than half a century.[7] Till now, nearly thirty randomized controlled trials (RCTs) have evaluated the efficacy of corticosteroids in these patients but yielded different results, including two well-known RCTs published in the year 2018.[8,9] Twelve systematic reviews since 2018 have been conducted to try to address the discrepancy in these previous trials by classifying the doses of steroids and the severity of shock.[10-21]

However, these studies and reviews have not yet addressed the heterogeneity of the patient population, such as the immunological state of a patient, which is another important clinical aspect and may result in significant enrollment bias.

Recently, focusing on immunocompromised patients with septic shock, we performed an observational cohort study, and found that corticosteroid therapy had adverse effects on survival, hemodynamic stability, and hospital duration in the selected population.[22] Therefore, we aim to perform a systematic review which eliminated the impact of immune status to assess the benefits and risks of corticosteroids in septic shock, and to identify the exact group of patients who may benefit from corticosteroid treatment.

METHODS

Search strategy

We systematically performed electronic search of Medline via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and EMBASE from inception to March 12, 2020. We combined MeSH and title/abstract keywords, such as "steroids", "glucocorticoids", "corticosteroids", "prednisolon", "methylprednisolon", "prednison", "dexamethasone", "triamcinolon", "fludrocortisone", "betamethasone", "hydrocortisone", "sepsis", and "shock, septic" to identify all RCTs comparing corticosteroids with a control group for immunocompetent patients with septic shock.

Study selection

Two authors independently identified the trials for inclusion based on their titles and abstracts, and evaluated the full texts of the papers.

Eligibility criteria

(1) Population. Immunocompetent adult patients with septic shock, defined based on the definition of included trials, were eligible for inclusion. Sepsis patients without circulatory failure were excluded. The immunocompetent patient was defined as the exclusion of one or more immunocompromised underlying conditions, including immunosuppression, immunodeficiency, immunosuppressive therapy, human immunodeficiency virus positive or acquired immune deficiency syndrome, advanced or end-stage neoplasm, and organ transplant recipients. (2) Intervention. All types of corticosteroids were included, regardless of the formula, dose, start time, and duration of treatment. (3) Control. The control group was allowed for the following interventions: placebo, saline, or no intervention. (4) Outcomes. The primary outcome was short-term mortality during intensive care unit (ICU) or hospital stay. The "short term" was defined as the mortality on day 28 or day 30. The secondary outcomes included mortality variables, the number of patients with shock reversal (stable hemodynamic status more than 24 hours after withdrawal of vasopressor therapy) within 28 days, and time to shock reversal. The safety outcomes included infection, gastrointestinal bleeding, and hyperglycemia. (5) Type of study. All trials included were RCTs, irrespective of language or publication status.

Data extraction and quality assessment

Characteristics of participants, study design, and outcomes for analyses were extracted following a standardized data extraction form by two reviewers independently. Two investigators independently assessed the risk of bias according to the *Cochrane Handbook for Systematic Review of Intervention* to assign a value of "high", "low", or "unclear" for each trial.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate the quality of evidence associated with each major outcome and present the results in the summary of findings (SoFs) table.

Statistical analysis

All statistical analyses were performed on Review Manager 5.3 software and trial sequential analysis (TSA) v.0.9.5.10 beta.[23] We presented results as relative risk ratio (*RR*) for dichotomous data and mean difference (*MD*) for continuous data, which were pooled using the Mantel-Haenszel (M-H) and inverse variance method, respectively. Both *RR* and *MD* were provided with 95% confidence interval (*CI*). Heterogeneity was assessed by the Chi-square test with significance set at a *P*-value of 0.05, and

quantitatively by inconsistency (I^2) statistics. We reported all results from a more conservative random-effect model taking into consideration clinical heterogeneity. Subgroup analyses were also performed for all outcomes based on the trial quality.

TSA

We performed TSA to assess the increased risk of random errors due to the relatively sparse data and repeated significance testing. The result was displayed on a TSA diagram with a TSA-adjusted *CI* and an adjusted level of statistical significance. TSA was used to appropriately reduce the risk of a wrong conclusion in a meta-analysis that did not achieve the required information size (RIS). TSA-adjusted *CI* was calculated by the random-effect model for diversity (D^2) with 5% risk of type I error and a power of 80%. For the estimate of the RIS, we set the intervention effect of a 15% relative risk reduction (*RRR*), and calculated the control event incidence from the conventional meta-analysis.

RESULTS

Study characteristics

Of the 4,034 records identified in our research, full texts of 207 records were reviewed, and 27 trials initially included were assessed for patients by immune status. Ultimately, nine RCTs were included in our systematic review.[24-32] The results of the search and selection flow diagram were shown in Figure 1. The detailed descriptions of the included trials were presented in Table 1. Nine RCTs with a total of 1,298 participants were finally analyzed, comprising 667 in the corticosteroid group and 631 in the control group.[24-32]

Mortality

The short-term mortality in the corticosteroid and the control groups was 43.8% (292/667) and 45.2% (285/631), respectively. The pooled analysis revealed no statistically significant effects of corticosteroids (*RR* 0.95, 95% *CI* 0.85 to 1.06, *P*=0.37, I^2=0%, TSA-adjusted *CI* 0.83 to 1.09, moderate-certainty evidence) (Figures 2 and 3, Table 2). TSA with *RRR* 15% produced an incidence of 45.1% and 38.3% in the control and corticosteroid groups, respectively. The cumulative *Z*-curves crossed the futility area, which excluded an effect size of 15% *RRR* or larger (Figure 3).

For the long-term mortality, the pooled estimate of *RR* for 1-year mortality for corticosteroids compared with control was 0.96 (95% *CI* 0.87 to 1.07, *P*=0.49, I^2=0%, high-certainty evidence). Compared with placebo or the control group, corticosteroids lowered the 7-day mortality (*RR* 0.68, 95% *CI* 0.51 to 0.90, *P*<0.01, I^2=0%, low-certainty evidence) in initial meta-analysis. However, the TSA-adjusted *CI* of the random-effect model was 0.39 to 1.16 without the TSA monitoring boundary being crossed, which was not statistically significant and indicated that the effect was uncertain.

Shock reversal

The conventional analysis revealed a statistically significant shortening of time to shock reversal in favor of corticosteroids (*MD* –21.56 hours, 95% *CI* –32.95 to –10.16, *P*<0.01, I^2=0%, TSA-adjusted *CI* –33.33 to –9.78, moderate-certainty evidence). For shock reversal within 28 days, there was no significant difference between the corticosteroid group and the control group.

Safety outcomes

Corticosteroids likely increased the rates of

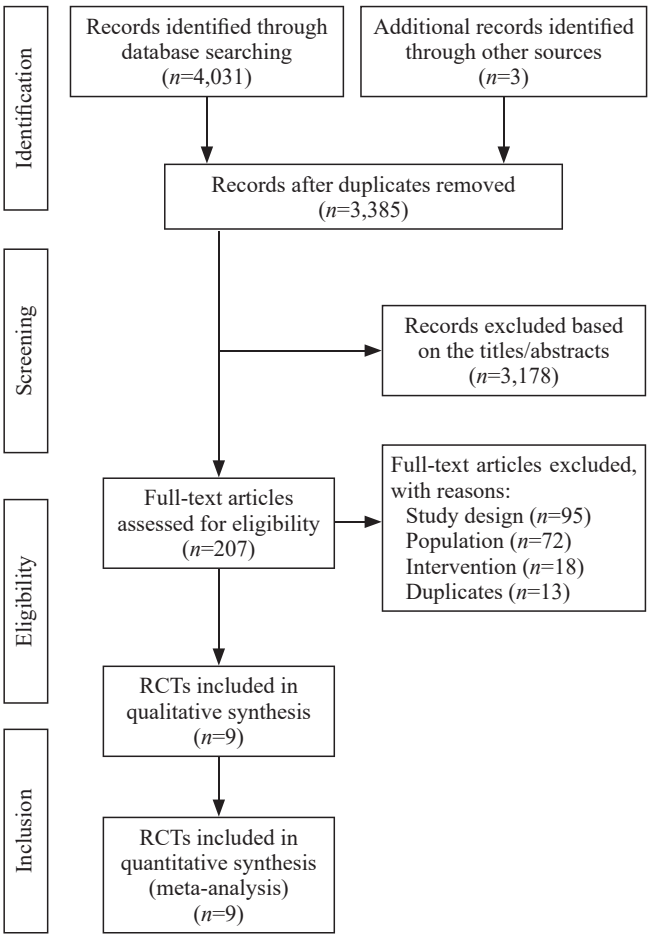

Figure 1. Flow diagram showing results of the search and selection of eligible studies. RCT: randomized controlled trial; study design: not RCT; population: no exclusion of immunosuppression or not septic shock; intervention: not corticosteroids.

hyperglycemia (*RR* 1.14, 95% *CI* 1.03 to 1.27, *P*=0.01, I^2=0%, TSA-adjusted *CI* 1.00 to 1.30, moderate-certainty evidence). However, the side effects of corticosteroids on infection and gastrointestinal bleeding were not significant.

Subgroup analyses for outcomes based on trial quality

Subgroup analyses for outcomes were performed according to the risk of bias. The results did not demonstrate a beneficial effect of corticosteroids in reducing short-term mortality in the subgroup of high-quality trials (*RR* 0.89, 95% *CI* 0.74 to 1.08, *P*=0.24; I^2=0%). For other mortality outcomes, results from trials at the low risk of bias did not substantially differ from the results of all trials.

Study quality

There were two trials classified as low risk of bias,[29,30] four trials as unclear risk of bias,[26-28,32] and three trials as high risk of bias.[24,25,31] Due to the number of studies included in each analysis less than ten, publication bias was not evaluated.

DISCUSSION

In this meta-analysis of nine RCTs with 1,298 patients with septic shock, we found no benefits of

Study	Corticosteroid Events	Corticosteroid Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% *CI*
Annane et al[29] (2002)	82	150	91	149	33.6%	0.90 (0.74–1.09)
Briegel et al[30] (1999)	3	20	4	20	0.7%	0.75 (0.19–2.93)
Cicarelli et al[27] (2007)	7	14	12	15	3.7%	0.63 (0.35–1.12)
Doluee et al[32] (2018)	38	56	39	52	22.2%	0.90 (0.71–1.15)
Luce et al[31] (1988)	22	38	20	37	7.8%	1.07 (0.72–1.60)
Lv et al[24] (2017)	23	58	19	60	5.3%	1.25 (0.77–2.04)
Oppert et al[28] (2005)	7	18	11	23	2.4%	0.81 (0.40–1.67)
Sprung et al[26] (2008)	86	251	78	248	20.1%	1.09 (0.85–1.40)
Wan et al[25] (2014)	24	62	11	27	4.2%	0.95 (0.55–1.65)
Total (95% *CI*)		667		631	100%	0.95 (0.85–1.06)
Total events	292		285			

Heterogeneity: Tau^2=0.00; Chi^2=5.68, *df*=8 (*P*=0.68); I^2=0%
Test for overall effect: *Z*=0.90 (*P*=0.37)

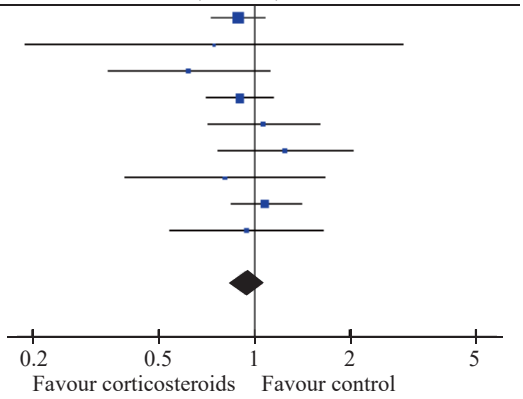

Figure 2. Forest plot of all trials for short-term mortality. *CI*: confidence interval; M-H: Mantel-Hansen; *df*: degrees of freedom.

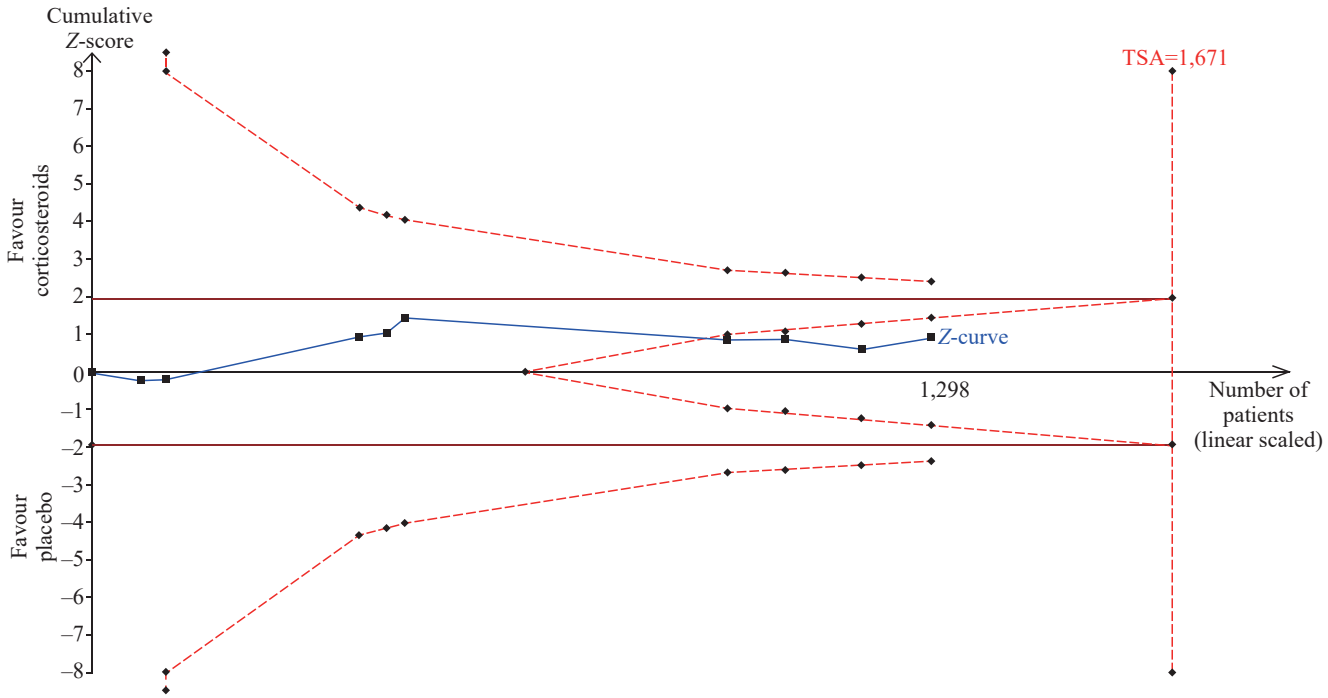

Figure 3. Trial sequential analysis of all trials for short-term mortality. TSA: trial sequential analysis. The required information size was 1,671 patients. The incidence in the control arm of 45.1% with a relative risk reduction of 15.0% produced an incidence of 38.3% in the corticosteroid group. The TSA-adjusted 95% confidence interval for a relative risk of 0.95 was 0.83 to 1.09 and the cumulative *Z*-curves crossed futility area.

Table 1. Characteristics of included RCTs comparing corticosteroids versus control in immunocompetent patients with septic shock

Study	Design and study place	Sample size (corticosteroids /control)	Excluded population (major selection criteria)	Intervention	Outcomes[a]
Annane et al[29] (2002)	Multicenter (19 sites), France	150/149	Advanced form of cancer or AIDS infection	IV hydrocortisone 50 mg bolus q6h and po fludrocortisone 50 μg qd versus placebo for seven days	ICU mortality, 28-day mortality, hospital mortality, one-year mortality, seven-day mortality,[b] shock reversal, and safety outcomes
Briegel et al[30] (1999)	One center, Germany	20/20	End-stage neoplasm, organ transplant recipients	IV hydrocortisone 100 mg loading, followed by 0.18 mg/(kg·h) continuous infusion until shock reversal, then reduced to 0.08 mg/(kg·h) for six days, then tapered off versus placebo (physiologic saline solution)	Shock reversal, 28-day mortality,[b] ICU mortality, hospital mortality, one-year mortality, seven-day mortality,[b] and safety outcomes
Cicarelli et al[27] (2007)	One center, Brazil	14/15	Immunosuppression therapy, end stage neoplasm with a life expectancy of less than three months	IV dexamethasone 0.2 mg/kg q36h for three doses versus placebo (0.9% physiological saline solution)	Seven-day mortality, 28-day mortality, and shock reversal
Doluee et al[32] (2018)	One center, Iran	56/52	Malignancy	IV hydrocortisone 50 mg q6h versus placebo (saline in the same volume) for seven days	Twenty-eight-day mortality
Luce et al[31] (1988)	One center, USA	38/37	Severe immunodeficiency and AIDS	IV methylprednisolone 30 mg/kg q6h for four doses versus mannitol placebo	Incidence of ARDS, hospital mortality, and safety outcomes
Lv et al[24] (2017)	One center, China	58/60	Immunosuppression	IV hydrocortisone 200 mg/d for six days, then tapered off versus placebo (normal saline)	Hospital mortality, 28-day mortality, shock reversal, and length of stay in ICU and hospital
Oppert et al[28] (2005)	One center, Germany	18/23	HIV positive or recipients of organ transplants	IV hydrocortisone 50 mg bolus, followed by 0.18 mg/(kg·h) continuous infusion until shock reversal, then tapered off versus placebo	Time to cessation of vasopressor support, 28-day mortality, and shock reversal
Sprung et al[26] (2008)	Multicenter (52 sites), Europe and Israel	251/248	Immunosuppression	IV hydrocortisone 50 mg q6h for five days, then tapered to 50 mg q12h for three days, then 50 mg QD for three days versus placebo	Mortality in ICU and hospital, 28-day mortality, one-year mortality, shock reversal, length of stay in ICU and hospital, and safety outcomes
Wan et al[25] (2014)	One center, China	62/27	Advanced form of cancer or HIV infection	IV hydrocortisone 50 mg q6h for seven days or five days versus saline	Shock reversal, 28-day mortality, seven-day mortality, length of stay in ICU, and safety outcomes

RCTs: randomized controlled trials; AIDS: acquired immunodeficiency syndrome; IV: intravenous; ICU: intensive care unit; HIV: human immunodeficiency virus; [a]: only primary outcome of included trials and outcomes analyzed in this meta-analysis were presented in the table; [b]: data were calculated by Kaplan-Meier curves.

Table 2. Summary of findings for all included RCTs (grading of recommendations assessment, development, and evaluation)

Outcomes	Anticipated absolute effects [a] (95% *CI*)		Relative effect (95% *CI*)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with control	Risk with corticosteroids			
Short-term mortality	452 per 1,000	429 per 1,000 (384–479)	*RR* 0.95 (0.85–1.06)	1,298 (nine RCTs)	⊕⊕⊕⊖ moderate[b]
Long-term mortality	606 per 1,000	582 per 1,000 (528–649)	*RR* 0.96 (0.87–1.07)	816 (three RCTs)	⊕⊕⊕⊕ high
Seven-day mortality	412 per 1,000	280 per 1,000 (210–371)	*RR* 0.68 (0.51–0.90)	457 (four RCTs)	⊕⊕⊖⊖ low[b, c]
Time to shock reversal	Ranging from 75.81 to 91.2 hours	*MD* –21.56 (–32.95 to –10.16)		263 (four RCTs)	⊕⊕⊕⊖ moderate[b]
Shock reversal	648 per 1,000	700–1,000 (642–765)	*RR* 1.08 (0.99–1.18)	997 (five RCTs)	⊕⊕⊕⊖ moderate[b]
Infection	257 per 1,000	280 per 1,000 (224–352)	*RR* 1.09 (0.87–1.37)	894 (four RCTs)	⊕⊕⊕⊖ moderate[c]
Gastrointestinal bleeding	88 per 1,000	100 per 1,000 (69–143)	*RR* 1.14 (0.79–1.63)	927 (four RCTs)	⊕⊕⊖⊖ low[b, c]
Hyperglycemia	657 per 1,000	749 per 1,000 (676–834)	*RR* 1.14 (1.03–1.27)	539 (two RCTs)	⊕⊕⊕⊖ moderate[b]

RCTs: randomized controlled trials; *CI*: confidence interval; *MD*: mean difference; ICU: intensive care unit; *RR*: relative risk; [a]: the risk in the corticosteroid group (and its 95% confidence interval) was based on the assumed risk in the control group and the relative effect of the corticosteroid (and its 95% *CI*); [b]: downgraded one level for serious risk of bias; [c]: downgraded one level for serious imprecision.

corticosteroids on either short-term mortality or long-term mortality. Our pooled analysis revealed that the administration of corticosteroids resulted in shorter time to shock reversal compared with the control group.

To the best of our knowledge, this is the first systematic review or meta-analysis to assess the efficacy and safety of corticosteroids in patients with septic shock based on the patients' immune status. Previous reviews mainly enrolled patients with sepsis or septic shock and performed subgroup analyses based on the trial quality, the doses and regimens of corticosteroids, and the severity of diseases.[10-15] However, there was no differentiation or discussion of the immunological status of patients.

There is a consensus on the definitions for the immunocompetent state and the immunocompromised status: the former is usually defined as the exclusion of the latter. There were some variations in the definition of "immunocompromised" in each of the aforementioned studies.

The mechanism of corticosteroids in septic shock may be its ability to down-regulate the pro-inflammatory response.[33] However, the balance between the immune enhancement and suppression is highly dependent on the immune activation of the host as well as the dose and duration of corticosteroid therapy.[33,34] Immunocompetent patients may exhibit a profound hyper-inflammatory response followed by the cascade of events in the early stage of the disease, when the application of corticosteroids for control of systemic inflammatory response syndrome may be beneficial. The theory might partially account for the findings that corticosteroids significantly reduced the time to shock reversal. While signs of compensated anti-inflammatory response syndrome may predominate in the whole stages of immunocompromised patients, the assignment of corticosteroids might strengthen the immunosuppression resulting in the accelerated deterioration of septic shock.[34,35] Although corticosteroids did not reduce the short-term and long-term mortalities in immunocompetent patients with septic shock, it was helpful in shock reversal without increasing the risk of infection. Given the findings, the administration of corticosteroids could be considered in immunocompetent patients suffering from septic shock to achieve hemodynamic stability.[36]

Our study has several limitations. Firstly, the systematic review was not registered in the International Prospective Register of Systematic Reviews (PROSPERO), and no protocol has been published. Secondly, we tried to contact the authors of included trials to gather data on immunocompetent persons, but many trials were excluded because of the lack of detailed data on the patients' immune status. Thirdly, there were many "unclear" ratings for risk of bias assessments, although we attempted to contact trial authors to clarify these ambiguities.

CONCLUSIONS

Corticosteroid therapy is not associated with the lower short- or long-term mortalities compared with placebo in immunocompetent patients with septic shock. However, corticosteroids significantly shorten the time to shock reversal without increasing the risk of infection. The patient's immune status should also be considered during clinical treatment and clinical trials in future.

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Contributors: XL proposed and wrote the paper. All authors have reviewed and approved the final version of manuscript for publication.

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