Systematic Review and Meta-Analysis

Medicine®

OPEN

Controversies in the application of corticosteroids for pediatric septic shock treatment: a preferred reporting items for systematic reviews and meta-analysis-compliant updated meta-analysis

Jing Yang, MD[a,*], Shaobo Sun, MD[b]

Abstract

Objectives: Septic shock is the major cause of childhood mortality. However, the application of corticosteroids remains controversial. This work aimed to analyze the source of controversy based on existing data and recent randomized controlled trials by meta-analysis and to assess whether it can avoid these factors to guide clinical treatment.

Methods: We searched the public databases up to 8 June 2019 and included only randomized controlled trials. The primary outcome was mortality. Sensitivity analysis, subgroup analysis, and dose-response meta-analysis were performed in this work.

Results: We included twelve studies consisting of 701 children in the meta-analysis. For primary outcome, the fixed-effect model showed steroids could significantly reduce the mortality compared to the control (Odds Ratio: 0.67; 95% confidence interval: 0.46–0.98; $P = .041$). However, the random-effect model showed a negative result (Odds Ratio: 0.69; 95% confidence interval: 0.32–1.51; $P = .252$). None of the subgroup results rejected the null hypothesis that the overall effect equaled zero. Dose-response effect analysis showed that increased dosage at a low dosage might reduce the mortality, while at a high dosage, increasing the dose might increase the mortality. Moreover, the grading of recommendations assessment, development, and evaluation level of evidence is low for mortality.

Conclusions: Corticosteroid application is not recommended for septic shock children under current medical conditions.

Abbreviations: BSA = body surface area, BW = body weight, CI = confidence interval, ORs = odds ratios, RCTs = randomized controlled trials, SMDs = standard mean differences.

Keywords: corticosteroids, meta-analysis., pediatric, septic shock, systematic review

1. Introduction

Pediatric septic shock is a serious, life-threatening condition with a complex pathophysiology, including an amplified immune response, multiple organ dysfunction, and insufficient cortisol.[1–3] In early recovery, volume replacement, vasoactive-inotropic support, and adjunctive corticosteroid therapy must be considered, in addition to antibiotic application.[4] Hormonotherapy has been indicated to be able to improve the hemodynamic status of a patient. However, the drug can also significantly reduce the immune response, especially adaptive immunity. Therefore, the application of corticosteroids in patients with septic shock is still a controversial issue.[5]

Currently, there is a lack of large-scale randomized controlled trials (RCTs) due to the relatively low incidence of the disease. Therefore, the varying results are generally based on small-scale RCTs, which include children with varying characteristics and provide little significant guidance for clinical applications. In the Surviving Sepsis Campaign Guidelines, hydrocortisone therapy is recommended for fluid-refractory, catecholamine-resistant, and suspected or proven adrenal insufficiency shock treatment.[6] However, in a recent review, corticosteroids were recommended for children with infection regardless of their shock status, while corticosteroids were not recommended for pediatric nonseptic shock, neonates, and adrenal insufficiency patients.[7] In addition, the treatment of septic shock should not be the same in pediatric patients as that in adults, as children are not small adults, and steroid metabolism in children has specific characteristics.[8]

A previous meta-analysis suggested that the application of steroids has no significant effect on overall mortality (relative risk: 0.744; 95% confidence interval (CI): 0.475, 1.165; $P = .197$). A network meta-analysis also failed to demonstrate statistically significant results regarding mortality associated with corticosteroid and placebo treatments, even though it included children and adult patients.[9] The conclusions are still mainly limited by small sample sizes and varying methodological quality,

Editor: Girish C Bhatt.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Supplemental Digital Content is available for this article.

[a] *Department of Pediatric Respiration, Lanzhou University Second Hospital,* [b] *College of Pharmacy, Gansu University of Chinese Medicine, Lanzhou, Gansu, P R. China.*

[*] *Correspondence: Jing Yang, No. 80, Cuiyingmen, Chengguan District, Lanzhou City, Gansu province, P R. China, 730000 (e-mail: yangjing037@126.com).*

How to cite this article: Yang J, Sun S. Controversies in the application of corticosteroids for pediatric septic shock treatment: a preferred reporting items for systematic reviews and meta-analysis-compliant updated meta-analysis. Medicine 2020;99:30(e20762).

Received: 23 October 2019 / Received in final form: 22 April 2020 / Accepted: 19 May 2020

http://dx.doi.org/10.1097/MD.0000000000020762

and meta-analyses considering well-designed and large-scale RCTs are needed.[9–12] However, due to the low incidence and urgent pathogenesis, it is difficult to carry out large-scale RCTs.[13] Additionally, more than 90% of pediatric intensivists still consider steroids to be needed after two or more vasoactive infusions in children with septic shock.[14] Therefore, the need to analyze the source of controversy based on the existing data and recent RCTs with a meta-analysis to explore the controversial factors and to assess whether these factors can be avoided to guide clinical treatment is urgent.

2. Materials and methods

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[15] Ethical approval was not necessary because this study was a meta-analysis. Therefore, our data were based on published studies only.

2.1. Data sources and search strategy

The two authors independently performed a literature search using the PubMed, EMBASE, and Cochrane Library databases; the search period was from the date of inception of the databases to 8 June 2019. The following terms were used in the search strategy: (((sepsis or septic or infectious or infective or infectivity or pyohemia or pyemia) AND Shock) AND (paediatric or children or pediatric or newborn)) AND (random* or randomised or randomized). The details are listed in the supplementary material http://links.lww.com/MD/E618. Because of the small number of RCTs on pediatric septic shock, we relaxed the restrictions on hormones in the search strategy. If there was disagreement regarding the search results, it was solved by discussion. Manual searches of the reference lists of the relevant reviews were also performed to identify additional eligible studies.

2.2. Inclusion and exclusion criteria

A study was included in the meta-analysis if it met the following criteria: the study had an RCT design; the study included children with septic shock; the study compared corticosteroid treatment with other treatments; and the study reported mortality results. The exclusion criteria included the following: the study did not specify the types of corticosteroids. Due to the small number of studies on this topic, this study also included conference abstracts if they met the inclusion criteria. The study selection was independently undertaken by two authors.

2.3. Data collection and quality assessment

The two authors extracted the following information from each eligible study: the first author's name, publication year, location, sample size, reason for shock, type of steroids, first-day dose, treatment duration, total dose, control treatment, and follow-up period. Because of the different types of steroids and units of measurement used in the included studies, it was necessary to convert the different types of steroids into an equivalent dose of hydrocortisone. The conversion standard was hydrocortisone 20 mg = methylprednisolone 4 mg = dexamethasone 0.75 mg.[16] For pediatric medications, the conversion between body weight (BW) and body surface area (BSA) was as follows: in children with a BW less than 30 kg, $BSA(m^2) = 0.035 \times BW(kg) + 0.1$; in children with a BW more than 30 kg, the BSA on a 1.15 m^2 basis increased by 0.1 m^2 per 5 kg increase from a 30 kg BW basis. The primary outcome in our analysis was mortality at the last follow-up. We assessed the methodological quality of the included trials using a risk of bias approach according to the methods described by the Cochrane Collaboration, which include 7 specified domains.[17] We also used the Grades of Recommendation Assessment, Development and Evaluation system to rank certainty of the evidence of primary outcome.[18] The data extraction and quality assessments were conducted independently by 2 authors.

2.4. Statistical analysis

The dichotomous data results were pooled and reported as odds ratios (ORs) with 95% CIs. The continuous data results were reported as standard mean differences (SMDs) with 95% CIs. The I^2 statistic was used to estimate the degree of heterogeneity among the studies. We also used prediction interval to present the expected range of true effects in similar studies.[19] For dichotomous data, the Mantel-Haenszel method, which has been shown to have better statistical properties when the study size is small, was used in a fixed-effect model.[20] For continuous data, the inverse-variance method, which minimizes the imprecision of the pooled effect estimate, was used in a fixed-effect model.[21] For a random-effect model, the Sidik-Jonkman estimator, which is less dependent on levels of true heterogeneity, was used to assess overall treatment effect.[22,23] Continuity correction was adopted to adjust zero-event study.[24] Egger test and a funnel plot were used to check for potential publication bias. For the primary results, a sensitivity analysis was performed to determine the impact of a single study on the overall result.[25] Subgroup analyses were also carried out according to first-day corticosteroid dose, total corticosteroid dose, publication year, country type, disease type, drug type, and design risk of bias (whether the design was a blinded method) by a random-effect model. Then, we conducted a dose-response meta-analysis of mortality, first-day steroid dose and total dose. To derive a dose-response curve, we modeled the dose by using restricted cubic splines with 3 knots at fixed percentiles of 10%, 50%, and 90% of the distribution.[26] All the p-values were reported as two-sided, and p-values less than 0.05 were regarded as statistically significant for all the trials. R (version 3.6.2), Stata (version 14.0) and Review Manager (version 5.3) were used for the meta-analysis.

3. Results

We identified 800 articles after removing duplicate studies. After screening the titles and abstracts, 784 of the articles were excluded, and the full texts of 16 articles were assessed. Of these articles, 4 were excluded due to post hoc research (1); the analysis of children without shock (1); and no reported mortality results (2). Ultimately, 12 articles and conference abstracts were included in our meta-analysis.[27–38]

The included studies had a significant time gap, with an initial period from 1975 to 1996 and a second period from 2009 to 2017. The early studies were conducted in Southeast Asian and African countries. The recent studies were conducted in countries with relatively advanced medical standards, such as the UK and Canada.[27,29] However, no more than 100 children were included in each study. The reasons for shock included sepsis and dengue fever.

Table 1

Characteristics of included studies.

Author	Year	Location	Sample size	Reason for shock	Type of steroids	First-day dose	Treatment duration	Total dose	Follow-up
Menon K[27]	2017	Canada	57	Sepsis	Hydrocortisone	5mg/kg	7 d	17mg/kg	NA
El-Nawawy A[28]	2017	Egypt	96	Sepsis	Hydrocortisone	2mg/kg	5 d	10mg/kg	30 d
H.de Graaf[29]	2014	UK	29	Sepsis	Hydrocortisone	4mg/kg	2 d	8mg/kg	NA
Mansour MGE[30]	2012	Egypt	30	Sepsis	Dexamethasone	NA	NA	NA	28 d
Valoor HT[31]	2009	India	38	Sepsis	Hydrocortisone	5mg/kg	7 d	35mg/kg	NA
Tina Slusher[32]	1996	African	72	Sepsis	Dexamethasone	0.6mg/kg(16mg/kg)*	2 d	32mg/kg	NA
Tassniyom S[33]	1993	Thailand	63	Dengue	Methylprednisolone	30mg/kg(150mg/kg)	1 d	150mg/kg	14 d
Sumarmo[34]	1982	Indonesia	97	Dengue	Hydrocortisone	50mg/kg	1 d	50mg/kg	NA
Futrakul[35]	1981	Thailand	22	Dengue	Methylprednisolone	30mg/kg(150mg/kg)	1 d	150mg/kg	NA
Min[36]	1975	Myanmar	98	Dengue	Hydrocortisone	25mg/kg	3 d	50mg/kg	NA
Pongpanich[37]	1973	Thailand	71	Dengue	Hydrocortisone	25mg/kg	1 d	25mg/kg	NA
Widya and Martoatomdjo[38]	1975	Indonesia	28	Dengue	Hydrocortisone	37.5mg/kg	1 d	37.5mg/kg	NA

NA = not available.
* Dose after convert.

Steroids such as hydrocortisone, methylprednisolone, and dexamethasone were applied. The treatment durations were 1 to 7 days. One study did not specify the steroid dose or the applied duration.[30] The characteristics of the control groups in all the included studies were similar to those in the experimental groups, except for steroid use. Most of the studies did not describe the follow-up period, except for 3 studies with 14, 28, and 30 days of follow-up, respectively[28,30,33] (Table 1). All the studies used an RCT design, and 6 studies adopted a blind method. Therefore, the overall level of evidence in this study was ideal (Fig. 1).

For the primary outcome, the fixed-effect model showed that steroid application significantly reduced mortality compared to the control treatments (OR: 0.67; 95% CI: 0.46–0.98; $P = .041$), with moderate heterogeneity ($I^2 = 42\%$, $P = .06$). However, the random-effect model yielded a result that failed to reject the null hypothesis (OR: 0.69; 95% CI: 0.32–1.51; $P = .252$) (Fig. 2), although no publication bias was detected (Begg test: $P = .213$; Egger test: $P = .356$).

In the sensitivity analysis, 3 studies significantly influenced the overall results: Pongpanich 1973,[37] Widya and Martoatomdjo 1975,[38] and Mansour MGE 2012.[30] Deleting any of these 3 studies resulted in a negative fixed-effect model result (Fig. 3). Two of the studies were early studies on dengue shock syndrome in children.[37,38] The other key study, Mansour MGE 2012, reported 7-day mortality rates of 20% in the dexamethasone group (3/15) and 53.3% in the control group (8/15). However, the study also reported that there was no significant difference in mortality at the 30-day follow-up, but it did not mention the specific number of deaths.[30] Notably, compared with the other studies, these 3 studies did not demonstrate low mortality in the corticosteroid group but demonstrated high mortality in the control group (approximately 50% to 100%). Therefore, the decision to use steroids based on these 3 studies was not robust.

Further, subgroup analyses based on the random-effect model were conducted according to steroid dose, publication year, country category, disease type, drug type, and evidence level to explore the source of the heterogeneity and controversy. None of the subgroup results rejected the null hypothesis that the overall effect equaled zero (Fig. 4).

It was necessary to confirm whether there was a dose-response effect to indicate whether the steroid dose should be increased. For the first-day steroid dosage, the generalized least-squares regression showed that the dose was negatively correlated with mortality (beta = 0.984, $P = .013$), suggesting that an increase in the first-day dosage would reduce mortality in children with septic shock. However, nonlinear detection showed that a nonlinear model was needed ($P = .0165$). Restricted cubic spline regression (10%, 50%, 90%) showed that in the low-dose group (0.6–5 mg/kg), increasing the dose reduced mortality (beta = 0.943, p = 0.053), but in the high-dose group (5–37.5 mg/kg), increasing the dose increased mortality (beta = 1.21, $P = .154$) (Fig. 5, A). For the total steroid dosage, there were no statistically significant differences in either the linear (beta = 0.996, $P = .289$) (Fig. 5, B) or nonlinear regression (dose(8–25 mg/kg): beta = 0.984, $P = .052$; dose(32–50 mg/kg): beta = 1.012, $P = .101$) results.

For other outcomes, the results of pediatric intensive care unit duration from 2 studies in 2017 indicated that the control groups had shorter durations than the steroid groups (SMD: 0.52; 95% CI: 0.13, 0.92; $P = .006$). Regarding shock reverse time, the pooled result based on the 2 studies showed that the steroid application group had a shorter shock reverse time than the control group (SMD: -1.34; 95% CI: -2.48, -0.21; $P = .020$). The other results were not statistically significant (Fig. 6).

Within the Grades of Recommendation Assessment, Development and Evaluation approach, we downgraded the certainty of evidence for mortality to low owing to a high risk of bias at study level across studies due to inconsistency and indirectness (Table 2).

4. Discussion

For pediatric septic shock patients, corticosteroid application is controversial. Meta-analysis results, guidelines, and clinical practice often yield inconsistent conclusions. However, the sources and characteristics of the controversy are unknown. Almost all meta-analyses hope to obtain more robust conclusions with large-scale sample sizes and well-designed RCTs. However, this research is difficult and undesired. We hope to improve medical conditions to reduce the incidence of life-threatening pediatric septic shock. However, it is still necessary to clarify whether the corticosteroids are beneficial or harmful to these children.

This study aimed to identify the causes of the controversy with a meta-analysis and to suggest how to avoid these disputes in clinical application. This research found that the overall mortality results were not robust, and the variations arose from studies with the following characteristics: studies that were published

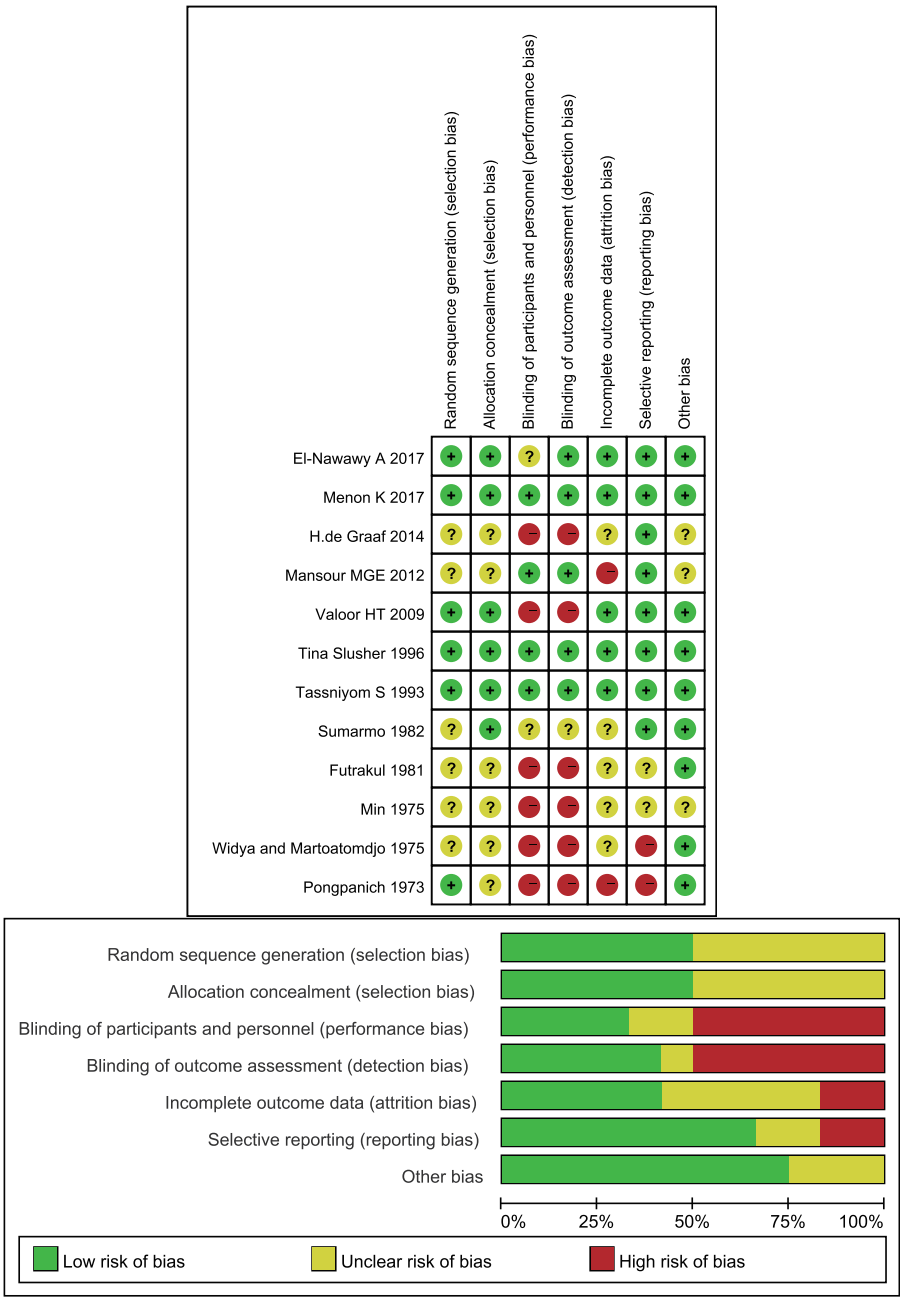

Figure 1. Risk of bias of the included studies.

early, studies conducted in developing countries, studies including children with dengue shock syndrome, studies with a high first-day steroid dose, and studies with a design with a high risk of bias. These characteristics obviously do not apply to current treatment conditions. There was no controversy among the studies with the following characteristics: studies published after 2000, studies conducted in developed countries, and studies with a design with a low risk of bias. These studies suggest that corticosteroid application is not associated with mortality.

This study hopes to answer the question of whether increasing the first-day or total steroid dosage can reduce mortality. The dose-response effect analysis showed that increasing the dosage from a low dosage may reduce mortality, while increasing the dosage from a high dosage may increase mortality. Thus, we suggest that currently, corticosteroids are not beneficial to children with septic shock, and simply increasing the first-day steroid dosage may result in negative effects.

In a previous meta-analysis, Gibbison analyzed the use of corticosteroids for septic shock in adults and children with a network meta-analysis and showed that no specific drug effectively reduced mortality and the incidence of gastrointestinal bleeding or superinfection. A hydrocortisone bolus resulted in a shorter shock reversal time than the placebo or methylprednisolone. However, the meta-analysis was inappropriate because of the included patients. A separate analysis of adults and children was necessary. Therefore, it is doubtful whether this conclusion is applicable to children.[9] Kusum Menon analyzed whether corticosteroid application was beneficial or harmful to pediatric

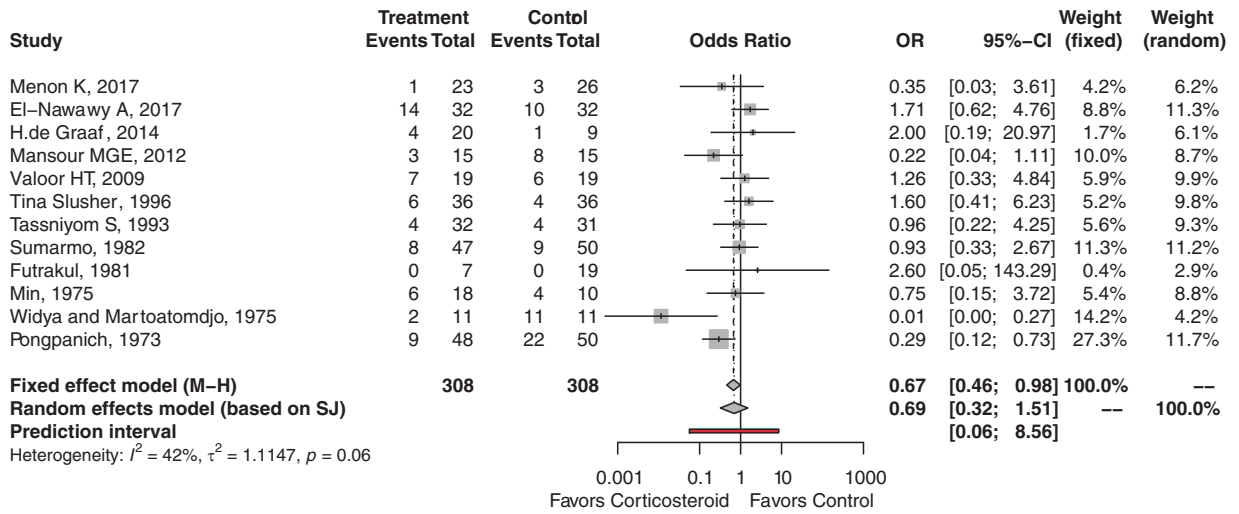

Figure 2. Forest plot of the meta-analysis comparing corticosteroid and control treatments for pediatric septic shock patients in terms of mortality.

septic shock patients by qualitative assessment. The finding indicated that only 2 early RCTs demonstrated that steroids provided survival benefits to children, and no studies showed that steroids were are harmful.[10] This systemic review was published in 2016, and additional RCTs published in 2017 also suggested that steroids were neither beneficial nor harmful to children with septic shock in terms of mortality. Therefore, it seems certain that steroids have no benefit to septic shock in children, and it is not meaningful to conduct further small-scale RCTs.

Unlike corticosteroids, fluids and vasoactive drugs affect the mortality of children. A recent study analyzed the choice of vasoactive drug in the treatment of children with septic shock. Based on two small-scale RCTs, epinephrine was found to be safer than dopamine at 40 ml/kg in fluid resuscitation-unresponsive children.[39] For fluid strategies, a Cochrane review suggested that liberal fluid therapy may increase mortality in children with septic shock compared with conservative fluid therapy.[40] Unfortunately, our study did not analyze the impact of concomitant treatment because most of the included studies did not describe this in detail. Further studies could define subgroups of children with shock, such as catecholamine-resistant shock.[10] However, such a grouping would further reduce the sample size and increase the difficulty of RCT implementation.

In conclusion, the results of this study suggest that corticosteroid application is not recommended for children with septic shock under current medical conditions. There is still an ongoing large-scale RCT (NCT03401398) that will be carried out in the United States and Canada; this RCT plans to recruit 1032 children. The corticosteroid application strategy is an initial bolus of 2 mg/kg IV hydrocortisone, followed by 1 mg/kg of hydrocor-

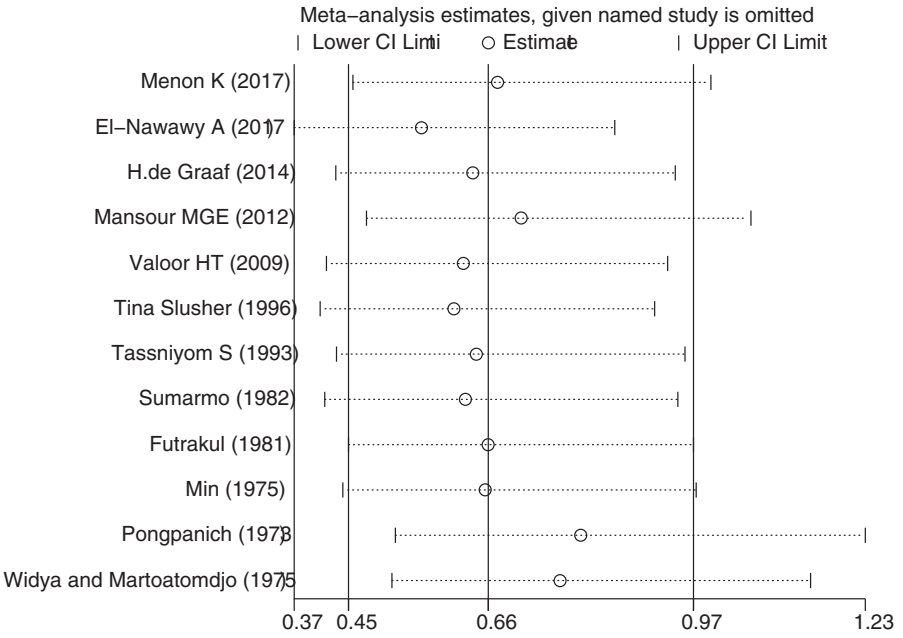

Figure 3. Sensitivity analysis of the meta-analysis in terms of mortality.

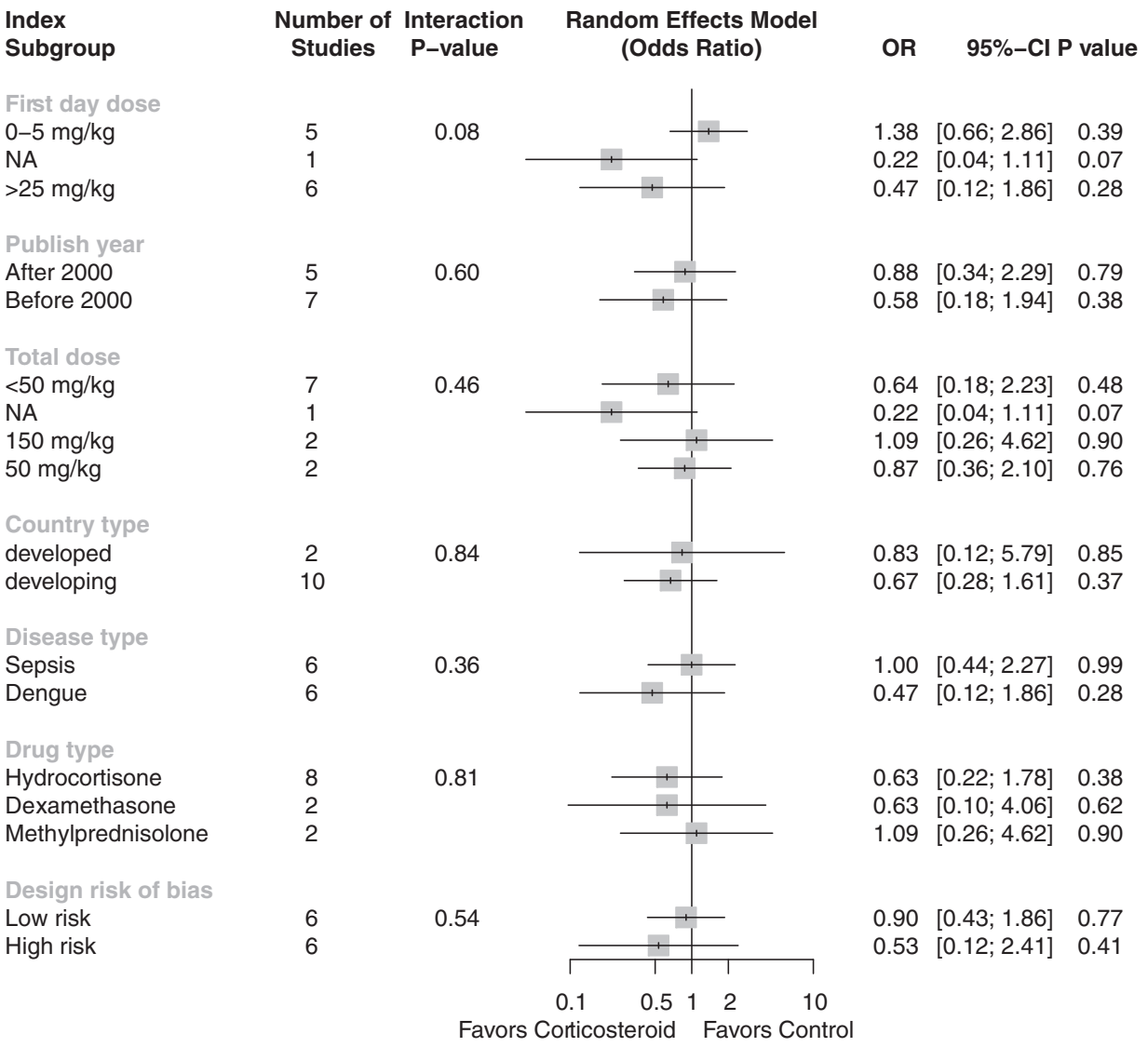

Figure 4. Subgroup analysis of the meta-analysis in terms of mortality.

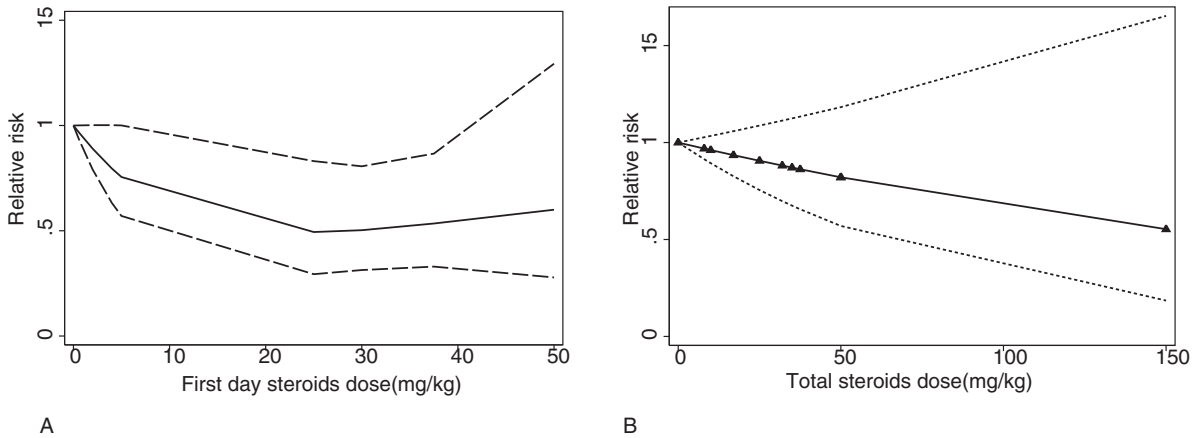

Figure 5. Dose-response meta-analysis of the association between mortality and first-day steroid dose (A) and total steroid dose (B).

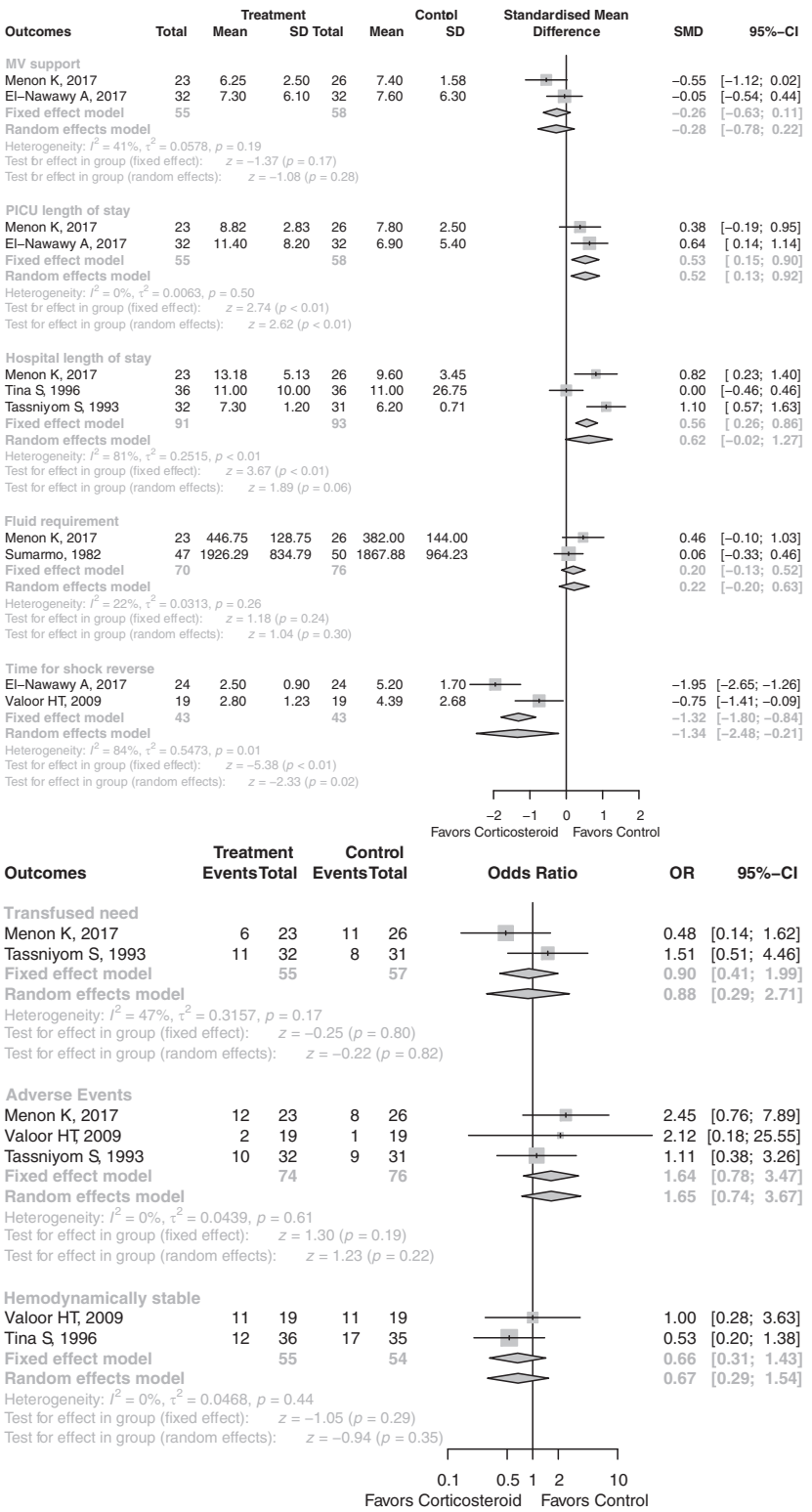

Figure 6. Forest plot of the meta-analysis of other related results.

tisone dosed every 6 hours for a maximum of 7 days or until all vasoactive infusions have been discontinued for at least 12 hours. The primary outcomes include 28-day hospital mortality and a ≥25% decrease in the baseline health-related quality of life score. We hope that this large-scale RCT will show positive results.

5. Limitations

There were several limitations in this study. First, this work was performed at the study level instead of at the individual level. Individual-level analysis contained multiple patient-level covariates

Table 2

GRADE evidence for mortality results in the application of corticosteroids for pediatric septic shock treatment.

Steroid for Pediatric septic shock					
Patient or population: Pediatric septic shock Settings: Intervention: Steroid					
	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)			
	Assumed risk	Corresponding risk	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Outcomes	Control	Steroid			
Mortality Follow-up: 14-30 d	266 per 1000	203 per 1000 (121 to 317)	OR 0.70 (0.38 to 1.28)	616 (12 studies)	⊕⊕⊖⊖ low[1,2]

CI = confidence interval, GRADE = grades of recommendation assessment, development and evaluation, OR = odds ratio.

* The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

[1]Difference results between random- and fixed-effect models. [2]Difference disease type (Sepsis or Dengue).

and interactions, but the study-level information is prone to low power and ecological bias.[41] Second, the total number of included septic shock patients was low, which may have impacted the final results. Third, we analyzed only the injection dose according to BW with a mg/kg unit but could not analyze the absolute injection dose for each child. Fourth, most of the included studies did not specify the follow-up period, which was 1 source of heterogeneity that could not be analyzed.

Acknowledgments

None.

Author contributions

Conceptualization: Jing Yang and Shaobo Sun.
Data curation: Shaobo Sun.
Statistical analysis: Jing Yang.
Literature search and data collection: Jing Yang and Shaobo Sun.
Supervision: Jing Yang.
Writing – original draft: Jing Yang.
Writing – review & editing: Shaobo Sun.

References

[1] Gatica-Andrades M, Vagenas D, Kling J, et al. WNT ligands contribute to the immune response during septic shock and amplify endotoxemia-driven inflammation in mice. Blood Adv 2017;1:1274–86.
[2] Martin K, Weiss SL. Initial resuscitation and management of pediatric septic shock. Minerva Pediatr 2015;67:141–58.
[3] Yan HP, Li M, Lu XL, et al. Use of plasma mitochondrial DNA levels for determining disease severity and prognosis in pediatric sepsis: a case control study. BMC Pediatr 2018;18:267.
[4] Ismail J, Jayashree M. Advances in the management of pediatric septic shock: old questions, new answers. Indian Pediatr 2018;55:319–25.
[5] Wong HR, Cvijanovich NZ, Anas N, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. Am J Respir Crit Care Med 2015;191:309–15.
[6] Nishida O, Ogura H, Egi M, et al. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016). J Intensive Care 2018;6:7.
[7] Lamontagne F, Rochwerg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ 2018;362:k3284.
[8] Darmaros LF, Delgado AF, Carvalho WB. Corticosteroids in septic shock: what should the decision in pediatrics be? Rev Assoc Med Bras (1992) 2016;62:482–4.
[9] Gibbison B, Lopez-Lopez JA, Higgins JP, et al. Corticosteroids in septic shock: a systematic review and network meta-analysis. Crit Care 2017;21:78.
[10] Menon K, Wong HR. Corticosteroids in pediatric shock: a call to arms. Pediatr Crit Care Med 2015;16:e313–7.
[11] Menon K, McNally D, Choong K, et al. A systematic review and meta-analysis on the effect of steroids in pediatric shock. Pediatr Crit Care Med 2013;14:474–80.
[12] Menon K. Use of hydrocortisone for refractory shock in children. Crit Care Med 2013;41:e294–5.
[13] Kumar Angurana S, Kumar P. Assessing feasibility of randomized controlled trials of corticosteroids in pediatric septic shock in developed countries: only half the answer to the problem. Pediatr Crit Care Med 2017;18:1087.
[14] Menon K, McNally JD, Choong K, et al. A survey of stated physician practices and beliefs on the use of steroids in pediatric fluid and/or vasoactive infusion-dependent shock. Pediatr Crit Care Med 2013;14:462–6.
[15] Nawijn F, Ham WHW, Houwert RM, et al. Quality of reporting of systematic reviews and meta-analyses in emergency medicine based on the PRISMA statement. BMC Emerg Med 2019;19:19.
[16] Yang J, Jing M, Yang X. Association between genetic polymorphisms and osteonecrosis in steroid treatment populations: a detailed stratified and dose-response meta-analysis. Biosci Rep 2019;39:20190024.
[17] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[18] Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv 2018;2:3317–59.
[19] Borenstein M, Higgins JP, Hedges LV, et al. Basics of meta-analysis: I(2) is not an absolute measure of heterogeneity. Res Synth Methods 2017;8:5–18.
[20] Mathes T, Kuss O. A comparison of methods for meta-analysis of a small number of studies with binary outcomes. Res Synth Methods 2018;9:366–81.
[21] Hollands GJ, Naughton F, Farley A, et al. Interventions to increase adherence to medications for tobacco dependence. Cochrane Database Syst Rev 2019;8:CD009164.
[22] Pateras K, Nikolakopoulos S, Mavridis D, et al. Interval estimation of the overall treatment effect in a meta-analysis of a few small studies with zero events. Contemp Clin Trials Commun 2018;9:98–107.
[23] Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods 2016;7:55–79.
[24] Kuss O. Statistical methods for meta-analyses including information from studies without any events-add nothing to nothing and succeed nevertheless. Stat Med 2015;34:1097–116.
[25] Xue J, Li H, Zhou Q, et al. Comparison of peritoneal dialysis with hemodialysis on survival of diabetic patients with end-stage

kidney disease: a meta-analysis of cohort studies. Ren Fail 2019;41: 521–31.
[26] Chang VC, Cotterchio M, Khoo E. Iron intake, body iron status, and risk of breast cancer: a systematic review and meta-analysis. BMC Cancer 2019;19:543.
[27] Menon K, McNally D, O'Hearn K, et al. A Randomized controlled trial of corticosteroids in pediatric septic shock: a pilot feasibility study. Pediatr Crit Care Med 2017;18:505–12.
[28] El-Nawawy A, Khater D, Omar H, et al. Evaluation of early corticosteroid therapy in management of pediatric septic shock in pediatric intensive care patients: a randomized clinical study. Pediatr Infect Dis J 2017;36:155–9.
[29] De Graaf H, Ramakrishnan KA, Pappachan J, et al. Evaluation of corticosteroid replacement therapy in children with severe septic shock - a randomised intervention trial. Pediatric Crit Care Med 2014;15:141.
[30] Mansour MGE, Tarek MAM, Zayton Y, et al. Effect of dexamethasone therapy on the expression of macrophage migration inhibitory factor in critically ILL children with septic shoc. Arch Dis Child 2012;97:A446.
[31] Valoor HT, Singhi S, Jayashree M. Low-dose hydrocortisone in pediatric septic shock: an exploratory study in a third world setting. Pediatr Crit Care Med 2009;10:121–5.
[32] Slusher T, Gbadero D, Howard C, et al. Randomized, placebo-controlled, double blinded trial of dexamethasone in African children with sepsis. Pediatr Infect Dis J 1996;15:579–83.
[33] Tassniyom S, Vasanawathana S, Chirawatkul A, et al. Failure of high-dose methylprednisolone in established dengue shock syndrome: a placebo-controlled, double-blind study. Pediatrics 1993;92:111–5.
[34] Sumarmo , Talogo W, Asrin A, et al. Failure of hydrocortisone to affect outcome in dengue shock syndrome. Pediatrics 1982;69:45–9.
[35] Futrakul P, Vasanauthana S, Poshyachinda M, et al. Pulse therapy in severe form of dengue shock syndrome. J Med Assoc Thai 1981;64: 485–91.
[36] Min M, U.T. , Aye M, et al. Hydrocortisone in the management of dengue shock syndrome. Southeast Asian J Trop Med Public Health 1975;6:573–9.
[37] Pongpanich B, Bhanchet P, Phanichyakarn P, et al. Studies on dengue hemorrhagic fever. Clinical study: an evaluation of steroids as a treatment. J Med Assoc Thai 1973;56:6–14.
[38] Widya MS. MartoatmodjoClinical observations on dengue shock syndrome (an evaluation of steroid treatment). Paediatr Indones 1975;15:151–60.
[39] McVea S, Turner A. Which vasoactive drug should be first choice in paediatric septic shock? Arch Dis Child 2019;104:303–5.
[40] Li D, Li X, Cui W, et al. Liberal versus conservative fluid therapy in adults and children with sepsis or septic shock. Cochrane Database Syst Rev 2018;12:CD010593.
[41] Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med 2017;36:855–75.