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The Efficacy, Safety, and Optimal Regimen of Corticosteroids in Sepsis: A Bayesian Network Meta-Analysis

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Objectives: Conventional systematic reviews have indicated that corticosteroids might result in a slight reduction in mortality in sepsis. However, the efficacy, safety, and optimal regimen of different corticosteroids partly remain unknown. In this study, we conducted a Bayesian network meta-analysis for a head-to-head comparison of the therapeutic efficacy and safety of currently used corticosteroids in sepsis.

Design: A Bayesian network meta-analysis for a head-to-head comparison of the therapeutic efficacy and safety of currently used corticosteroids in sepsis.

Setting: A total of 35 eligible randomized controlled trials of corticosteroid use in sepsis.

Patients: The present Bayesian network meta-analysis included 8,859 patients with sepsis.

Interventions: Randomized controlled trials were screened from PubMed, Embase, and the Cochrane Library up to December 28, 2019. A head-to-head comparison of the therapeutic efficacy and safety between the different categories of corticosteroids from the trials was conducted by Bayesian network meta-analysis. An empirical Bayesian meta-regression and a post hoc Bayesian network meta-analysis were performed to explore the appropriate dose and therapeutic duration of steroids for sepsis.

Measurements and Main Results: A total of 35 randomized controlled trials including 8,859 patients with sepsis were enrolled in the final analysis. Bayesian network meta-analysis revealed that methylprednisolone and dexamethasone might be more effective in reducing short-term mortality in sepsis than placebo: methylprednisolone versus placebo (relative risk, 0.65, 95% credible interval 0.40–0.93), dexamethasone versus placebo (relative risk, 0.42, 95% credible interval, 0.24–0.84). Hydrocortisone and hydrocortisone plus fludrocortisone were superior to placebo in days to shock resolution (**e-Table 5**, Supplemental Digital Content 1, http://links.lww.com/CCX/A150): hydrocortisone versus placebo (mean difference, −1.70, 95% credible interval, −2.83 to −0.92), hydrocortisone plus fludrocortisone versus placebo (mean difference, −2.54, 95% credible interval, −4.19 to −0.84). Hydrocortisone was superior to placebo in reducing the length of stay in the ICU (mean difference, −1.43, 95% credible interval, −3.36 to −0.15). Methylprednisolone was superior to placebo in improving ventilation-free days (mean difference, 7.71, 95% credible interval, 1.15–14.42). In addition, further analysis indicated that the optimal therapeutic dosage was 200–400 mg per day of hydrocortisones or equivalents (relative risk, 0.83, 95% credible interval, 0.64–0.98), and the appropriate therapeutic duration was 4–7 days (relative risk, 0.78; 95% credible interval, 0.57–0.96).

Conclusions: This study provided moderate evidence that the dosage of 200–400 mg per day of hydrocortisone or equivalent for 4–7 days was most likely to benefit septic patients.

Key Words. Bayesian network analyses; corticosteroids; meta-regression; optimal regimen; sepsis

Sepsis is a critical syndrome that is associated with high morbidity and mortality. Early antibiotic administration and adequate fluid resuscitation to maintain sufficient tissue perfusion remains the mainstay in sepsis resuscitation according to the Surviving Sepsis Campaign (2016). Despite improvements in basic science and clinical research, therapeutic strategies for sepsis are still limited, and mortality remains as high as 10%–35% (1).

The pathophysiology of sepsis is described as a maladaptive host response to infection, and thus, corticosteroids may have some benefits for patients with sepsis (2). As corticosteroids are capable of improving the cardiovascular response to exogenous catecholamines, they have been recommended for the treatment of patients

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with sepsis since the 1950s (3). In addition, sepsis is identified as a dysregulated systemic inflammatory host response to infection in the presence of organ dysfunction. Corticosteroids might provide some benefits to block sepsis-induced systemic inflammatory host responses due to immunosuppressive effects. Furthermore, corticosteroids have a relatively low cost and address the adrenal cortical hypofunctions that could occur in states of extreme stress (4).

Recently, conventional systematic reviews indicated that corticosteroids might result in a slight decrease in mortality in sepsis (5, 6). Nevertheless, not all therapeutic steroids presented the same efficacy and safety. Even at dose equivalency, some steroids showed more immunosuppressive effects, and some had more mineralocorticoid and vasoactive properties (7). Conventional meta-analyses were limited to comparisons between one type of steroid and placebo and failed to compare different types of corticosteroids. Furthermore, previous meta-analyses did not provide detailed recommendations for the optimal dosage and therapeutic duration of corticosteroids in sepsis. These important details remain largely unknown.

Bayesian network analyses and Bayesian meta-regression are useful tools to tackle these problems. The Bayesian network analyses of existing studies made it possible to evaluate comparative efficacy, summarizing and interpreting the wider picture of the evidence base, and to understand the relative merits and defects of the multiple interventions (8).

In this study, Bayesian network analyses were conducted for the comprehensive assessment of the efficacy and safety of different corticosteroids. Bayesian meta-regression and further Bayesian network analyses were used to identify the optimal dose and therapeutic duration of corticosteroids for patients with sepsis (9).

MATERIALS AND METHODS

The protocol was registered at the International prospective register of systematic reviews (International prospective register of systematic reviews registration CRD42018110022).

Data Sources and Searches

We searched a collection of databases including PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE up to December 28, 2019. We included randomized controlled trials (RCTs) and excluded case reports, case series, and observational studies. The eligibility criteria followed the participants, interventions, comparators, outcomes, and study design criteria: the participants were adults (age ≥18 yr) who were diagnosed with sepsis, severe sepsis, septic shock, or any combinations thereof. The inclusion criteria of patients with sepsis were determined by the individual study authors. The intervention was any type of corticosteroid, comparing one corticosteroid with another or to a placebo in patients with sepsis regardless of the drug delivery method and excluded case reports and observational studies. Only RCTs were included. The exclusion criteria were as follows: studies on children (<18 yr) and RCTs without the outcome of short-term mortality (28–31 d) or survival curves.

Key words including "septic shock" OR "sepsis" OR "septicemia" OR "toxic shock", AND "corticosteroids" OR "steroids" OR "corticoids" OR "hydrocortisone" AND "randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "placebo" OR "RCT" were used for the search process, and the full search strategy is detailed in the **supplementary material** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150). If the relevant meta-analysis or review was screened, further snowballing was conducted (supplementary material, Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

Study Selection

After implementing the search strategy, two investigators (S-Z., J-F.X.) independently assessed the titles and abstracts, followed by the full articles to identify possible eligible studies. Disagreements were resolved by discussion and third party adjudications as needed. The following information was extracted from the articles: efficacy, safety, dosage, and therapeutic duration of corticosteroids.

The efficacy of corticosteroids included all-cause short-term mortality (28–31 d), time to resolution of shock, length of stay in the ICU, ventilation-free days to day 28, and duration of mechanical ventilation. The safety of corticosteroids included the occurrence rate of any adverse events, superinfection, gastrointestinal bleeding, hyperglycemia, and hypernatremia. The thresholds of adverse events were determined by the individual study authors.

Risk of Publication Bias and Consistency Estimation

Two reviewers with no affiliation with any of the included RCTs evaluated the risk of bias of the included studies independently according to the Cochrane risk of bias tool, including the seven domains shown in **e-Figures 1** and **2** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150). Funnel plots were performed to assess the risk of publication bias.

Data Analysis

We estimated the summary relative risk (RR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes, all with 95% credible intervals (CrIs), using pairwise and network meta-analyses. In this study, a statistical assessment of consistency (i.e., the agreement between direct and indirect evidence) was performed through the design-by-treatment test and by separating indirect evidence from direct evidence.

The Brooks–Gelman–Rubin method was used to ensure the convergence of every comparison. We fitted all models using the binomial likelihood for dichotomous outcomes, uninformative prior distributions for the treatment effects, and a minimally informative prior distribution for the common heterogeneity SD. We assumed uninformative priors—i.e., N (0, 1,000)—for all coefficients. The convergence of models was ensured by visual inspection of three chains and after considering the Brooks–Gelman–Rubin diagnostic.

Furthermore, rank probability analysis was performed for efficacy and safety ranking using a consistent model. The rank probability was calculated through the surface under the cumulative ranking curve and the mean ranks (10).

To our knowledge, dosage, therapeutic duration, and sepsis populations are the main factors influencing drug efficacy. However, secondary analysis limited our assessment of the original data from these RCTs and failed to exactly classify patients

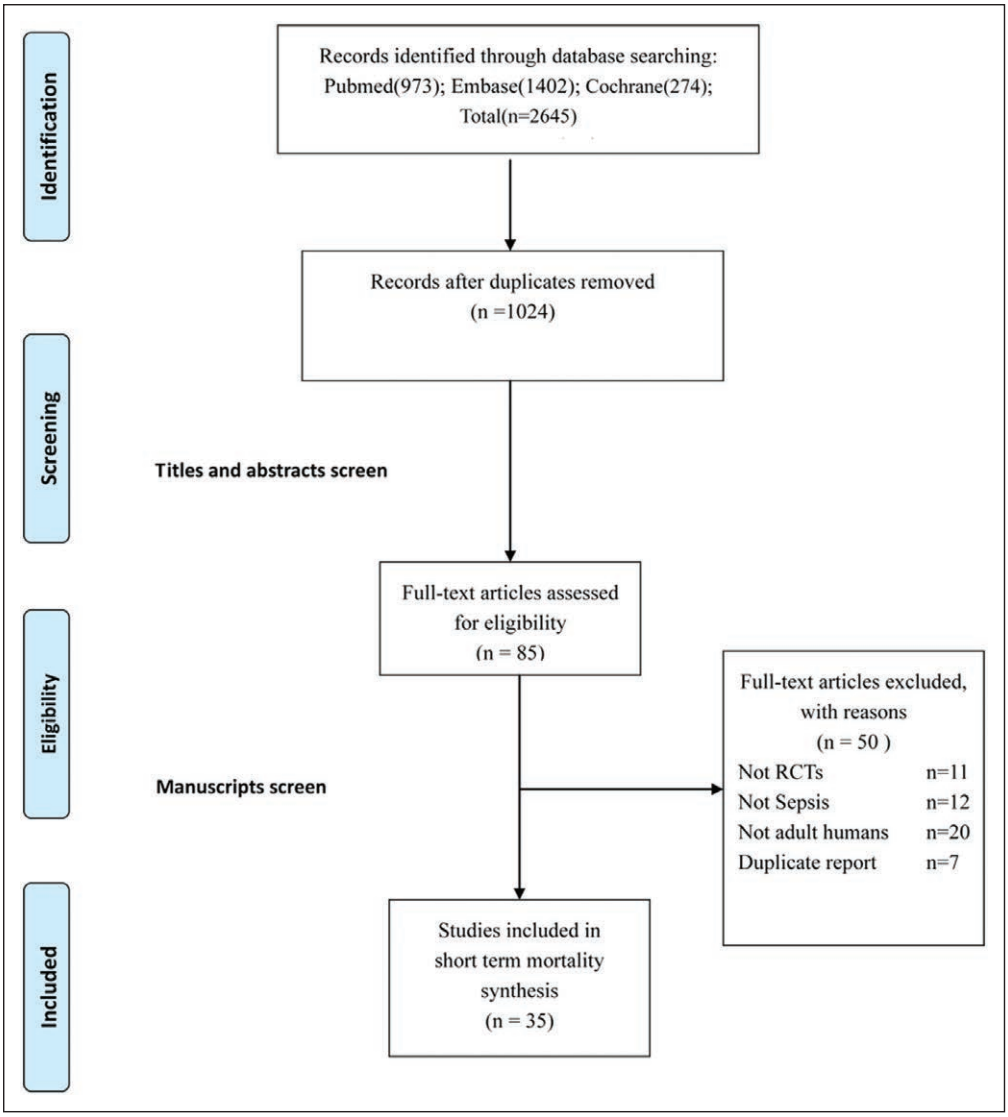

Figure1. Flow diagram of process in search and reasons for exclusion of studies. RCT = randomized clinical trial.

into different subgroups. Therefore, we performed a meta-regression to assess the influence of different dosages and therapeutic durations on short-term mortality. The meta-regression model was constructed through an empirical Bayesian algorithm. After meta-regression, we further conducted a Bayesian network meta-analysis to explore the optimal dosage or therapeutic duration.

The Bayesian network meta-analyses were conducted by the GeMTC R package. The meta-regression and subgroup analyses were performed using Stata 12.0. The figures were plotted by Stata 12.0 (Stata Corporation, College Station, TX) or R 3.4.4 (University of Auckland, Auckland, New Zealand). A *p* value of less than 0.05 was set for statistical significance.

Grading the Evidence

We graded the quality of the evidence by applying the Grading of Recommendations Assessment, Development, and Evaluation (GRADEprofiler Version 3.6; https://gradepro.org/). The grades included high, moderate, low, and very low according to the quality of the design, limitations, inconsistencies, indirectness, imprecision, and possible publication bias. Two investigators (S-Z., J-F.X.) independently assessed the studies to grade the evidence.

RESULTS

Literature Search and Details of the Enrolled Trials

After employing the searching strategies, 2,645 studies were recruited in the current analysis. Then, 1,024 studies remained after removing duplicates. After scanning the titles and abstracts, 939 studies were excluded. Furthermore, 85 of the remaining papers were rejected after reviewing the full text. We eventually obtained 35 studies, and the process is shown in **Figure 1**. The details of the included trials are presented in **e-Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150). For the included RCTs, the published years ranged from 1971 to 2019.

A total of 35 RCTs with 8,859 patients with sepsis were finally enrolled in the current analyses (11-45), including 46 patients in the betamethasone group, 298 in the methylprednisolone group, 230 in the dexamethasone group, 2,946 in the hydrocortisone group, 151 in the prednisolone group, 775 in the hydrocortisone plus fludrocortisone group, and 4,459 in the placebo group.

In the analysis of the consistency estimation plot (**e-Fig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCX/A150), the median consistency variances were estimated at 0.615. The funnel plot of this study is shown in **e-Figure 4** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

The network graph of the studies in groups is shown in **e-Figure 5** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150). The contribution graph is shown in **e-Figure 6** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150). Surface under the cumulative ranking curve (SUCRA) for the therapeutic efficacy of corticosteroids were found in **e-Tables 15-22** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

Comparison of the Safety of Corticosteroid Use in Sepsis

The results of the Bayesian network analyses suggested no significant differences among the groups in the occurrence rate of any adverse events, superinfection, gastrointestinal bleeding,

TABLE 1. Head-to-Head Comparisons for Effect of Various Types of Corticosteroids on Short-Term Mortality

Placebo	1.18 (0.38–3.02)	0.65 (0.40–0.93)	0.42 (0.24–0.84)	0.86 (0.62–1.04)	0.86 (0.42–1.96)	0.78 (0.44–1.17)
	Betamethasone	0.50 (0.18–1.78)	0.37 (0.12–1.42)	0.71 (0.26–2.23)	0.70 (0.23–3.05)	0.63 (0.22–2.13)
		Methylprednisolone	0.68 (0.35–1.56)	1.31 (0.82–2.18)	1.29 (0.61–3.88)	1.15 (0.64–2.29)
			Dexamethasone	2.01 (0.94–3.62)	2.13 (0.78–5.25)	1.81 (0.74–3.54)
				Hydrocortisone	1.00 (0.48–2.41)	0.90 (0.53–1.57)
					Prednisolone	0.89 (0.34–1.99)
						Hydrocortisone + fludrocortisone

hyperglycemia, hypernatremia, or neuromuscular weakness, with a moderate grade of evidence. with a moderate grade of evidence (**e-Tables 9-14**, Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

Comparison of the Therapeutic Efficacy of Corticosteroids in Sepsis

The head-to-head comparison by Bayesian network analysis showed that methylprednisolone and dexamethasone might be more effective in reducing short-term mortality in sepsis than placebo (**Table 1**): methylprednisolone versus placebo (RR, 0.65; 95% CrI, 0.40–0.93), dexamethasone versus placebo (RR 0.42, 95% CrI 0.24–0.84), with a low evidence grade. No significant differences were found in hospital mortality, as shown in **e-Tables 2-4** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

In the present Bayesian network analyses, hydrocortisone and hydrocortisone plus fludrocortisone were superior to placebo in days to shock resolution (e-Table 5, Supplemental Digital Content 1, http://links.lww.com/CCX/A150): hydrocortisone versus placebo (MD, –1.70; 95% CrI, –2.83 to –0.92), hydrocortisone plus fludrocortisone versus placebo (MD, –2.54; 95% CrI, –4.19 to –0.84), with a moderate evidence grade. As shown in **e-Table 6** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150), hydrocortisone was superior to placebo in reducing the length of stay in the ICU (MD, –1.43; 95% CrI, –3.36 to –0.15), with a moderate evidence grade. As shown in **e-Table 7** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150), methylprednisolone was superior to placebo in improving ventilation-free days (MD, 7.7; 95% CrI, 1.15–14.42), with a moderate evidence grade. No significant differences were found in the duration of ventilation, as shown in **e-Table 8** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

TABLE 2. Head-to-Head Comparisons for Effect of Various Doses of Corticosteroids on Short-Term Mortality

Placebo	0.84 (0.43–1.48)	0.83 (0.64–0.98)	1.10 (0.74–1.70)
	<200 mg/d	0.98 (0.53–2.06)	0.76 (0.32–1.53)
		200–400 mg/d	0.74 (0.46–1.15)
			> 400 mg/d

Comparison of the Safety of Corticosteroid Use in Sepsis

The results of the Bayesian network analyses suggested no significant differences among the groups in the incidence of any adverse events, superinfection, gastrointestinal bleeding, hyperglycemia, hypernatremia, or neuromuscular weakness, with a moderate grade of evidence. SUCRA for the safety of corticosteroids were found in **e-Tables 23-28** (Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

Selection of the Optimal Therapeutic Regimen for Corticosteroid Use in Sepsis

The meta-regression results showed that dosage or therapeutic duration influenced corticosteroid efficacy on short-term mortality (**e-Figs. 7** and **8**, Supplemental Digital Content 1, http://links.lww.com/CCX/A150). The Bayesian network meta-analysis further indicated that short-term mortality was significantly lower in patients using corticosteroids in dosages of 200–400 mg per day of hydrocortisones or equivalents (RR, 0.83; 95% CrI, 0.64–0.98) and treatment durations of 4–7 days (RR, 0.78; 95% CrI, 0.57–0.96), as shown in **Tables 2** and **3**, with a moderate evidence grade.

DISCUSSION

To our knowledge, the present Bayesian network analyses had the largest sample size for evaluating the efficacy and safety of diverse corticosteroids for sepsis to date. Previous conventional meta-analyses could only indicate that corticosteroids were superior to placebo in improving short-term mortality (5, 6). However, detailed therapeutic strategies lack further discussion. The present Bayesian network analyses first indicated that methylprednisolone or dexamethasone might be superior to other steroids in reducing the short-term mortality of sepsis. Furthermore, the dose of 200–400 mg/d hydrocortisones or equivalents and treatment duration of 4–7 days might be the appropriate dose and ideal therapy time of glucocorticoids in sepsis. In addition, the current study indicated that the most effective interventions to increase ventilation-free days were methylprednisolone or prednisolone.

The Bayesian network analyses identified that methylprednisolone or dexamethasone might be superior to other steroids in reducing the short-term mortality of sepsis. This finding might be because methylprednisolone and dexamethasone have a relatively

TABLE 3. Head-to-Head Comparisons for Effect of Various Therapeutic Durations of Corticosteroids on Short-Term Mortality

Placebo	0.52 (0.23–1.06)	0.80 (0.42–1.44)	0.78 (0.57–0.96)	0.91 (0.61–1.19)
	<1 d	1.54 (0.61–3.94)	1.52 (0.70–3.48)	0.56 (0.24–1.31)
		1–3 d	1.03 (0.54–2.03)	0.87 (0.44–1.80)
			4–7 d	0.85 (0.59–1.29)
				> 7d

longer duration of efficacy than other glucocorticoids and are beneficial for improving cortisol deficiency in sepsis. However, a large publication bias from Schumer's study seemed to be the main reason for this result. It was obvious that Schumer's study was out of the funnel plot. In Schumer's study, there were very high effective rates of methylprednisolone and dexamethasone, with RRs of 0.30 (95% CrI, 0.13–0.72) and 0.24 (95% CrI, 0.09–0.64), respectively. After removing Schumer's study, we identified no significant difference among various corticosteroids in reducing short-term mortality (**e-Table 29**, Supplemental Digital Content 1, http://links.lww.com/CCX/A150). In consideration of this, the evidence grade of this result was low.

The appropriate dose and ideal therapy time of glucocorticoids in sepsis remain unknown. High doses of corticosteroids or long durations may increase the occurrence rate of adverse events; on the other hand, low doses of corticosteroids or insufficient durations could not address the adrenal cortical hypofunctions that can occur in sepsis. The current analysis first pointed out that the dose of 200–400 mg/day hydrocortisones or equivalents and treatment duration of 4–7 days ranked first compared with other strategies, with a moderate evidence grade. After removing Schumer's study, the optimal dosage or therapeutic duration was also dose of 200–400 mg/day hydrocortisones or equivalents and treatment duration of 4–7 days (**e-Tables 30** and **31**, Supplemental Digital Content 1, http://links.lww.com/CCX/A150).

In addition, the present findings regarding the efficacy of improving ventilation-free days indicated that methylprednisolone or prednisolone ranked first for successfully weaning patients from mechanical ventilatory support. Acute respiratory distress syndrome is identified as pulmonary edema and respiratory failure due to damage to the endothelial-epithelial barrier caused by an excessive immune response. Langhoff et al (46) indicated that methylprednisolone was superior to other corticosteroids for its immunosuppressive effects. The use of methylprednisolone and prednisolone for sepsis accompanied by adult respiratory distress syndrome might decrease the duration of mechanical ventilatory support, leading to potential improvement in ventilator-induced lung injury. Therefore, methylprednisolone was recommended for patients with sepsis-associated acute respiratory distress syndrome by the Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency in critically ill patients (47).

Conventional meta-analyses were limited to direct comparisons (one type of steroid vs placebo) and did not provide indirect evidence (comparisons among various corticosteroids). Bayesian network algorithms allowed us to obtain more reliable estimates for these indirect comparisons, especially for the different interventions (8). The immune system and hypothalamic pituitary-adrenal axis of adults are largely different from those of children, resulting in varied host responses to corticosteroids in sepsis. The data of juveniles would introduce additional heterogeneity if assimilated with that of adults, and consequently, studies regarding children were excluded from the final analyses.

There are several limitations to the present study. We incorporated the types, dosages, and durations of corticosteroids in the main results of our analysis to highlight the most robust findings for further use in clinical applications. However, many trials did not report adequate information about randomization and allocation concealment, which restricts the interpretation of these results. Furthermore, heterogeneity of the population, such as sepsis or septic shock, was not clearly discussed because it was difficult to distinguish patients based on the limited information of many RCTs. In addition, the Bayesian network analysis was an indirect comparison and did not have a high quality of evidence, so validation RCTs are warranted to further assess the findings.

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Drs. Zhang and Qiu had full access to all of the data in the study and take responsibility for their integrity and the accuracy of the data analysis. Drs. Zhang, Chang and Wu performed the systematic review, study selection, statistical analysis, and preparation of the article for publication. Drs. Xie and Yang contributed to the data extraction and quality assessment. All authors participated in writing the article and preparing the figures.

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