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SYSTEMATIC REVIEW

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Prophylactic corticosteroids for infants undergoing cardiac surgery with cardiopulmonary bypass: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Prophylactic corticosteroids have been widely used to mitigate the inflammatory response induced by cardiopulmonary bypass (CPB). However, the impact of this treatment on clinically important outcomes in infants remains uncertain.

Methods We systematically searched databases (Medline, Embase, and Cochrane Central Register of Controlled Trials), Clinical Trials Registry, and Google Scholar from inception to March 1, 2024. Randomized controlled trials (RCTs) in which infants undergoing on-pump cardiac surgery received prophylactic corticosteroids or placebo were selected. The risk of bias was assessed using the Cochrane Collaboration risk-of-bias tool. Considering clinical heterogeneity between studies, the random-effects model was used for analysis. Subgroup analyses on the neonatal studies and sensitivity analyses by the leave-one-out method were also conducted.

Results Eight RCTs comprising 1,920 patients were included. Our analysis suggested no significant difference in postoperative mortality (2.1% *vs.* 3.3%, risk ratio (RR) = 0.71, 95% confidence interval (CI) [0.41, 1.21]). Significantly increased insulin treatment in infants (19.0% *vs.* 6.5%, RR = 2.78, 95% CI [2.05, 3.77]) and significantly reduced duration of mechanical ventilation in neonates (mean difference = -22.28 h, 95% CI [-42.58, -1.97]) were observed in the corticosteroids group. There were no differences between groups for postoperative acute kidney injury, cardiac arrest, extracorporeal membrane oxygenation support, low cardiac output syndrome, neurologic events, infection, or length of postoperative intensive care unit stay.

Conclusions Current evidence does not support the routine prophylactic use of corticosteroids in infants undergoing cardiac surgery with CPB. Further large-scale research is needed to investigate the optimal agent, dosing regimen, and specific impact on various types of cardiac surgery.

Trial registration This systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (CRD42023400176).

Keywords Corticosteroids, Cardiac surgery, Infants, Perioperative medicine

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Background

Outcomes for infants undergoing cardiac surgery have improved significantly over the past several decades with advances in surgical and anesthesia techniques [1–4]. However, infants undergoing cardiac surgery with cardiopulmonary bypass (CPB) remain at high risk of death, serious complications, and prolonged length of intensive care unit (ICU) stay [5–7].

The severe systemic inflammatory response resulting from CPB, which can lead to capillary leakage and organ dysfunction, has been recognized as a major contributor to adverse outcomes [8–12]. Corticosteroids, steroid hormones secreted by the adrenal glands, have been shown to have anti-inflammatory effects in cardiac surgery patients [13–15]. For decades, synthetic corticosteroids such as methylprednisolone, dexamethasone, and hydrocortisone have been routinely administered in many centers to mitigate the CPB-induced systemic inflammatory response [16, 17]. However, this practice has also raised concerns due to the uncertain evidence of beneficial effects on clinically relevant outcomes.

The routine use of prophylactic steroids for adult patients undergoing cardiac surgery is not recommended by current guidelines, but a more pronounced inflammatory response in younger patients and potentially beneficial effects of corticosteroids are suggested [18]. However, recommendations for pediatric and infant patients are lacking. Previous studies and meta-analyses have failed to demonstrate significant benefits of prophylactic corticosteroids use in adults and children undergoing on-pump cardiac surgery [19–27]. A recent meta-analysis by Losiggio et al. revealed a significant reduction in mortality and postoperative inotropic score in patients younger than 65 years old who received prophylactic corticosteroids [28]. To the best of our knowledge, infants have not been exclusively evaluated in previous meta-analyses. In recent years, several large-scale randomized controlled trials (RCTs) regarding the prophylactic use of corticosteroids in infants undergoing cardiac surgery have been conducted [16, 29, 30]. These studies have revealed the uncertain influence of corticosteroids on infants and possible confounders, such as age, type of surgery, and CPB strategy and duration [16, 29, 30].

Therefore, we performed a systematic review and meta-analysis by analyzing all relevant RCTs to investigate the impact of prophylactic corticosteroids on infants submitted to cardiac surgery with CPB. The null hypothesis stated that there would be no significant difference in perioperative outcomes between infants treated with prophylactic corticosteroids and those treated with placebo.

Methods

We reported this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]. Before our study started, the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42023400176).

Search strategy and selection criteria

We systematically searched Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to March 1, 2024. Medical Subject Heading (MeSH) terms and free text terms related to corticosteroids, infants, and cardiac surgery were selected. Search strategies are shown in Supplementary Material 1. We also searched the Clinical Trials Registry (www.clinicaltrials.gov) and Google Scholar to identify grey literature. In addition, the reference lists of all the included studies were screened to identify additional studies missed from the original electronic search. The inclusion criteria were as follows: (1) design: randomized controlled trials; (2) population: infants ($\leq$12 months) scheduled for cardiac surgery with CPB; (3) intervention: perioperative (preoperative, intraoperative, or postoperative) administration of corticosteroids (methylprednisolone, dexamethasone, hydrocortisone, or other corticosteroids) for prophylactic purposes; (4) control: placebo or none; and (5) outcomes: eligible studies must report at least one of the predetermined outcomes. The primary outcome was in-hospital postoperative mortality. Secondary outcomes included in-hospital postoperative acute kidney injury (AKI), cardiac arrest, extracorporeal membrane oxygenation (ECMO) support, low cardiac output syndrome (LCOS), neurologic events, infection, insulin treatment, duration of postoperative mechanical ventilation, and length of postoperative ICU stay. Exclusion criteria were as follows: (1) organ transplantation; (2) corticosteroid administration for other purposes, such as supplement therapy, and allergy treatment; and (3) patients with abnormalities of the hypothalamic–pituitary–adrenal axis.

Data extraction

Two authors (SYW and YX) independently screened the literature and extracted data using the standard data collection form. A third author (HY) was involved when discrepancies appeared. We extracted the following data: first author, title, journal, year of publication, study design, country, number of enrolled patients, distribution in both groups, patient characteristics, type of surgery, type of corticosteroids, corticosteroid administration regimen, in-hospital postoperative mortality, AKI,

cardiac arrest, ECMO support, LCOS, neurologic events, infection, insulin treatment, duration of postoperative mechanical ventilation, and length of postoperative ICU stay. Authors were contacted for missing data relevant to our study.

Risk of bias assessment

Two authors (SYW and YX) independently evaluated the risk of bias in the included studies according to version 2.0 of the Cochrane Collaboration risk-of-bias tool [32]. The following domains were assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was evaluated as having low risk of bias, some concerns, or high risk of bias. The overall risk of bias was assessed based on the judgment for individual domains. Any disagreement was resolved through consultation with a third author (HY).

Quality of evidence assessment

We evaluated the overall quality of evidence for each outcome by the recommendation of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system using GRADEpro software [33]. Two authors (SYW and YX) independently assessed the quality of evidence and categorized the certainty of evidence for each outcome as high, moderate, low, or very low. The following five domains participated in the assessment: risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Statistical analyses

Dichotomous outcomes were presented as risk ratios (RR) and 95% confidence intervals (CI); continuous outcomes were presented as mean differences (MD) and 95% CI. Heterogeneity was measured by using the I^2 value for each outcome. Considering clinical heterogeneity between studies, including the type of surgery, duration of aortic cross-clamp, type and dose of corticosteroids used, a random-effects model was used for analysis. For studies with a zero-cell count, the treatment arm continuity correction was used. We performed prespecified subgroup analyses on the studies that enrolled only neonatal patients ($\leq$1 month). Sensitivity analyses were also conducted using the leave-one-out method. To evaluate publication bias, both visual assessments using funnel plot asymmetry and statistical analysis using Egger's regression test were employed. A symmetric funnel plot would suggest the absence of publication bias, while Egger's test with a p-value less than 0.05 would indicate significant publication bias. All analyses were performed using R software version 4.2.2 (2022 The R Foundation for Statistical Computing).

Results

Study selection and characteristics

The initial electronic search retrieved 2,437 citations from databases (Medline 735; Embase 895; CENTRAL 807), and the grey literature search identified an additional 83 studies. After removing duplicates, 2,066 studies were screened for titles and abstracts. We excluded 1,983 studies based on their titles and abstracts, which led to 83 studies eligible for full-text review. 75 studies were excluded after full-text assessment. Reasons for major excluded articles are provided in Supplementary Material 2. Finally, 8 RCTs with a total of 1,920 participants fulfilled the predefined criteria and were included in our systematic review and meta-analysis (Fig. 1) [14, 16, 29, 30, 34–37].

All included studies were published between 2005 and 2022, with sample sizes ranging from 20 to 1,200 patients. Among the included studies, three studies were multicenter RCTs, and the remainder were single-center RCTs. All studies included patients $\leq$1 year, with five studies comprising only neonatal patients ($\leq$1 month). A variety of corticosteroids were used, including methylprednisolone, dexamethasone, and hydrocortisone. Corticosteroids were administered before surgery in one study, during the surgery in five studies, and during both intraoperative and postoperative periods in two studies. The type of surgery was miscellaneous in four studies and unreported in one study (Table 1).

The risk of bias assessment is shown in Supplementary Material 3. All the included studies had a low risk of bias or some concerns.

The quality of evidence assessment for the included studies is reported in Supplementary Material 4. All decisions to downgrade the certainty of the evidence were justified in footnotes.

Primary outcome

All eight studies reported in-hospital postoperative mortality, with two studies reporting no events. Overall, 1,920 patients were assessed for in-hospital postoperative mortality. Of these, 20 of 948 patients in the corticosteroids group and 32 of 972 patients in the placebo group died after surgery during hospitalization. The in-hospital postoperative mortality between the two groups showed no significant difference (2.1% *vs.* 3.3%), with RR = 0.71, 95% CI [0.41, 1.21], and $I^2 = 0\%$ (Fig. 2A). However, the study by Hill et al. included more than half of the population in the analysis. Therefore, a sensitivity analysis was performed to detect the influence of each study on the outcomes. Consequently,

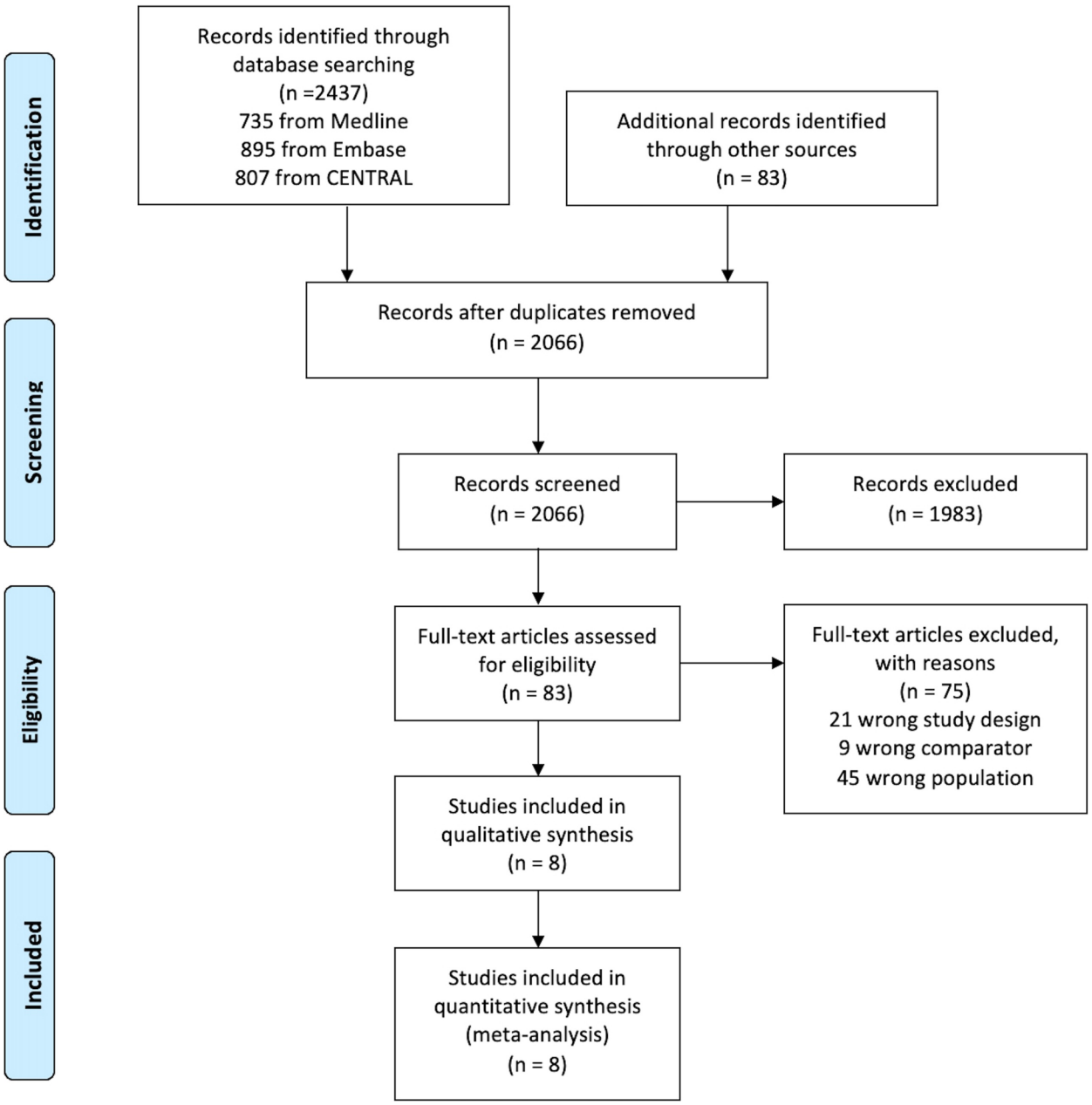

Fig. 1 Flow diagram of study selection

removing any single study did not influence the result regarding mortality (Fig. 2B). The subgroup analysis of the neonatal studies also revealed consistent results (five studies: 3.6% *vs.* 7.1%, RR = 0.68, 95% CI [0.27, 1.75], $I^2 = 0\%$) (Fig. 2C). The funnel plot is provided in Supplementary Material 5. Additionally, the Egger's test suggested that publication bias did not significantly affect our results ($P = 0.70$).

Secondary outcomes

In-hospital postoperative AKI was reported in four studies. From these, 51 of 894 patients in the corticosteroids group and 64 of 916 patients in the placebo group developed AKI during the postoperative period, with no significant difference between the two groups (5.7% *vs.* 7.0%, RR = 0.92, 95% CI [0.68, 1.24], $I^2 = 0\%$)

Table 1 Characteristics of included studies

Study	Center	Country	No. of patients	Age	Type of surgery	Type of corticosteroids	Timing	Regimen	Control
Ando2005 [34]	1	Japan	20(10/10)	≤ 28 days	complete biventricular repair	hydrocortisone	intraoperative, postoperative	0.18 mg/kg/h for 3 days, 0.09 mg/kg/h for 2 days, 0.045 mg/kg/h for 2 day	placebo
Graham2019 [29]	2	US	176(81/95)	≤ 31 days	miscellaneous	methylprednisolone	intraoperative	30 mg/kg, after induction of anesthesia	placebo
Heying2012 [14]	1	Germany	20(9/11)	8-21 days	arterial switch	dexamethasone	preoperative	1 mg/kg, 4 h before scheduled start of CPB	placebo
Hill2022 [16]	24	US	1200(599/601)	< 1 year	miscellaneous	methylprednisolone	intraoperative	30 mg/kg, CPB pump-priming fluid	placebo
Keski-Nisula2013 [35]	1	Finland	40(20/20)	≤ 28 days	miscellaneous	methylprednisolone	intraoperative	30 mg/kg, after induction of anesthesia	placebo
Keski-Nisula2020 [36]	1	Finland	30(15/15)	2-12 months	bidirectional Glenn procedure	methylprednisolone	intraoperative	30 mg/kg, after induction of anesthesia	placebo
Lomivorotov2020 [30]	4	Brazil, China, Russia	394(194/200)	≤ 12 months	not reported	dexamethasone	intraoperative	1 mg/kg, after induction of anesthesia	placebo
Suominen2017 [37]	1	Finland	40(20/20)	≤ 28 days	miscellaneous	methylprednisolone, hydrocortisone	intraoperative, postoperative	2 mg/kg methylprednisolone after induction, hydrocortisone infusion 0.2 mg/kg/h for 48 h, 0.1 mg/kg/h for 48 h, and 0.05 mg/kg/h for 24 h	placebo

(Fig. 3A). Furthermore, subgroup analysis of two neonatal studies showed consistent results (Fig. 3B).

Three studies reported in-hospital postoperative cardiac arrest, and two studies reported in-hospital postoperative ECMO support. No significant difference between corticosteroids and placebo groups was revealed (cardiac arrest: 2.5% *vs.* 3.8%, RR = 0.67, 95% CI [0.40, 1.14], $I^2 = 0\%$; ECMO support: 1.8% *vs.* 4.7%, RR = 0.41, 95% CI [0.15, 1.10], $I^2 = 0\%$) (Fig. 3C, D). The neonatal study by Graham et al. reported consistent results.

In-hospital postoperative LCOS and neurologic events were reported in two studies. There was no significant difference between corticosteroids and placebo groups (LCOS: 10.0% *vs.* 13.2%, RR = 0.80, 95% CI [0.63, 1.03], $I^2 = 0\%$; neurologic events: 2.9% *vs.* 3.7%, RR = 0.75, 95% CI [0.37, 1.53], $I^2 = 38\%$) (Fig. 4A, B).

Five studies reported postoperative insulin administration. Our analysis found that prophylactic corticosteroid treatment significantly increased postoperative insulin treatment (19.0% *vs.* 6.5%, RR = 2.78, 95% CI [2.05, 3.77], $I^2 = 0\%$) (Fig. 4C). Subgroup analysis of three neonatal studies showed consistent results (Fig. 4D).

In-hospital postoperative infection was reported in five studies. There was no significant difference between corticosteroids and placebo groups (6.0% *vs.* 5.6%, RR = 1.07, 95% CI [0.74, 1.55], $I^2 = 0\%$) (Fig. 5A). The analysis of

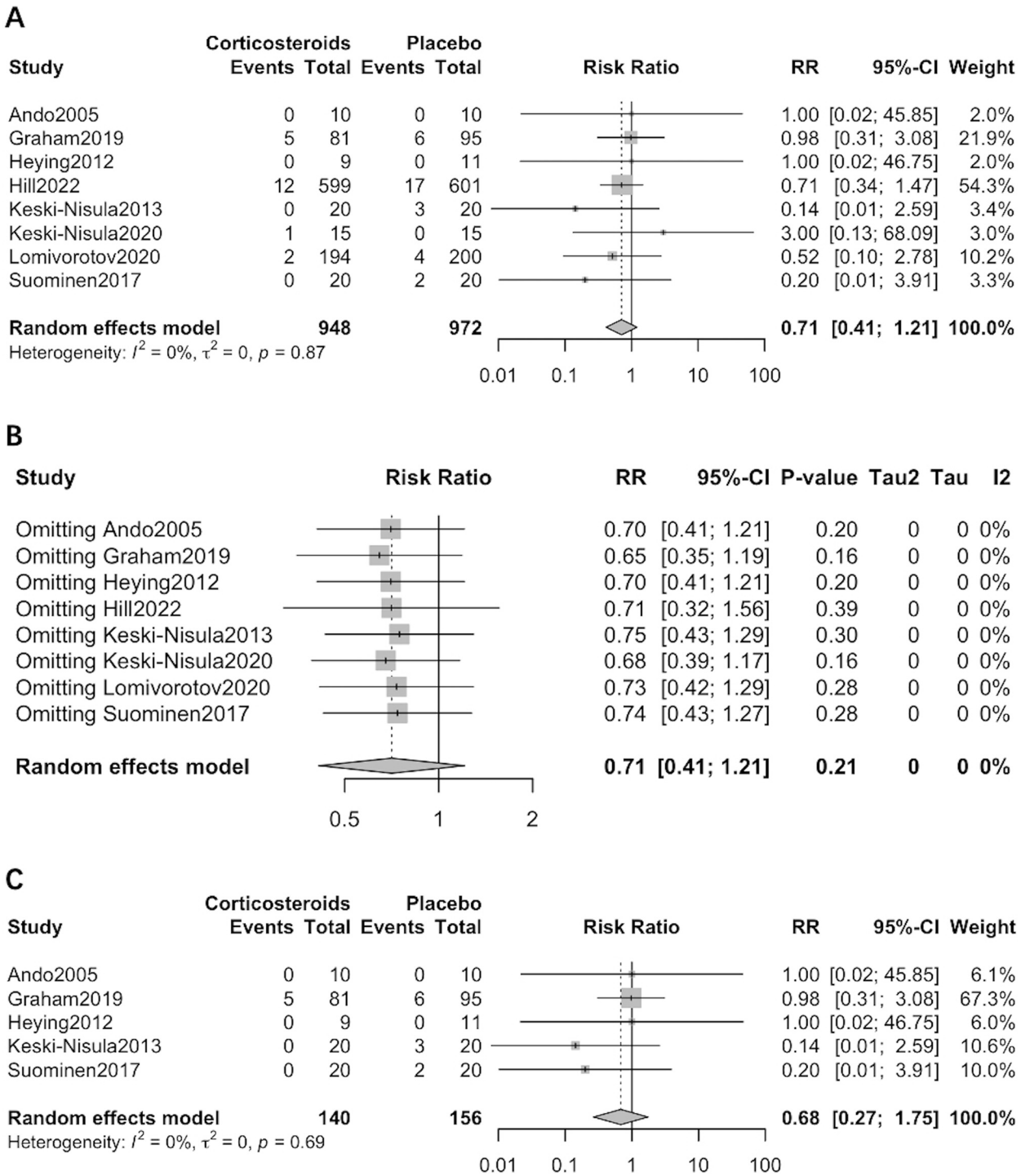

Fig. 2 **A** Forest plot for the impact of corticosteroids versus placebo on postoperative mortality. **B** Sensitivity analysis on postoperative mortality by the leave-one-out method. **C** Subgroup analysis of neonatal studies on postoperative mortality

three neonatal studies also showed consistent results (Fig. 5B).

Duration of postoperative mechanical ventilation was available in five studies. No significant difference was found (MD = -12.17 h, 95% CI [-27.35, 3.02], I^2 = 29%) (Fig. 6A). However, the subgroup analysis of neonatal studies suggested a significantly decreased duration of postoperative mechanical ventilation in patients treated with corticosteroids (MD = -22.28 h, 95% CI [-42.58, -1.97], I^2 = 0%) (Fig. 6B).

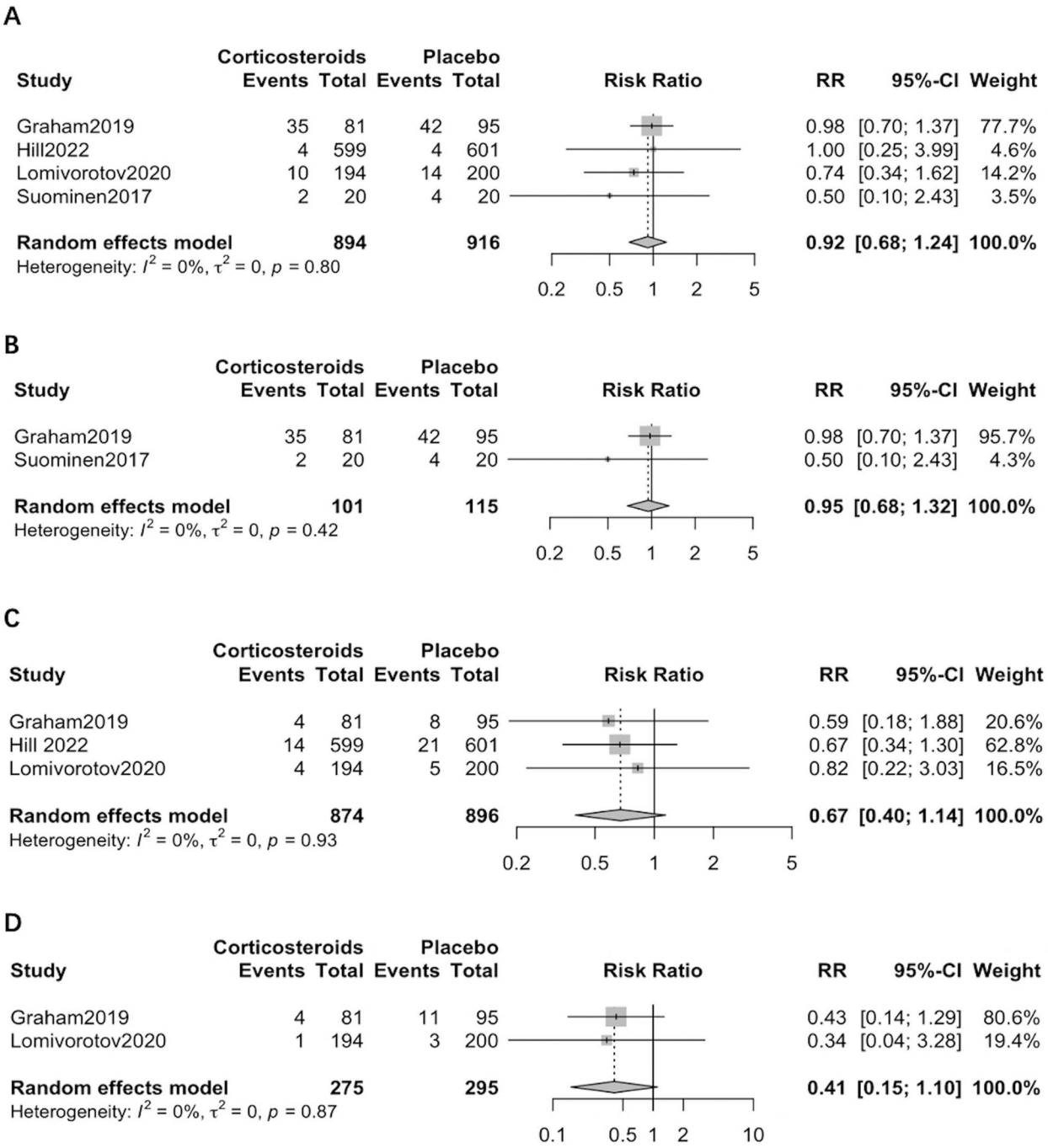

Fig. 3 **A** Forest plot for the impact of corticosteroids versus placebo on postoperative AKI. **B** Subgroup analysis of neonatal studies on postoperative AKI. **C** Forest plot for the impact of corticosteroids versus placebo on postoperative cardiac arrest. **D** Forest plot for the impact of corticosteroids versus placebo on postoperative ECMO support

Length of postoperative ICU stay was assessed in six studies, and no significant difference between groups was found (MD = -0.37 days, 95% CI [-0.84, 0.10], I^2 = 0%) (Fig. 6C). The subgroup analysis of four neonatal studies revealed consistent results (Fig. 6D).

Discussion

This systematic review and meta-analysis found no significant benefit of prophylactic corticosteroids in infants undergoing on-pump cardiac surgery in terms of in-hospital postoperative mortality, AKI, cardiac arrest, ECMO

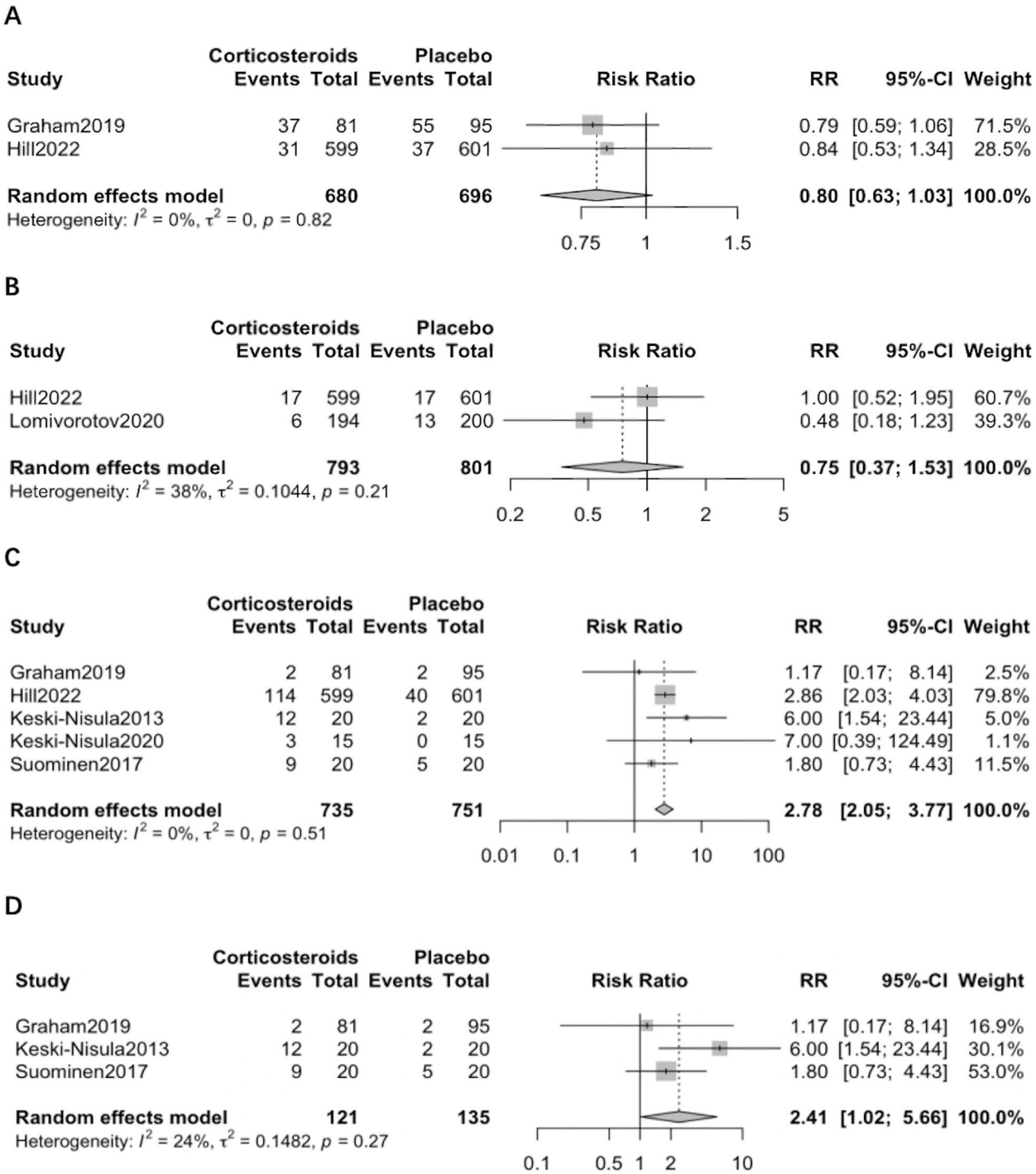

Fig. 4 **A** Forest plot for the impact of corticosteroids versus placebo on postoperative LCOS. **B** Forest plot for the impact of corticosteroids versus placebo on postoperative neurologic events. **C** Forest plot for the impact of corticosteroids versus placebo on postoperative insulin treatment. **D** Subgroup analysis of neonatal studies on postoperative insulin treatment

support, LCOS, neurologic events, infection, or length of ICU stay. However, a significant reduction in the duration of postoperative mechanical ventilation was observed in neonatal studies. Notably, prophylactic corticosteroids were associated with an increased incidence of postoperative insulin treatment.

Corticosteroids have been widely used in infants undergoing cardiac surgery for decades. According to

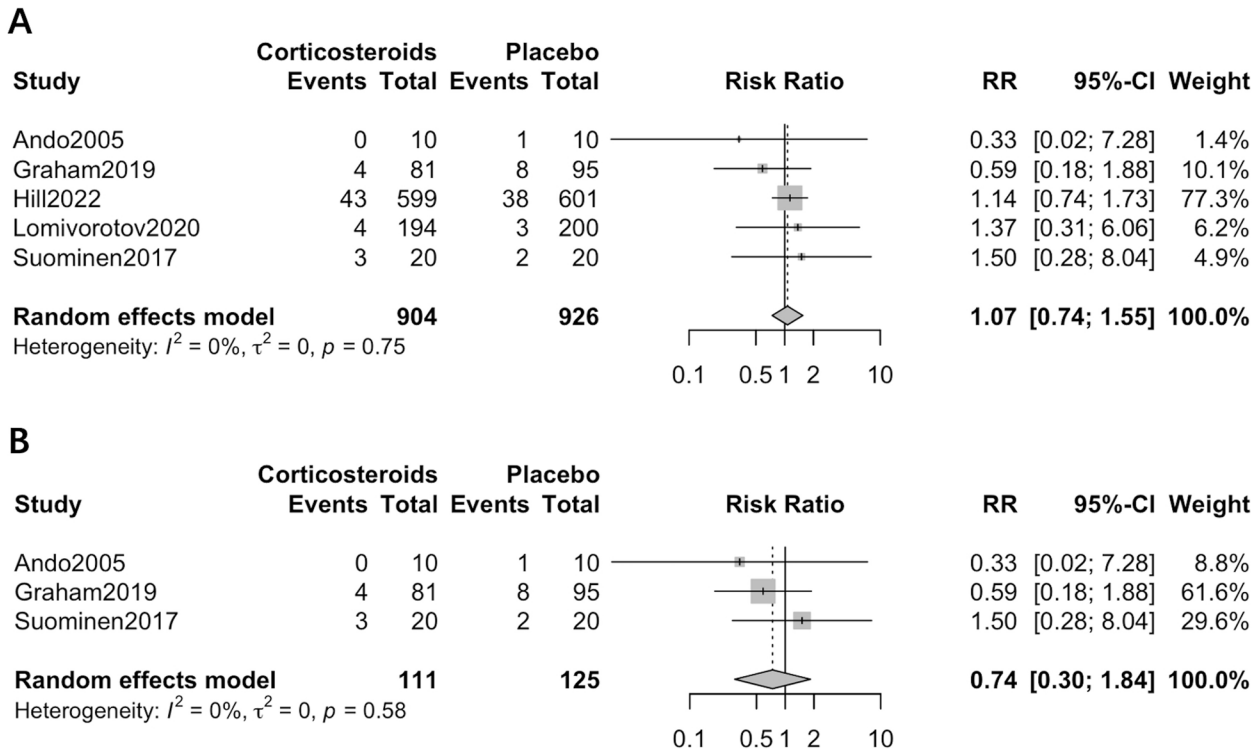

Fig. 5 **A** Forest plot for the impact of corticosteroids versus placebo on postoperative infection. **B** Subgroup analysis of neonatal studies on postoperative infection

the analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD), over half of infants undergoing cardiac surgery were treated with corticosteroids during the perioperative period [16]. The mechanism of the potential benefit of corticosteroids on patients undergoing cardiac surgery is mainly related to their anti-inflammatory effect [13–15]. However, the benefit of corticosteroids on clinical outcomes remains uncertain. Additionally, potential detrimental effects, such as hyperglycemia, have been reported [38]. Previous studies and meta-analyses on adult and pediatric patients have shown that corticosteroids do not improve clinical outcomes in cardiac surgical patients [19–27]. A significant reduction in mortality and postoperative inotropic score in younger patients who received prophylactic corticosteroids was reported by a recent meta-analysis [28]. Infants are believed to experience more pronounced inflammatory responses to CPB due to immature organ function and a disparity between the CPB circuit size and the patient [39]. The report from STS-CHSD also demonstrated worse clinical outcomes in infants and neonates [6]. Currently, there is a lack of systematic reviews and meta-analyses focusing on prophylactic corticosteroids in infants undergoing cardiac surgery with CPB.

Our analysis demonstrated that prophylactic corticosteroids might not significantly decrease postoperative mortality, AKI, cardiac arrest, ECMO support, neurologic events, infection, or length of ICU stay in infants undergoing cardiac surgery. This result was consistent with the meta-analyses in pediatric patients [22–27]. It was noteworthy that three recent meta-analyses conducted subgroup analyses of infants and neonates regarding postoperative mortality, which also showed consistent results with our study [26–28]. However, other clinically important outcomes were not reported. To the best of our knowledge, this is the first systematic review and meta-analysis focusing on infants and neonates. Our findings were also in line with recent large-scale RCTs [16, 29, 30]. However, given the low event rates of the aforementioned outcomes, it is possible that the potential beneficial effects provided by corticosteroids are not significant enough to be detected with the current sample size. Thus, further large-scale RCTs are needed, and composite clinical outcomes may be used due to the declining event rates.

The meta-analysis also revealed no significant difference in postoperative LCOS. This finding was not consistent with previous meta-analyses in the pediatric

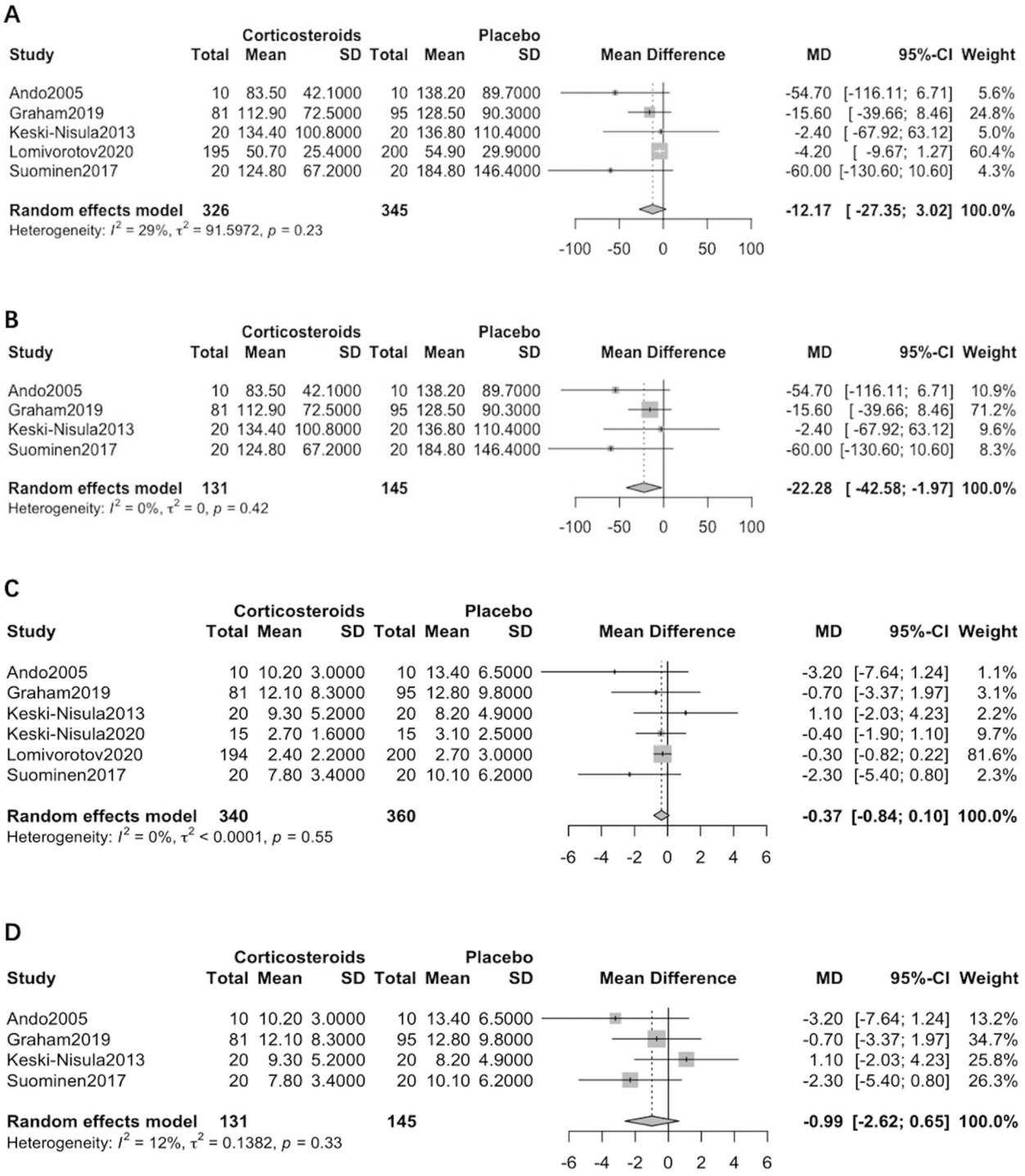

Fig. 6 **A** Forest plot for the impact of corticosteroids versus placebo on duration of postoperative mechanical ventilation (hours). **B** Subgroup analysis of neonatal studies on duration of postoperative mechanical ventilation (hours). **C** Forest plot for the impact of corticosteroids versus placebo on length of postoperative ICU stay (days). **D** Subgroup analysis of neonatal studies on length of postoperative ICU stay (days)

population [26, 27]. The inconsistency may be due to the different ages of the patients. Previous research has identified age as a risk factor for LCOS, with a higher incidence found in younger children [40, 41].

Our analysis detected an increase in postoperative insulin treatment in infants who received prophylactic corticosteroids. Meta-analyses of the pediatric population by Cheema et al. and Takeshita et al. revealed

consistent results [26, 27]. This finding indicates a potential increase in the rate of postoperative hyperglycemia and insulin resistance, which might lead to severe complications [42]. However, it is difficult to assess the impact on insulin use, as it may be related to the dose of corticosteroids and the institutional protocol for insulin initiation and use. Prophylactic corticosteroids should be used more cautiously and with more rigorous blood glucose monitoring in infants to ensure their safety.

The subgroup analysis suggested a significantly reduced duration of mechanical ventilation in neonates who received prophylactic corticosteroids. This result was not highlighted in recent RCTs but was in accordance with the meta-analyses involving pediatric patients [25–27]. The rationale for this finding is that, in addition to the anti-inflammatory effect on the lungs, corticosteroids could also reduce the incidence of post-extubation stridor and extubation failure [43, 44]. Hence, prophylactic corticosteroids might be considered for neonates at high risk of pulmonary complications and extubation failure.

Our review has several strengths. First, this is the first systematic review and meta-analysis to investigate the effect of prophylactic corticosteroids on clinically important outcomes in infants and neonates undergoing on-pump cardiac surgery. In addition, we comprehensively searched and screened literature from three large databases and other sources. Furthermore, this review followed a rigorous methodology. Assessment of eligibility criteria, data extraction, and outcome grading were conducted in duplicate with a high degree of agreement. Finally, subgroup and sensitivity analyses were performed to address potential confounding factors.

Limitations are also presented in the study. Firstly, the overall low postoperative mortality and morbidity of AKI, ECMO support, cardiac arrest, and neurologic events may limit the ability to draw definite conclusions with the current sample size. Secondly, there is clinical heterogeneity between studies, including the type of surgery, CPB strategy and duration, duration of aortic cross-clamp, and regimen of corticosteroid administration. Subgroup analysis of these confounders was not performed due to miscellaneous and insufficient data from the included RCTs. The studies by Hill et al. and Bronicki et al. revealed controversy regarding the effect of corticosteroids stratified by the complexity of surgery, and the study by Graham et al. showed that corticosteroids were protective mainly in palliative procedures [16, 22, 29]. This question was unresolved in our analysis, and further studies are needed. Lastly, it is worth noting that the study by Hill et al. contributed to 1,200 out of 1,920 samples, which might have influenced the result [16]. To address this confounder, sensitivity analysis was conducted using the leave-one-out method, which led to consistent results.

Conclusions

In conclusion, our systematic review and meta-analysis demonstrated that prophylactic corticosteroids could not improve in-hospital postoperative mortality, AKI, cardiac arrest, ECMO support, LCOS, neurologic events, infection, or length of ICU stay, but might significantly reduce the duration of postoperative mechanical ventilation in neonates undergoing cardiac surgery with CPB. We also observed significantly increased postoperative insulin treatment in infants who received prophylactic corticosteroids. Therefore, current evidence does not support the routine prophylactic use of corticosteroids in infants undergoing on-pump cardiac surgery. We recommend further large-scale research to validate our findings and investigate the most effective agent, optimal dosing regimen, and specific impact on various types of cardiac surgery.

Abbreviations

CPB	Cardiopulmonary bypass
ICU	Intensive care unit
RCT	Randomized controlled trial
CENTRAL	Cochrane Central Register of Controlled Trials
AKI	Acute kidney injury
ECMO	Extracorporeal membrane oxygenation
LCOS	Low cardiac output syndrome
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
RR	Risk ratio
CI	Confidence interval
MD	Mean difference
STS-CHSD	Society of Thoracic Surgeons Congenital Heart Surgery Database

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Authors' contributions

SYW and HY were involved in the concept and design of the study. All authors contributed to the acquisition, analysis, and interpretation of the data. SYW and YX were responsible for drafting the manuscript. HY oversaw the project. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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