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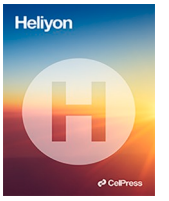

# Delivery exogenous nitric oxide via cardiopulmonary bypass in pediatric cardiac surgery reduces the duration of postoperative mechanical ventilation-A meta-analysis of randomized controlled trials

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ABSTRACT

*Objectives:* Cardiopulmonary bypass (CPB) is a major part of cardiac surgery that provokes systemic inflammatory reactions, myocardial ischemia, and ischemia and reperfusion damage. The aim of this study is to summarize the available evidence and evaluate whether exogenous nitric oxide administered via CPB circuits can improve recovery after cardiac surgery in children.

*Method:* A comprehensive search of the PubMed Medline, Ovid, Cochrane Library and Embase databases was conducted in September 2022. Only randomized controlled trials that compared nitro oxide with placebo or standard care were included.

*Results:* This pooled analysis included 5 RCTs containing 1642 patients. There were significant differences in the duration of postoperative mechanical ventilation between the nitric oxide group and the control group (mean difference −5.645 h; 95% CL = −9.978, −1.313; P = 0.01). Meta-analysis of the length of ICU stay and hospital stay showed no significant differences.

*Conclusion:* Delivering nitric oxide via CPB in pediatric cardiac surgery has an effect on reducing the duration of mechanical ventilation. Considering the small effect size, we should be cautious and think comprehensively in clinical practice.

## 1. Introduction

Although the development of cardiac surgery has greatly improved the survival prospects of children with congenital heart disease, more than 90% of children can live to adulthood [1]. However, studies published in the past 20 years show that congenital heart disease is still the main cause of infant mortality and incident rate. Physical, developmental or cognitive problems greatly affect quite a few postoperative survivors [2,3]. Cardiopulmonary bypass (CPB) is the key method to accomplish cardiac surgery, causing a wide range of endothelial, inflammatory, and coagulation system responses [4]. The complicated effects of CPB and cardioplegic arrest can cause myocardial cell necrosis in nearly 40% of cardiac surgeries [5]. Myocardial ischemia and reperfusion injury caused by CPB always imposes several disadvantages during the postoperative period. The exposure of blood to artificial surfaces, surgical trauma, ischemia–reperfusion injury, changes in body temperature and endotoxin release have been proven to promote the occurrence of

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systemic inflammatory response syndrome (SIRS). SIRS may develop into clinical organ dysfunction and mltiorgan [6–9].It is well known that the molecular mechanisms responsible for these pathological phenomena are complicated.

The nitric oxide (NO) pathway is a major component of this process. NO could regulate cell apoptosis, and played an active role in inhibiting platelet adhesion and aggregation, Monocyte adhesion, migration and production of oxygen free radicals [10–13]. Previous study have shown NO plays a variety of protective roles in inflammatory response, ischemia/reperfusion injury and cell apoptosis [14]. Some studies support the addition of nitric oxide through extracorporeal circulation circuits in pediatric cardiac surgery due to its improvement in postoperative outcomes [15,16]. James et al. [16] reported that the incidence of low cardiac output syndrome was reduced from different degrees by delivery of nitric oxide to the oxygenator gas flow during paediatric cardiopulmonary bypass. Checchia et al. [15] *demonstrated its beneficial effects on myocardial protection*, fluid balance, postoperative recovery in pediatric cardiac surgery. In addition, there were still some studies with opposite opinions on the same issue [16,17]. Recent results based on a large-sample randomized study suggested that ventilator-free days were not significantly increased, delivering nitric oxide via cardiopulmonary bypass in pediatric cardiac surgery was not advised in this study [18]. It is evident that previous studies vary considerably in size and focus. To further clarify the impact of this adjuvant treatment on postoperative recovery in children, this study systematically reviewed publications reporting randomized controlled trials (RCTs) about the effect of exogenous NO delivered via

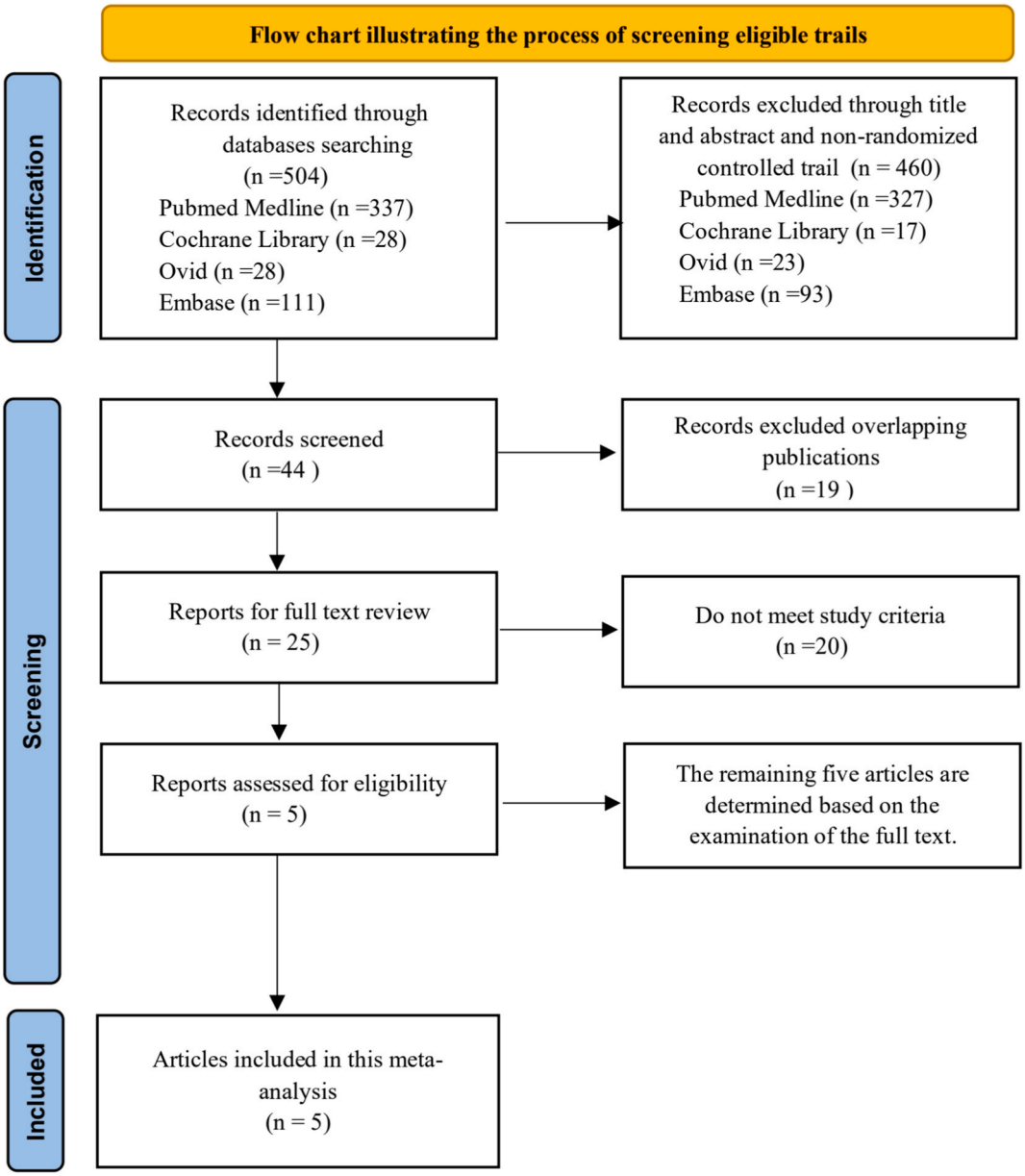



**Fig. 1.** Flowchart describing the selection of studies.

**Table 1**
Summary of characteristics of included studies.

| Study | country | design | number | admission | intervention | Group | Patient | | | | | | Time | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Mean age (week) | SD | Mean Weight (kg) | SD | Male | Sample size | Mean CPB (time) | SD | Mean Cross-clamp time (min) | SD |
| Paul A 2013 | USA | Single-center | 16 | All children complete repair of tetralogy of Fallot | received nitric oxide at a dose of 20 ppm | NOG | 27.29 | 16 | – | – | 7 | 8 | 118 | 31 | 60 | 10 |
| | | | | | | CG | 30.86 | 16.29 | – | – | 4 | 8 | 128 | 36 | 67 | 9 |
| Chawki Elzein 2020 | USA | Single-center | 24 | the first few days of life Norwood procedure | started and maintained at a dose of 40 ppm during the procedure | NOG | 0.81 | 0.27 | 3.35 | 0.44 | 8 | 12 | 143 | 17.1 | 50.83 | 8.71 |
| | | | | | | CG | 0.84 | 0.25 | 3.08 | 0.7 | 7 | 12 | 150.63 | 20.36 | 53.58 | 6.56 |
| Christopher James 2016 | Australia | Single-center | 198 | All children cardiac surgery with CPB | received nitric oxide at a dose of 20 ppm | NOG | 24 | 124.44 | 6.3 | 9.19 | 61 | 101 | 131.5 | 72.96 | 62.5 | 57.04 |
| | | | | | | CG | 16 | 109.64 | 4.8 | 7.93 | 55 | 97 | 107 | 89.63 | 60.5 | 55.56 |
| Robert A. Niebler 2021 | USA | Single-center | 40 | less than one year surgery requiring CPB | received nitric oxide at a dose of 20 ppm | NOG | 14.37 | 11.1 | 4.62 | 1.5 | – | 18 | 123.5 | 41.85 | 77.4 | 40.6 |
| | | | | | | CG | 16.06 | 13.21 | 4.8 | 1.48 | – | 22 | 115 | 47.63 | 74.1 | 45.4 |
| Luregn J. Schlapbach 2022 | Australia | Multicenter | 1364 | younger than 2 years cardiac surgery with CPB | received nitric oxide at a dose of 20 ppm | NOG | 13.6 | 18.3 | 4.7 | 2.3 | 413 | 679 | 113 | 71.11 | 69 | 45.19 |
| | | | | | | CG | 14.2 | 21.33 | 4.8 | 2.67 | 368 | 685 | 114 | 67.41 | 71 | 45.19 |

NOG nitric oxide group, CG control group, SD standard deviation, CPB cardiopulmonary bypass.

CPB on postoperative recovery in children undergoing cardiac surgery.

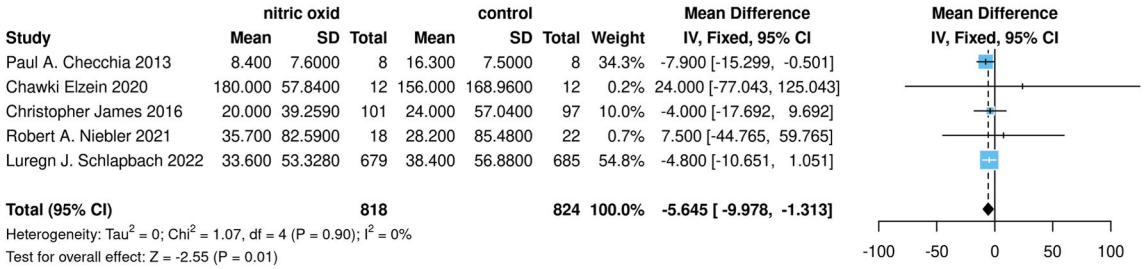
## 2. Method

The systematic review was conducted according to the systematic preferred report and meta-analysis (PRISMA) statement. Given that this study was a systematic review, neither ethical approval nor informed consent was needed. A comprehensive search covering the PubMed Medline, Ovid, Cochrane Library and Embase databases was conducted in September 2022. Using the following terms: nitric oxide and pediatric and (cardiac surgery or cardiopulmonary bypass).

The inclusion criteria for this study were as follows: 1) randomized controlled trial (RCTs). 2) The qualified intervention was delivering exogenous NO via CPB circuits during cardiac surgery. 3) The population was all children undergoing any planned cardiac surgery with the use of cardiopulmonary bypass. 4) The control group is placebo or standard care. 5) Interest outcomes included the duration of postoperative mechanical ventilation, length of intensive care unit (ICU) stay and length of hospital stay. 6) Case reports, retrospective studies, reviews, letters, comments, and editorials were excluded. 7) The publication language of the included studies was restricted to English.

Two trained investigators independently screened the results of the literature search and identified the included studies. The differences were resolved through discussion, and senior researchers were invited to answer if necessary. All literature retrieved from each database was screened for the first time based on randomized clinical control, title and abstract. Then, these selected documents

a

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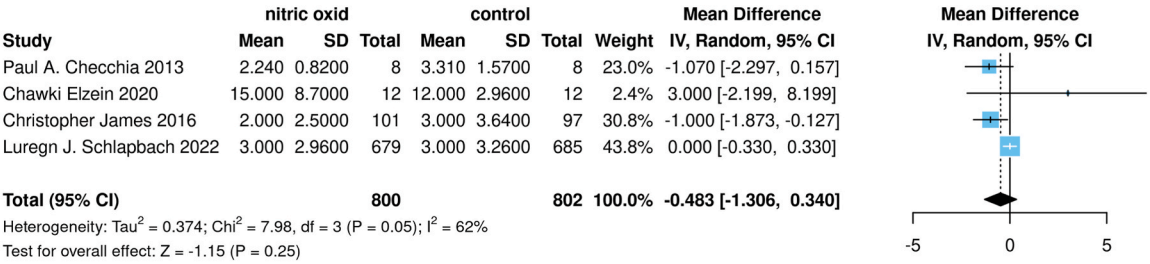


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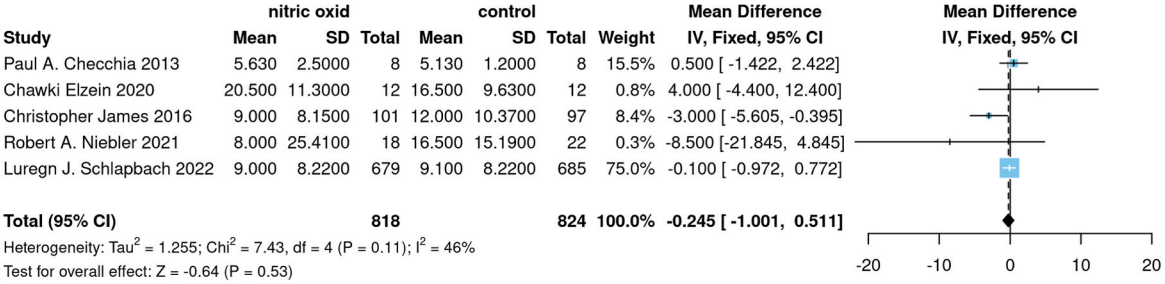


**Fig. 2.** **a** Analysis of the duration of mechanical ventilation (hours); **b** Analysis of the length of ICU day; **c** Analysis of the length of hospital day.

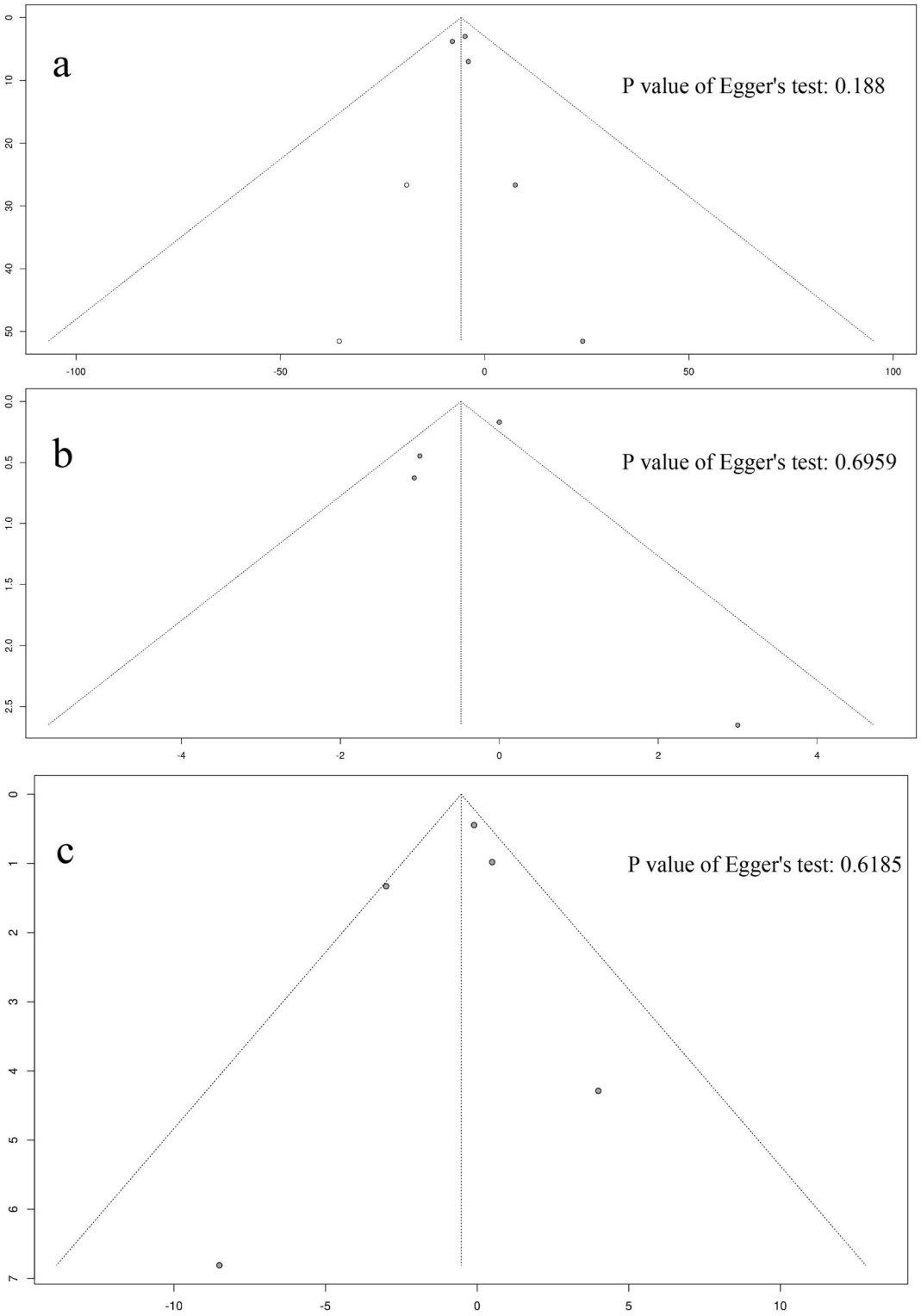


**Fig. 3.** **a** The funnel plot for the mechanical ventilation days; **b** The funnel plot for the length in ICU days; **c** The funnel plot for the length in hospital days.

were imported into Endnotes to remove duplicate contents. The remaining articles were determined by full-text reading. Fig. 1 describes the screening process. The risk of bias in each study was assessed by the Cochrane Bias Risk Tool.

Data extracted from the literature included general data (sample size, age, sex, body weight, CPB transit time, aortic occlusion time) and outcome data (time of mechanical ventilation, length of ICU stay, length of hospital stay). The data on continuous variables included quartiles and standard deviations and were analysed after unifying the mean and standard deviation. All the missing data were calculated following the Cochrane Collaboration for Systematic Reviews guidelines. Onlinemeta v1.0 [19] (https://doi.org/10.1101/2022.04.13.488126 ) was used to performing the statistical analysis and drawing the related plots.

## 3. Results

### 3.1. Literature search

A total of 504 studies were identified in the first step of the literature search. After screening the title, abstract and research type, 44 studies remained. Nineteen duplicate studies were excluded in the endnotes analysis. Through full-text reading, 25 reports did not meet the study criteria. Five articles were finally included in the meta-analysis (Fig. 1).

### 3.2. Study characteristics

Included studies in this study were published between 2013 and 2022. Three were from America, and two were from Australia. Only one was a multicenter study, and the others were single-center studies. There were a total of 1642 children included in this meta-analysis; 818 patients received placebo or standard care, and 824 patients received nitric oxide intervention. Other relevant details of this study are described in Table 1.

### 3.3. Length of postoperative mechanical ventilation

The pooled analysis for the length of postoperative mechanical ventilation was conducted based on the data of five studies. Pooled analysis showed that a significant difference was observed between the nitric oxide group and the control group. The trend toward reducing the duration of mechanical ventilation objectively existed in the nitric oxide group compared with the control group. (mean difference −5.645 h; 95% CL = −9.978, 1.313; P = 0.01) (Fig. 2a).

### 3.4. Length of intensive care unit stay

The available data were from four studies and used to summatively analyse the length of ICU stay. These studies included 1602 patients, 800 of whom received nitric oxide intervention and 802 of whom did not. Pooled analysis showed that there was an insignificant difference in the length of ICU stay between patients who received nitric oxide intervention and those who did not. (mean difference 0.171 days; 95% CL = −0.47,0.128; P = 0.26) (Fig. 2b).

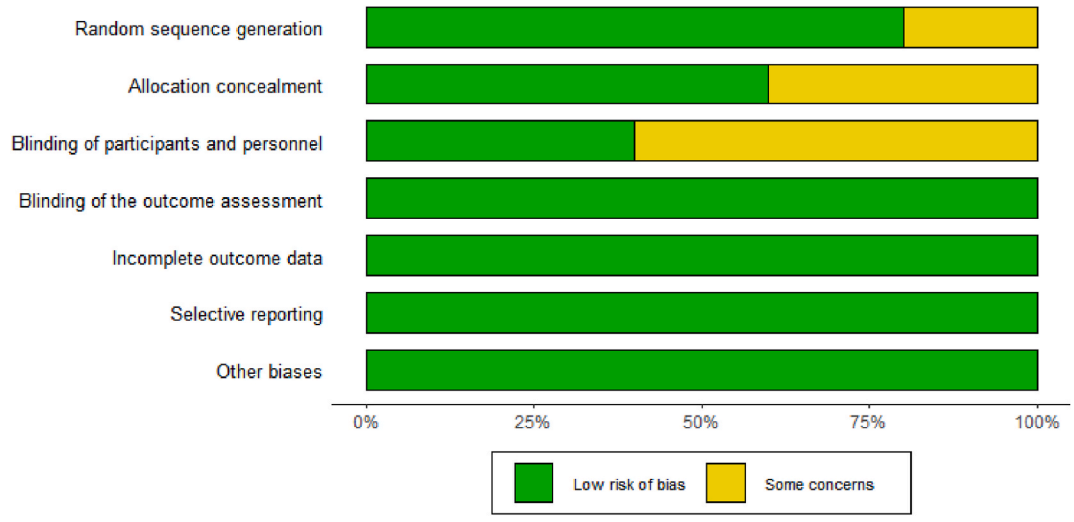


**Fig. 4.** The overall risk of bias of the included studies. The green region means a low risk of bias. The yellow region means unclear bias.

### 3.5. Length of hospital stay

A total of five studies provided relevant data for the length of hospital stay. Pooled analysis demonstrated that the length of hospital stay was not significantly different in the comparison between patients who received and did not receive nitric oxide intervention. (mean difference −0.245 days; 95% CL = −1.001,0.511; P = 0.53) (Fig. 2c).

### 3.6. Bias analysis

Funnel plots were used to test the publication bias from the included articles. Publication bias was not significantly obvious in ventilation mechanical time, length of ICU stay or length of hospital stay (Fig. 3). Heterogeneity was acceptable for analyses relating duration of mechanical ventilation and length of hospital stay but was somewhat high for analyses of length of ICU stay. Specific content was performed in the forest map (Fig. 2).

### 3.7. Quality assessment

The overall risk of bias of the included reports remained low. Performance bias may be the major issue. Schlapbach et al. (2022), Checchia et al. (2013) and Elzein et al. (2020) did not clearly report the blinding of personnel. Checchia et al. (2013) and Elzein et al. (2020) did not describe allocation concealment in detail. Selection bias was found in Elzein et al. (2020) (Fig. 4).

## 4. Discussion

The five included studies were well designed to perform randomized clinical controlled trials. In all studies, the basic characteristics of the intervention group and the control group were balanced. Data extracted from a total of 1642 patients were used to analyse the impact on mechanical ventilation time and length of hospital stay, and 1604 patients were included for the pooled analysis of ICU stays. No serious publication bias was presented in the summary analysis. The heterogeneity of studies performed well in the result analysis. Pooled analysis showed that delivery of nitric oxide via the CPB circuit was significantly related to a reduction in mechanical ventilation time but not in the length of ICU stay and hospital stay.

The experimental application of delivery nitric oxide via CPB circuits was based on Gianetti et al.'s research, which found that NO could play a partial anti-inflammatory role through the CPB diffusion pathway [20]. The myocardial protection mediated by exogenous nitric oxide added to CPB circuits was confirmed in a previous systematic analysis [21]. There is no clear statement on the improvement of clinical results because of the limited size and number in previous studies. In the included literatures, the techniques of NO delivery on CPB are not entirely consistent, but the continuity and time window of this method are consistent. It is worth noting that there are also certain differences between the initial flow rate and the maintained concentration, with four studies having a maintained concentration of 20 ppm and one being 40 ppm. Only one study mention the use of NO after surgery, while other studies are not clear. At present, there is no unified standard for the implementation of this method. Further research and improvement are needed.

Postoperative mechanical ventilation time indirectly reflects the postoperative performance of patients. Its duration is considered to be one of the strongest predictors of prognosis [22].This indicator was analysed in all five included studies. Overall, the duration of mechanical ventilation in the intervention group tended to decrease. The final result was of statistical significance but opposite to several separate studies. Considering the similar age distribution of subjects and great differences in sample size, we conclude that this is a meaningful performance based on comprehensive summary differences. Our finding is similar to a previous pooled analysis [23]. Many studies have confirmed its positive affection in cardiac surgery. This result may be a reflection of postoperative improvement. Actually, its influential factors are complicated in clinical practice including the treatment factors related to the extubation strategy of the institution [24–26]. Due to the lack of perioperative management evidence and differences in medical level, mechanical ventilation time as a postoperative recovery indicator cannot yet form an inevitable connection with the clinical outcomes of patients. We should take a cautious attitude towards the result.

The length of ICU stay was analysed in four included studies. A recent large sample size study showed similar median and mean values after intervention [18].A trend towards a positive effect of the intervention was obtained in two small sample size analyses [15, 16]. The results analysed in small sample size of newborn babies showed a negative effect on the intervention group without a significant difference [17]. The heterogeneity of surgery and study processes may explain the inconsistent findings. The final pooled analysis indicated that the intervention did not significantly reduce the length of ICU stay. This is consistent with a previous analysis covering adults and pediatrics [21]. In this study, the reduction in postoperative mechanical ventilation time did not have a positive impact on the length of ICU stay. We note that the research unit of mechanical ventilation time is hours, and the unit of ICU stay is days, which may be one of the reasons why the result is not significant. In addition, it is easily confused by various factors, such as preoperative condition, immediate response of CPB and surgery, postoperative treatment strategy and so on.

The length of hospital stay was analysed in all five studies. The result was not statistically significant. There was no breakthrough compared with a previous meta-analysis [21]. Heterogeneity was aceptable during the analysis of this result. We found a negative trend reported in a small study focusing on newborns. It is important to note that other studies also included this subset of patients, but trends in this study were unusually prominent. The effect of age distribution bias was objective. Stratified analysis with increased data volume might lead to more meaningful results in the future.

The pooled analysis demonstrated that the effect of this intervention was weak and mainly reflected in the duration of mechanical

ventilation. We have not yet seen any sustained clinical effects of this result on ICU or hospital stay. Schlapbach et al. [18] indicated that neither recent results nor the number of ventilator-free days from initiation of cardiopulmonary bypass to day 28 were statistically significant. The impact of our results is not yet prominent in clinical practice referring to recent research. Although some studies have confirmed that nitric oxide plays positive roles in myocardial protection, anti-inflammation, descending pulmonary vasculature, and reducing pulmonary arterial hypertension [20,27–34]. The positive effects based on physiology and pathology were not reflected in clinical outcomes during our study. Some systematic reviews comprising larger data have assessed the role of inhaled nitro oxide in other intensive care environments. One study focusing on patients with hypoxemia showed that the oxygenation index was improved, but there was no benefit for survival [35]. Furthermore, nitric oxide may cause potential environmental pollution, high cost and methemoglobinemia [36–39]. Overall, the implementation of this strategy still needs to be treated with caution.

This systematic review is the first to specifically explore the importance of nitric oxide delivery via a CPB circuit on clinical outcomes in pediatric cardiac surgery. There are some limitations in this study. First, the number of included studies was limited, most were single-center studies, and the geographical distribution of the study population was not wide. Second, because the specificity of researcher blinding was not clear in some of the included studies, the risk of bias in the distribution and heterogeneity of research processes was inevitable. Third, the complexity of postoperative recovery and its multiple pathophysiological mechanisms are objectively present, which reduces the reliability of single index analysis. Fourth, limited to the included results, a comprehensive assessment of the adverse effects of the intervention has not yet been made.

## 5. Conclusion

Delivering nitric oxide via CPB circuit in pediatric cardiac surgery has an effect on reducing the duration of mechanical ventilation. Considering the small effect size, we should be cautious and think comprehensively in clinical practice. Larger studies are still needed to strengthen the results and reduce heterogeneity between studies in the future.

## Author contribution statement

Fei Xu, Weina Li: Conceived and designed the experiments; Performed the experiments; Analysed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

## Data availability statement

No data was used for the research described in the article.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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