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REVIEW ARTICLE

# Transfusion Strategies for Pediatric Cardiac Surgery: A Meta-Analysis and Trial Sequential Analysis

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## Abstract
This study aimed to compare the effects of restrictive and liberal red blood cell (RBC) transfusion strategies on pediatric patients undergoing cardiac surgery, including cyanotic and non-cyanotic children. A literature search of the MEDLINE, EMBASE, PubMed, and the Cochrane Library database was conducted. Meta-analyses were carried out comparing restrictive and liberal transfusion strategies. Subgroup analyses were performed based on the basis of cyanotic status. Five randomized controlled trials with a total of 497 children were included. There was no significant difference in the risk of in-hospital mortality between the two transfusion strategies (risk ratio 1.21; 95% confidence interval 0.49 to 2.99; $P=0.68$). The trial sequential analysis suggested that the current meta-analysis had an absence of evidence for in-hospital mortality, and the data were insufficient. Moreover, no significant differences existed between groups in terms of risk of infection, blood loss, duration of mechanical ventilation, pediatric intensive care unit (PICU) stay duration, or hospital stay duration. Cyanotic children treated with a liberal transfusion strategy had a shorter ventilator duration, but the transfusion strategy did not affect in-hospital mortality, infection, hospital stay, or PICU stay duration. On the basis of the available data, our analysis indicates that a liberal transfusion strategy did not lead to a better outcomes, but the data are extremely sparse, which highlights the need for clearer transfusion guidelines specific to this specific population.
**Trial registration number** CRD42018102283.

**Keywords** Pediatrics · Cardiac surgery · Restrictive transfusion · Liberal transfusion · Meta-analysis

**Abbreviations**

| | |
|---|---|
| RCTs | Randomized controlled trials |
| RR | Risk ratio |
| PICU | Pediatric intensive care unit stay |
| RBC | Red blood cell |
| LOS | Length of hospital stay |
| MD | Mean difference |
| GRADE | Grading of Recommendations, Assessment, Development, and Evaluation |
| SMD | Standardized mean difference |
| CI | Confidence intervals |
| TSA | Trial sequential analysis |
| RIS | Required information size |
| *R* | Restrictive transfusion strategy |
| *L* | Liberal transfusion strategy |
| TRIPICU | Transfusion Requirements in Pediatric Intensive Care Units |
| MODS | Multiple organ dysfunction syndrome |
| F | Fixed-model effect |
| R | Random-model effect |

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## Introduction

Approximately, 180,000 to 220,000 newborns worldwide are diagnosed with congenital heart disease annually, which is the leading cause of birth defects, and nearly 40% of patients require surgical intervention [1]. In the USA, more than 20,000 cardiac surgeries are performed every year, whereas in China, the number of cardiac surgeries performed in children has increased from 14,708 in 2011 to 18,766 in 2015 [2].

Currently, the mortality rate for children undergoing cardiac surgery has surged to 25.3% in pediatric patients aged < 6 months and 34.1% in pediatric patients aged < 1 year [3]. The risk factors for increased mortality and morbidity after cardiac surgery in children includes age at the time of operation, complexity of surgery, transfusion, and bypass time [4, 5]. Previous studies have suggested that perioperative transfusion is a modifiable factor associated with increased mortality and morbidity in children undergoing cardiac surgery [5, 6].

Anemia occurs in 36.7% of critically ill children [7]. Evidence shows that perioperative anemia-induced tissue hypoxia in patients undergoing cardiac surgery is associated with a higher risk of mortality and postoperative complications [6, 8]. Red blood cells (RBC) transfusion are generally considered to improve oxygen delivery; therefore, treatment of anemia is the main rationale for RBC transfusion in pediatric cardiac surgery patients [9]. However, the optimal RBC transfusion strategy in pediatric cardiac surgery patients is unknown.

Studies support the notion that RBC transfusion in cardiac surgery is associated with an increased risk of mortality and serious morbidity, including renal failure, pneumonia, heart failure, increased duration of mechanical ventilation, and longer intensive care unit stay [5, 10]. Recently, studies demonstrated that a restrictive transfusion strategy is non-inferior to liberal strategy in adult cardiac surgery in terms of all-cause mortality, myocardial infarction, stroke, or new-onset renal failure with dialysis on 28 days or 6 months after surgery [11, 12]. However, whether a restrictive RBC transfusion strategy in pediatric cardiac surgery achieves similar effects in comparison to the liberal strategy remains controversial.

A previous meta-analysis of four studies suggested that a restrictive transfusion strategy is non-inferior to a liberal transfusion strategy in pediatric cardiac surgery [13]. However, this study has a limitation. It did not analyze potential differences in the effects of transfusion strategies in cyanotic and non-cyanotic children. Cyanotic and non-cyanotic children have significantly different tolerances to hypoxia, and their needs for blood transfusion are different. Moreover, pediatrics patients with unstable cardiac disease or cyanotic cardiac disease may benefit from a more liberal transfusion strategy [14]. Research shows that the proportion of cyanotic children who received blood transfusion and underwent cardiac surgery was up to 90%, compared to 65% of non-cyanotic children [15]. Therefore, the transfusion strategy for pediatrics patients undergoing cardiac surgery remains controversial and inconclusive, especially in cyanotic and non-cyanotic children. This meta-analysis of randomized controlled trials (RCTs) was conducted to compare the efficacy and safety of restrictive and liberal transfusion strategies in pediatric cardiac surgery, including cyanotic and non-cyanotic children.

## Methods

The current meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. All analyses were made based on previously published studies; thus, no ethical approval or patient consent were required. This study was registered in the international prospective register of systematic reviews (Registration: CRD42018102283).

### Search Strategy and Criteria

Two investigators independently searched for relevant RCTs in the electronic databases (PubMed, Cochrane Library, EMBASE, and MEDLINE) from inception to January 1st, 2019; the EMBASE and MEDLINE databases were searched through OvidSP. We used the search terms “liberal transfusion” and “restrictive transfusion”. The search was conducted with the assistance of Ya Na Qi (Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University, Chengdu, China), and the details of the search strategy are provided in Additional File 1. Search results from each database were combined, and duplicates were removed. In addition, we checked the reference lists of all included studies and relevant reviews identified by our search for additional eligible references. No language or publication date restrictions were applied. The last retrieval was performed on February 15th, 2019.

Exclusion and inclusion criteria were defined by all authors. RCTs were included if the following criteria were fulfilled: pediatric cardiac surgery patients, received restrictive transfusion or liberal transfusion, and clinical outcomes were assessed. RCTs were excluded if no transfusion strategy was adopted or no outcomes were reported. There was no restriction placed on publication date, language, or status. The references of relevant reviews and retrieved studies were examined to identify any new eligible trials in a manual search.

### Selection Process

References were managed using EndNote X8 software (Thomson Reuters, New York, NY, USA). Two reviewers independently performed an initial screening of titles and abstracts to select RCTs that met the inclusion criteria. Full texts were screened to identify the final eligible studies. Disagreements were reconciled through discussion with a third reviewer.

### Data Extraction

Data regarding authors, publication date, participants, operation type, sample size, transfusion strategy, and investigated outcomes were extracted. The investigated outcomes included in-hospital mortality, infection, blood loss, mean units of RBCs transfused, proportion of patients who received transfusion, duration of mechanical ventilation, length of hospital stay (LOS), and length of pediatric intensive care unit (PICU) stay.

### Assessment of Risk of Bias

The risk of bias of individual studies was assessed using the Cochrane Collaboration Handbook for Systematic Reviews of Interventions [17]. According to the domains of selection, performance, detection, attrition, and reporting and other biases, the risk of bias was classified as high, low, or unclear risk.

### Grading the Quality of Evidence

The quality of evidence of outcomes was judged according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, which classifies the quality of evidence into four categories, namely, very low, low, moderate, and high [17].

### Statistical Analysis

All analyses were conducted using Review Manager (RevMan for Windows, version 5.3; Cochrane Collaboration, Oxford, UK) and Stata statistical software version 13.0 (Stata Corp LP, College Station, TX, USA). The risk ratio (RR) and mean difference (MD) or standardized mean difference (SMD) with the corresponding 95% confidence intervals (CIs) were calculated for dichotomous and continuous outcomes, respectively. Subgroup analyses were planned a priori to examine the potential differences in outcomes between cyanotic and non-cyanotic children. Children with cyanotic heart disease included those who underwent the bidirectional Glenn procedure, Fontan procedures, or whose heart was not septate or there continued to be an intracardiac mixing. The $I^2$ test and $\chi^2$ test were used to estimate the heterogeneity. $I^2 > 50\%$ indicated significant heterogeneity. A random-effects model or fixed-effect model was used based on the results of the heterogeneity test. When $I^2$ was $\geq 50\%$, a random-effects model was used; otherwise, a fixed-effect model was used [18]. With significantly heterogeneous results, sensitivity or subgroup analysis was performed. We performed Begg's and Egger's regression tests by using the meta-bias command in Stata, and constructed funnel plots to detect publication bias. $P < 0.05$ was considered statistically significant.

For the primary outcome, a trial sequential analysis (TSA) was conducted using TSA software version 0.9 beta software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark) to prevent the risk of low sample sizes and repeated updates of included the studies included in the meta-analyses which could otherwise contribute to an increased risk of random errors [19]. The required information size (RIS) was adjusted for the present meta-analysis and trial sequential monitoring boundaries were calculated to determine whether the evidence in our meta-analysis was reliable [20]. The effect measure was set to "Relative Risk" and the model "Fixed-effect" as in TSA software. A two-sided TSA was performed to maintain a risk of 5% for type I error and a power of 80%.

## Main Results

### Study Selection

Five studies involving a total of 497 children were included (251 children in the restrictive transfusion group and 246 children in the liberal transfusion group). A PRISMA flow diagram depicting the selection process of eligible studies is shown in Fig. 1. No new eligible RCTs were identified observed by reviewing the references of these studies.

### Study Characteristics

Five studies that compared a restrictive strategy with a liberal strategy in pediatric cardiac surgery patients were included [8, 21–24]. Table 1 describes the study characteristics. The sample size ranged from 43 to 162 neonates and children. The triggers for restrictive and liberal strategies were hemoglobin levels in the range of 7–9 g/dL and 9–13 g/dL, respectively. Only one pediatric RCT compared perioperative hemoglobin thresholds [24], while two RCTs focused on stable, critically ill children [21, 24].

### Risk of Bias and Quality of Evidence

The risk of bias of each study and summary assessment of the risk of bias are shown in Fig. 2. Additional File 2 provides the rationale for the assessment of the risk of bias. Three trials had three or fewer "unclear" or "high risk" items according to the Cochrane criteria and were considered of acceptable quality [8, 21, 23], but two trials were considered

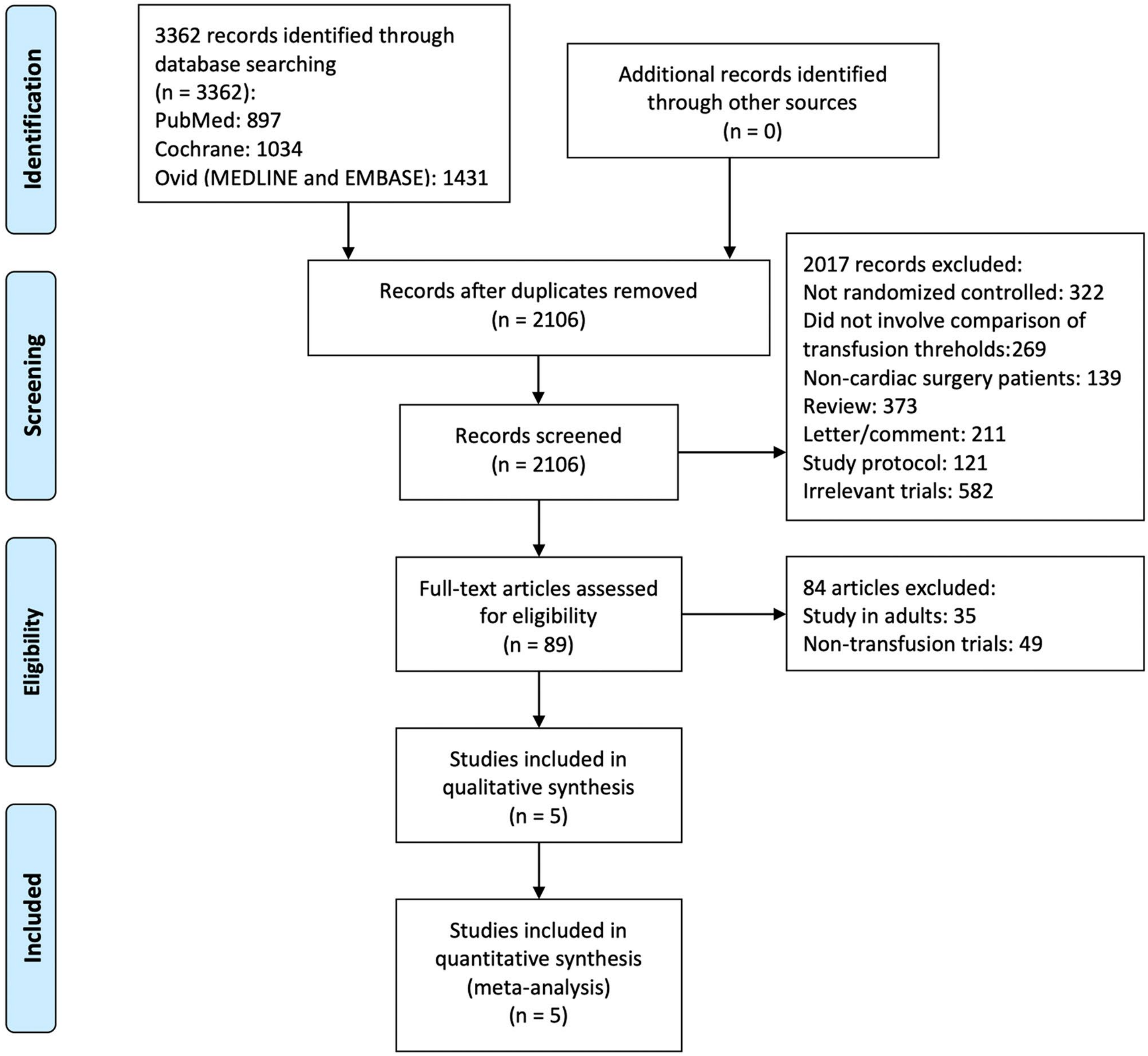


**Fig. 1** PRISMA flow diagram of literature search and the exclusion criteria

low quality [22, 24]. All RCTs were not blinded for outcome assessment. Only one pediatric RCT used random sequence generation [19], two were judged to have a low risk of reporting bias [21, 22], and four were regarded as having a low risk of attrition bias [8, 21, 23, 24]. The GRADE quality of evidence is presented in Additional File 3.

## Meta-analysis

In-hospital mortality was provided by 5 RCTs that included a total of 497 children [8, 21–24]; however, 1 RCT had zero events in both restrictive and liberal strategy groups and was, therefore, excluded from the meta-analysis [23]. The funnel plot suggested that there was no publication bias, which was also statistically supported by the results of Egger's test ($P=0.96$) and Begg's test ($P=0.60$). A total of 390 children (198 children who received restrictive RBC transfusion and 192 those who received liberal RBCs transfusion) were analyzed altogether; there was no difference in in-hospital mortality was observed between the 2 groups (RR 1.21; 95% CI 0.49 to 2.99; $P=0.68$; $I^2=0\%$), with 9 (4.55%) deaths in the restrictive group and 7 (3.65%) deaths in the liberal group (Fig. 3; Table 2). A high quality of evidence was observed as assessed using the GRADE method.

Figure 4 presents the TSA for the fixed-effect meta-analyses of in-hospital mortality. TSA revealed that the required

**Table 1** Demographic characteristics of the included studies

| Author/year | Study type | Operation type | Sample size | Participants | Patients | | Transfusion strategy | | Primary outcome | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cyanotic | Non-cyanotic | *R* (triggered Hb) | *L* (triggered Hb) | | |
| Willems et al. 2010 [21] | RCT (multicenter study) | Cardiac surgery or catheterization | $N=125$, $R=63$, $L=62$ | Participants are a subgroup of pediatric patients post-cardiac surgery from the TRIPICU study | No | Yes | < 7.0 g/dL | < 9.0 g/dL | The proportion of patients who developed or had progression of MODS | Restrictive transfusion strategy was not associated with any significant difference in new or progressive MODS, as compared with a liberal |
| Cholette et al. 2011 [8] | RCT (single-center study) | Cavopulmonary connection | $N=60$, $R=30$, $L=30$ | Infants and children with variations of single ventricle physiology presenting for cardiopulmonary connection | Yes | No | < 9.0 g/dL | < 13.0 g/dL | Mean and peak arterial lactate | Children do not benefit from a liberal transfusion strategy after cardiopulmonary connection |
| de Gast-Bakker et al. 2013 [22] | RCT (single-center study) | Corrective surgery on cardiopulmonary bypass | $N=107$, $R=53$, $L=54$ | Patients with non-cyanotic congenital heart defects | No | Yes | < 8.0 g/dL | < 10.8 g/dL | Length of stay in hospital | Restrictive transfusion during the entire perioperative period is safe, leads to a shorter hospital stay and is less expensive |
| Chkhaidze et al. 2014 [23] | RCT | Elective cardiac surgery | $N=43$, $R=23$, $L=20$ | Between 6 weeks and 6 years of age | No | Yes | < 8.0 g/dL | < 10 g/dL | Volume of transfused perioperatively | Restrictive transfusion strategy in pediatric cardiac surgery is at least as safe as liberal strategy |
| Cholette et al. 2017 [24] | RCT (single-center study) | Biventricular repair or palliative (non-septated) operation | $N=162$, $R=82$, $L=80$ | Patients with non-cyanotic congenital heart defects, age from 1 to 7 years, Underwent elective cardiac surgery | Yes | Yes | < 7.0 g/dL for biventricular repairs or < 9.0 g/dL for palliative procedures plus a clinical indication | < 9.5 g/dL for biventricular repairs or < 12 g/dL for palliative procedures regardless of clinical indication | Oxygen delivery (i.e., lactate, arteriovenous oxygen difference), or adverse clinical outcomes | Infants undergoing cardiac operation can be managed with a restrictive transfusion strategy |

*RCT* randomized controlled trails, *R* restrictive transfusion strategy, *L* liberal transfusion strategy, *TRIPICU* transfusion Requirements in Pediatric Intensive Care Units, *MODS* multiple organ dysfunction syndrome

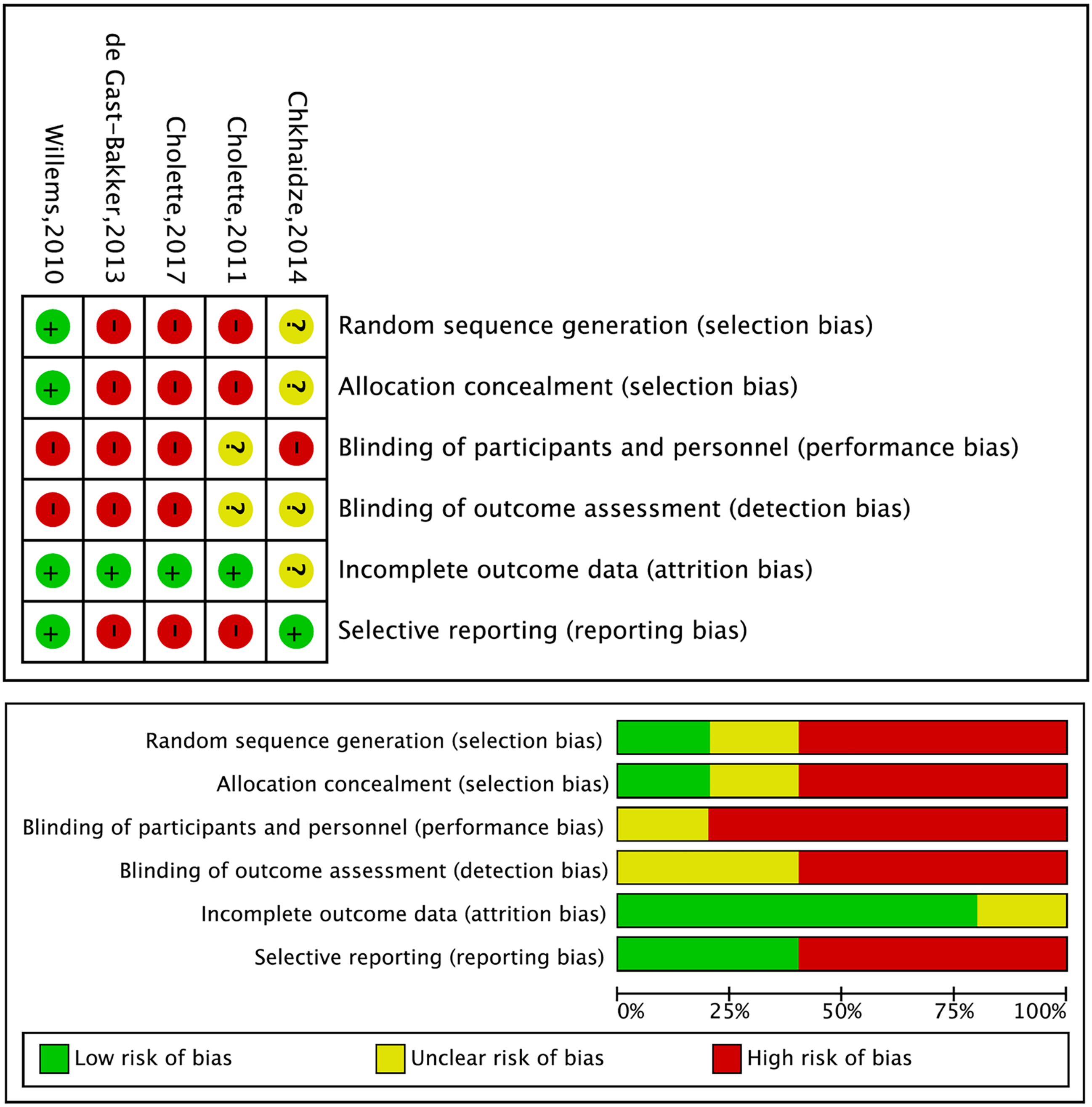


**Fig. 2** Risk of bias

information size was 6671 patients. The cumulative *z*-curve did not cross the conventional boundary for benefit or the trial sequential monitoring boundary for benefit. The TSA evaluations suggested that this meta-analysis had an absence of evidence for this outcome, and the data were insufficient.

Data for the effect of restrictive versus liberal transfusion strategies on infection risk were reported in three RCTs [21, 23, 24]. The pooled RR indicated no significant difference between groups in the incidence of infection (RR 1.18; 95% CI 0.74 to 1.92; $I^2=0\%$; $P=0.48$) (Table 2). Quality of evidence was moderate as assessed using GRADE.

Two, two, and three RCTs provided the data on blood loss [8, 24], mean units of RBCs transfused [8, 24], and proportion of patients who received transfusion [8, 21, 24], respectively. The summary results indicated that children treated with a restrictive RBC transfusion strategy were associated with fewer mean units of RBCs transfused (MD −0.97; 95% CI −1.31 to −0.64; $P<0.001$) and a smaller proportion of patients who received transfusion (MD 0.35; 95% CI 0.17 to 0.73; $P=0.005$), whereas there was no significant difference between restrictive and liberal transfusion strategies observed in terms of blood loss (MD 8.11; 95% CI − 28.97 to 45.19; $P=0.67$) (Table 2). There was significant heterogeneity in the mean units transfused and proportion of patients who received transfusion, but there was no heterogeneity in the blood loss.

The duration of mechanical ventilation was estimated by analyzing four RCTs [8, 21–23]. No significant difference was observed between groups (SMD 2.24; 95% CI − 0.11 to 4.6; $P=0.06$), with statistically significant heterogeneity ($I^2=99\%$, $P<0.001$) (Table 2). Due to the significantly heterogeneous results, we performed a sensitivity analysis, and applied the leave-out method by excluding some studies to reduce the inter-study heterogeneity. After excluding the study from Chkhaidz et al. [23], heterogeneity was not found and the conclusions remained unchanged (SMD − 0.015; 95% CI − 0.25 to 0.22; $I^2=0\%$; $P=0.90$), suggesting that the stability of this outcome was robust. The quality of evidence was high as assessed by GRADE.

Four RCTs reported LOS as an outcome [8, 22–24], demonstrating that there was no significant difference in LOS between the groups (MD − 0.52; 95% CI − 1.67 to 0.62; $P=0.37$; $I^2=0\%$) (Table 2). The GRADE quality of evidence was high. Moreover, the pooled result for PICU stay were available in four studies [8, 21–23]. No significant difference was observed between restrictive and liberal transfusion strategies for PICU (MD − 0.01; 95% CI − 0.67 to 0.64; $P=0.96$; $I^2=0\%$) (Table 2). The quality of evidence was high as assessed by GRADE.

### Subgroup Analysis

Cyanotic and non-cyanotic children have different levels of tolerance to hypo-hemoglobinemia, and their clinical outcomes are different. Considering the effect of cyanotic and non-cyanotic status on the outcome, we performed a subgroup analysis based on cyanotic status. After the subgroup analysis, no difference in the in-hospital mortality was observed between cyanotic children (RR 0.94; 95% CI 0.31 to 2.84; $P=0.92$; $I^2=0\%$) and non-cyanotic children (RR 2.17; 95% CI 0.34 to 13.99; $P=0.42$; $I^2=0\%$) (Additional File 4). Furthermore, a restrictive or liberal transfusion strategy did not affect the incidence of infection, LOS, or PICU stay in the children with or without cyanosis (Additional File 4). However, the pooled SMD indicated that cyanotic children treated with a liberal transfusion strategy had a shorter ventilator duration compared to those treated with a restrictive strategy (SMD 0.39; 95% CI 0.02 to 0.76; $P=0.04$; $I^2=0\%$), but we did not find the same results in non-cyanotic children (SMD 2.96; 95% CI − 0.80 to 6.72; $P=0.12$; $I^2=99\%$).

## Discussion

This meta-analysis of RCTs comparing restrictive and liberal RBC transfusion strategies in pediatric cardiac surgery patients revealed that a restrictive strategy did not result in an increased risk of in-hospital mortality, infection, blood loss, longer ventilator duration, prolonged PICU stay, or LOS. On the basis of the current evidence, we detected statistical differences in the proportion of patients who received a transfusion and the mean number of units of transfused RBCs. Cyanotic children treated with a liberal transfusion strategy had a shorter ventilator duration; there was no difference in in-hospital mortality, infection, LOS, or PICU stay length.

The milestone paper published by Lacroix stated that a restrictive transfusion strategy with a hemoglobin threshold of 7 g/dL in critically ill children decreases the demand for transfusion without increasing the risk of adverse outcomes, compared to a liberal transfusion strategy with a hemoglobin threshold of 9.5 g/dL [25]. A subgroup analysis published by Willems stated that a restrictive RBC transfusion strategy applied in pediatric cardiac surgery patients, compared to a liberal strategy (hemoglobin threshold of 9.5 g/dL), was not associated with any significant difference in multiorgan dysfunction syndrome or PICU stay duration [21]. A previous meta-analysis examined the effects of restrictive versus liberal transfusion thresholds on clinical outcomes in very low birth weight infants and demonstrated that restrictive transfusion thresholds may be utilized without increasing the risk of death or morbidity [26]. However, these studies focused on non-cardiac surgery, the results of which cannot not be generalized to pediatric cardiac surgery patients. Therefore, the current meta-analysis was conducted with a focus on pediatric cardiac surgery patients. It was revealed that restrictive RBC transfusion strategy did not increase the risk of in-hospital mortality, incidence of infection, blood loss, or prolong LOS or PICU stay, and that this strategy decreases the number of transfusions required. Moreover, considering that blood transfusion may have different effects in cyanotic and non-cyanotic children, we performed a subgroup analysis; the results showed that blood transfusion strategies did not affect postoperative outcomes in cyanotic and non-cyanotic children, except that the cyanotic children treated with a liberal transfusion strategy had a shorter ventilator duration. On the other hand, TSA analysis, using the defined model described in the Methods section, showed that the number of participants did not reached the RIS, and the cumulative $z$-curve did not cross the conventional boundary or trial sequential monitoring boundary. Therefore, TSA showed an absence of evidence for these outcomes, i.e., it is impossible to draw any conclusion from these results,

| Study or Subgroup | Restrictive Events | Restrictive Total | Liberal Events | Liberal Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Chkhaidze,2014 | 1 | 23 | 1 | 20 | 13.1% | 0.87 [0.06, 13.02] |
| Cholette,2011 | 0 | 30 | 1 | 30 | 18.4% | 0.33 [0.01, 7.87] |
| Cholette,2017 | 6 | 82 | 5 | 80 | 62.2% | 1.17 [0.37, 3.68] |
| de Gast-Bakker,2013 | 0 | 53 | 0 | 54 | | Not estimable |
| Willems,2010 | 2 | 63 | 0 | 62 | 6.2% | 4.92 [0.24, 100.49] |
| **Total (95% CI)** | | **251** | | **246** | **100.0%** | **1.21 [0.49, 2.99]** |
| Total events | 9 | | 7 | | | |

Heterogeneity: $Chi^2 = 1.53$, df = 3 (P = 0.68); $I^2 = 0\%$
Test for overall effect: Z = 0.41 (P = 0.68)

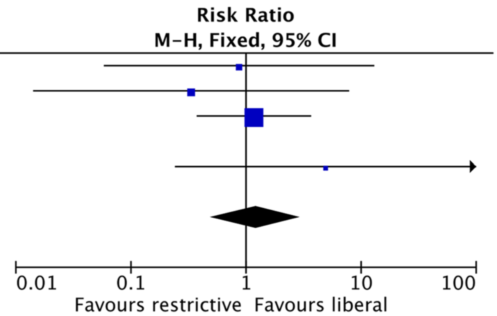


**Fig. 3** In-hospital mortality surgery in randomized controlled trials conducted on pediatric cardiac surgery patients

unless more high-quality and large sample sizes studies are available.

In our meta-analysis, only two trials included cyanotic children [8, 24], involving 116 patients undergoing pediatric cardiac surgery, and no significant difference was found between cyanotic and non-cyanotic children except for the ventilator duration, suggesting that the benefit of achieving high hemoglobin concentrations in cyanotic children may be overstated. Nonetheless, we believed that this is a complex group of patients who may need specialized blood management [15]. The limited sample size may have also contributed to this negative finding. This possibility should be explored further. Cyanotic children have been traditionally transfused to maintain the hematocrit level above 40% [15]. Data showed that the blood-transfused proportion of cyanotic children who received cardiac surgery was 85.4–90%, compared with 65–73.7% of similarly treated non-cyanotic children. Great variability remains among physicians regarding the hemoglobin levels and the "ideal" threshold for transfusion, especially in cyanotic children [15, 27]. On the basis of the current evidence, which is limited, we cannot draw any conclusions.

The transfusion threshold in cyanotic children remains unclear. Children with cyanotic congenital heart disease present with hemoglobin concentrations as high as 22.0 g/dL, which is a rare occurrence in adults [7]. Children with cyanotic heart disease deserve special consideration in relation to tolerable levels of anemia. Mink and Pollack [28] wrote that critically ill children with uncorrected cyanotic congenital cardiopathy should undergo transfusion if their hemoglobin concentration falls below 10.0 or 11.0 g/dL. Most textbooks on pediatric cardiology and pediatric cardiac surgery recommend that a higher hemoglobin concentration should be maintained in children with uncorrected cyanotic congenital cardiopathy. However, all thresholds are based on expert opinion, given that there are no randomized clinical trials and very few clinical, physiological, and observational studies in this very distinct pediatric population. Indeed, clinical observations from bloodless cardiac operations for the treatment of congenital heart diseases suggested that lower levels of hemoglobin may be tolerated well, even in children with cyanotic cardiopathy [7]. As stated by Bratton and Annich in 2003, the optimal hemoglobin levels remain understudied in cyanotic patients [29]. To conclude, there is no consensus regarding the hemoglobin concentration that should lead a physician to prescribe an RBC transfusion to critically ill children.

Results found in adult cardiac surgery patients should not be generalized to children as they have different cardiovascular physiology, pathology, and tolerance to anemia [7]. Despite the limited evidence, there are many guidelines for the transfusion practices in children [7, 30]. However, many experts do not recommend a specific threshold hemoglobin level, especially in the pediatric cardiac surgery patients [30]. Hence, an appropriate transfusion strategy is necessary to know the threshold for transfusion to avoid tissue hypoxia in pediatric cardiac surgery patients. Unfortunately, we did not know the transfusion threshold for each individual. Practice guidelines for perioperative blood transfusion and adjuvant therapies reported by the American Society of Anesthesiologists suggest that the threshold of transfusion needs to be defined precisely, and they strongly agreed that the perfusion and oxygenation of vital organs should be continuously monitored to avoid tissue hypoxia [31]. Pediatric cardiac surgery is associated with a substantial risk of bleeding and frequently requires transfusion. Efforts to optimize pre-operative hemoglobin, reduce bleeding, improve hemostasis, correct coagulopathy, and incorporate blood-sparing techniques (including a restrictive transfusion strategy) are key elements to blood management in the pediatric cardiac surgery population. Thus, the decision on whether to transfuse should be guided by an assessment of the individual patients on the basis of a combination of symptoms, clinical and physiological signs, cyanotic or non-cyanotic status, and laboratory measurements, rather than by a single factor, such as of hemoglobin level or threshold. Regretfully, we searched the Clinical Trial Registry and found no ongoing high-quality randomized controlled trials on the effects of restricted and liberal blood transfusions on pediatric cardiac

**Table 2** All outcomes of meta-analyses in included randomized controlled trials

| Variables | Study | Participants | Model | Heterogeneity | | Overall effect | | RR/MD/SMD | 95% CI | Evidence quality |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $I^2$ (%) | *P* | *z* | *P* | | | |
| In-hospital mortality | 5 | 497 | F | 0 | 0.68 | 0.41 | 0.68 | 1.21 | [0.49, 2.99] | High |
| Infection | 3 | 394 | F | 0 | 0.78 | 0.71 | 0.48 | 1.18 | [0.74, 1.92] | Moderate |
| Blood loss | 2 | 167 | F | 0 | 0.43 | 0.43 | 0.67 | 8.11 | [−28.97, 45.19] | High |
| Mean units of RBCs transfused | 2 | 222 | F | 94 | < 0.001 | 5.73 | **< 0.001** | −0.97 | [−1.31, −0.64] | Moderate |
| The proportion of patients received transfusion | 3 | 347 | R | 90 | < 0.001 | 2.79 | **0.005** | 0.35 | [0.17, 0.73] | Moderate |
| Duration of mechanical ventilation | 4 | 335 | R | 99 | < 0.001 | 1.86 | 0.06 | 2.24 | [−0.11, 4.60] | High |
| LOS | 4 | 343 | F | 0 | 0.50 | 0.90 | 0.37 | −0.52 | [−1.67, 0.62] | High |
| PICU stay | 4 | 335 | F | 0 | 0.73 | 0.04 | 0.96 | −0.01 | [−0.67, 0.64] | High |

Bold numbers indicate a statistically significant with a p-value less than 0.05

*OR* odds ratio, *MD* mean differences, *SMD* standardized mean difference, *F* fixed-model effect, *RBCs* red blood cells, *R* random-model effect

surgery; therefore, future studies focusing on such patients are warranted.

The limitations of this meta-analysis should be mentioned. First, the triggers for transfusion strategies varied among the RCTs. Thus, the appropriate transfusion threshold remains to be explored. Second, the age, sex, comorbidity conditions, complications in PICU, hemoglobin prior to surgery, hemoglobin value on admittance to PICU, status of children in restrictive and liberal groups, as well as cyanotic and non-cyanotic subgroups, were not known. Furthermore, ventilation times were lower in cyanotic children who received a liberal transfusion, but this was not shown in non-cyanotic children, with $I^2 = 99\%$ for the latter group but 0% for the former group. Further analysis found that their studies conducted by different groups in the non-cyanotic group, and only two studies in the cyanotic group, with both the latter studies from the same study group but different populations. These differences indicate that different surgical centers play an important role in the outcome of pediatric patients after surgery rather than just blood transfusion strategies alone. Therefore, further high-quality RCTs should be performed. Third, we could not provide more information about postoperative complications after RBC transfusion in pediatric cardiac surgery. Fourth, the sample sizes of the analyzed RCTs were too small; hence, our meta-analysis may be subject to small study effect bias, and the results should be interpreted with caution. Fifth, the target hemoglobin in transfusion and the duration of blood storage could have an effect on postoperative mortality and morbidity; however, we could not elucidate any effects using the current data [19, 32, 33]. Finally, at what degree of anemia in children do the benefits of RBC transfusion outweigh its risks remains unclear due to the lack of clinical evidence to address this question [7].

## Conclusion

The current data on the RBC transfusion strategies in children undergoing cardiac surgery did not provide sufficient evidence to make precise recommendations on the transfusion threshold, although children with cyanotic heart disease deserve special consideration. Further, large-scale RCTs should be conducted to verify these results and evaluate the long-term treatment effects of restrictive and liberal transfusion strategies on pediatric cardiac surgery patients, especially in children with cyanotic heart disease.

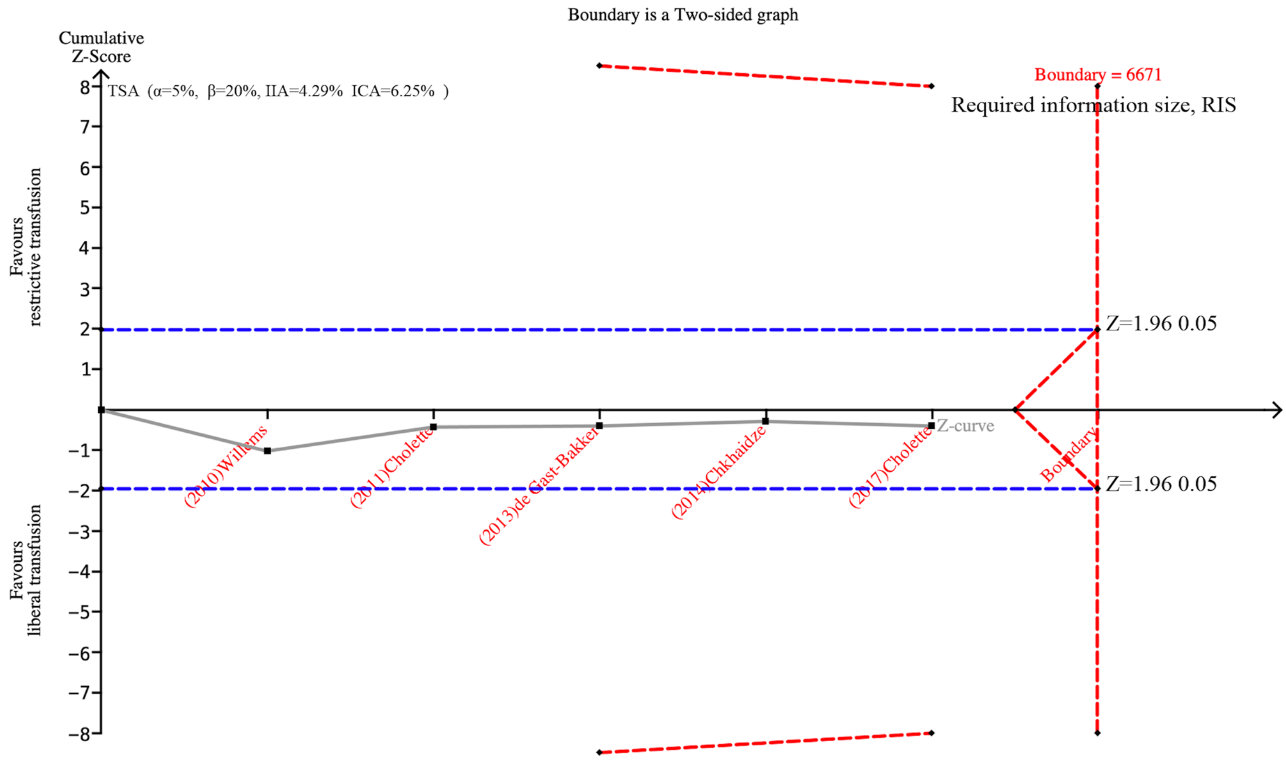


**Fig. 4** Trial sequential analysis for in-hospital mortality within 30 days of surgery for pediatric patients undergoing cardiac surgery using a fixed-effect model

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00246-021-02644-8.

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**Data Availability** The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

**Code Availability** Not applicable.

## Declarations

**Conflict of interest** All authors declare that they have no conflict of interest.

## References


1. Abdulla R (2002) Congenital heart disease management in developing countries. Pediatr Cardiol 23:481–482. https://doi.org/10.1007/s00246-002-0422-y
2. Yu XD, Wang W, Zhu DM (2017) The development situation of pediatric cardiac surgery in China from 2011 to 2015. Chin J ECC 15:1–4
3. Liu JF (2009) Challenges and progress of the pediatric cardiac surgery in Shanghai Children's Medical Center: a 25-year solid collaboration with project HOPE. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 12:12–18. https://doi.org/10.1053/j.pcsu.2009.01.020
4. Ip P, Chiu CS, Cheung YF (2002) Risk factors prolonging ventilation in young children after cardiac surgery: impact of noninfectious pulmonary complications. Pediatr Crit Care Med 3:269–274
5. Iyengar A, Scipione CN, Sheth P, Ohye RG, Riegger L, Bove EL, Devaney EJ, Hirsch-Romano JC (2013) Association of complications with blood transfusions in pediatric cardiac surgery patients. Ann Thorac Surg 96:910–916. https://doi.org/10.1016/j.athoracsur.2013.05.003
6. Kipps AK, Wypij D, Thiagarajan RR, Bacha EA, Newburger JW (2011) Blood transfusion is associated with prolonged duration of mechanical ventilation in infants undergoing reparative cardiac surgery. Pediatr Crit Care Med 12:52–56. https://doi.org/10.1097/PCC.0b013e3181e30d43
7. Desmet L, Lacroix J (2004) Transfusion in pediatrics. Crit Care Clin 20:299–311. https://doi.org/10.1016/S0749-0704(03)00113-1

8. Cholette JM, Rubenstein JS, Alfieris GM, Powers KS, Eaton M, Lerner NB (2011) Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy. Pediatr Crit Care Med 12:39–45. https://doi.org/10.1097/PCC.0b013e3181e329db
9. Székely A, Cserép Z, Sápi E, Breuer T, Nagy CA, Vargha P, Hartyánszky I, Szatmári A, Treszl A (2009) Risks and predictors of blood transfusion in pediatric patients undergoing open heart operations. Ann Thorac Surg 87:187–197. https://doi.org/10.1016/j.athoracsur.2008.09.079
10. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, Starr NJ, Blackstone EH (2006) Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 34:1608–1616. https://doi.org/10.1097/01.CCM.0000217920.48559.D8
11. Mazer CD, Whitlock RP, Fergusson DA, Belley-Cote E, Connolly K, Khanykin B et al (2018) Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. N Engl J Med 379:1224–1233. https://doi.org/10.1056/NEJMoa1808561
12. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K et al (2018) Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 377:2133–2144. https://doi.org/10.1056/NEJMoa1711818
13. Deng X, Wang Y, Huang P, Luo J, Xiao Y, Qiu J et al (2019) Red blood cell transfusion threshold after pediatric cardiac surgery: a systematic review and meta-analysis. Medicine 98(11):e14884. https://doi.org/10.1097/MD.0000000000014884
14. Lacroix J, Tucci M, Du Pont-Thibodeau G (2015) Red blood cell transfusion decision making in critically ill children. Curr Opin Pediatr 27:286–291. https://doi.org/10.1097/MOP.0000000000000221
15. Delgado-Corcoran C, Wolpert KH, Lucas K, Bodily S, Presson AP, Bratton SL (2016) Hematocrit levels, blood testing, and blood transfusion in infants after heart surgery. Pediatr Crit Care 11:1055–1063. https://doi.org/10.1097/PCC.0000000000000957
16. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1–9. https://doi.org/10.1186/2046-4053-4-1
17. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928. https://doi.org/10.1136/bmj.d5928
18. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188. https://doi.org/10.1016/0197-2456(86)90046-2
19. Brok J, Thorlund K, Wetterslev J (2009) Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol 38:287–298. https://doi.org/10.1093/ije/dyn188
20. Takwoing Y, Hopewell S, Tovey D, Sutton AJ (2013) A multicomponent decision tool for prioritising the updating of systematic reviews. BMJ 10:1–8. https://doi.org/10.1136/bmj.f7191
21. Willems A, Harrington K, Lacroix J, Biarent D, Joffe AR, Wensley D, Ducruet T, Hébert PC, Tucci M (2010) Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: a subgroup analysis. Crit Care Med 38:649–656. https://doi.org/10.1097/CCM.0b013e3181bc816c
22. de Gast-Bakker DH, de Wilde RB, Hazekamp MG, Sojak V, Zwaginga JJ, Wolterbeek R, de Jonge E, Gesink-van der Veer BJ (2013) Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: a randomized controlled trial. Intensive Care Med 39:2011–2019. https://doi.org/10.1007/s00134-013-3085-7
23. Chkhaidze M, Metreveli I, Tsintsadze A (2014) Comparison of two RBC transfusion strategies in pediatric cardiac surgery patients. Eur J Anaesthesiol 20:94
24. Cholette JM, Swartz MF, Rubenstein J, Henrichs KF, Wang H, Powers KS, Daugherty LE, Alfieris GM, Gensini F, Blumberg N (2017) Outcomes using a conservative versus liberal red blood cell transfusion strategy in infants requiring cardiac operation. Ann Thorac Surg 103:206–214. https://doi.org/10.1016/j.athoracsur.2016.05.049
25. Lacroix J, Hébert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al (2007) Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 356:1609–1619. https://doi.org/10.1056/NEJMoa066240
26. Ibrahim M, Ho SK, Yeo CL (2014) Restrictive versus liberal red blood cell transfusion thresholds in very low birth weight infants: a systematic review and meta-analysis. J Paediatr Child Health 50:122–130. https://doi.org/10.1111/jpc.12409
27. Mazine A, Rached-D'Astous S, Ducruet T, Lacroix J, Poirier N, Injury PAL, Network SI (2015) Blood transfusions after pediatric cardiac operations: a North American multicenter prospective study. Ann Thorac Surg 100:671–677. https://doi.org/10.1016/j.athoracsur.2015.04.033
28. Mink RB, Pollack MM (1990) Effect of blood transfusion on oxygen consumption in pediatric septic shock. Crit Care Med 18:1087–1091. https://doi.org/10.1097/00003246-199010000-00007
29. Bratton SL, Annich GM (2003) Packed red blood cell transfusions for critically ill pediatric patients: when and for what conditions? J Pediatr 142:95–97. https://doi.org/10.1067/mpd.2003.77
30. Stehling L, Luban NL, Anderson KC, Sayers MH, Long A, Attar S et al (1994) Guidelines for blood utilization review. Transfusion 34:438–448. https://doi.org/10.1046/j.1537-2995.1994.34594249058.x
31. Nuttall GA, Minnesota R, Brost BC, Minnesota R, Connis RT, Washington W et al (2006) Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 105:198–208. https://doi.org/10.1097/00000542-200607000-00030
32. Gauvin F, Lacroix J, Robillard P, Lapointe H, Hume H (2006) Acute transfusion reactions in the pediatric intensive care unit. Transfusion 46:1899–1908. https://doi.org/10.1111/j.1537-2995.2006.00995.x
33. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC (2016) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 10:CD002042. https://doi.org/10.1002/14651858.CD002042.pub4