

Systematic Review

CALCIFEROL STATUS AND CLINICAL OUTCOMES IN CHILDREN WITH CONGENITAL HEART DISEASE AFTER HEART SURGERY

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ABSTRACT

Calciferol is a micronutrient and a secosteroid hormone that plays a role in maintaining the health of bones and soft tissues in the body, such as the myocardium, as well as the immune system. Hypovitaminosis D has been reported to be associated with poor clinical outcomes and child mortality in pediatric intensive care units. Children with congenital heart disease (CHD) are vulnerable to critical conditions and require early intervention due to heart failure. This study aimed to investigate the influence of calciferol status on the clinical outcomes of pediatric CHD patients who underwent heart surgery. A systematic literature review was conducted using the electronic databases from PubMed, Elsevier, and Cochrane. This study included observational and randomized control studies that assessed the calciferol status of pediatric CHD patients undergoing cardiac surgery. From a total of 168 studies, 8 studies were selected for review. The preoperative and postoperative calciferol status as well as clinical outcomes following pediatric cardiac surgery were reviewed. According to the findings, most pediatric CHD patients suffered from calciferol deficiency prior to corrective heart surgery, which further decreased postoperatively and was associated with clinical outcomes in the intensive care unit (ICU). Preoperative calciferol supplementation has been reported to enhance serum calciferol levels and is associated with good clinical outcomes in pediatric patients undergoing cardiac surgery.

Keywords: Calciferol; congenital heart disease; child cardiac surgery; child mortality

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Highlights:

1. Calciferol has cardioprotective properties, and a severe deficiency of calciferol is associated with septic shock, a longer duration of mechanical ventilation and treatment in the intensive care unit, and mortality.
2. The role of calciferol in critical conditions has been described in several research reports, but relatively little is known about its function in pediatric cardiac surgery.
3. The information presented in this systematic review is quite beneficial, as the sources cited are relatively recent and pediatric cardiac surgery will continue to develop in the future.

INTRODUCTION

Congenital Heart Disease (CHD) was estimated to occur in 17.9 of 1,000 children worldwide, with 19.1 of 1,000 boys and 16.6 of 1,000 girls. Ventricular septal defects (VSD) and atrial septal defects (ASD) accounted for about 29.6% of all cases. The

prevalence of CHD in urban areas was 34.17% higher than in rural areas. Atrial septal defect (3.07 per 1,000 births), patent ductus arteriosus (PDA) (1.62 per 1,000 births), ventricular septal defect (1.18 per 1,000 births), tetralogy of Fallot (TOF) (0.62 per 1,000 births), and atrioventricular septal defect (0.47 per 1,000 births) are the five most

common subtypes (Morgan et al. 2013, Zhang et al. 2022). Epidemiological data in Indonesia are quite varied. Reports from Dr. Sardjito Central General Hospital, Sleman, Indonesia, revealed that the prevalence of CHD was 134 out of 10,000. Ventricular septal defects were the most common lesion among children (30%), followed by atrial septal defects (17%), patent ductus arteriosus (16%), and tetralogy of Fallot (7%). A study on the characteristics of infants born with CHD found that patent ductus arteriosus was present in 76.1% of the infants. Ventricular septal defects, atrial septal defects, and transposition of the great arteries were the most prevalent conditions following patent ductus arteriosus. About one in four infants with CHD are critically ill. Infants with critical CHD generally require surgery or other procedures in the first year of life. The lethality associated with critical CHD was 64.7%, with a mortality rate of 12.0%. The survival rates decreased by almost 70% in newborns with congenital heart disease, where the main cause of death was cardiogenic shock, respiratory tract infections (such as pneumonia and bronchiolitis), and malnutrition (Damayantie et al. 2019).

CHD management includes surgical procedures and transcatheter intervention, mostly performed within the first year of life. Most patients are in critical condition before and after the procedure. The defects and malformation abnormalities accompanied by comorbid diseases may worsen the child's condition. The condition of the child undergoing cardiopulmonary bypass (CPB) can lead to a critical condition. Some factors related to the critical condition post-cardiopulmonary bypass are young age, malnutrition, and congestive heart failure. The long duration of cardiopulmonary bypass and the complexity of the correction surgery are some of the intraoperative factors contributing to CHD mortality. In addition, the conditions of multiorgan dysfunction, bleeding, acute renal failure, and postoperative septic complications are also causes of death post-surgery (Morgan et al. 2013, Mamikonian et al. 2014, Guzzetta et al. 2015).

Vitamin D, also known as calciferol, is a micronutrient secosteroid hormone with two main forms, i.e., vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Generally, vitamin D is synthesized in the skin and obtained from animal-source foods. Calciferol, along with calcium, is important for bone health and the body's soft tissues, such as the myocardium and immune system. In the immune system, calciferol promotes the expression of an anti-inflammatory cytokine, i.e., interleukin 10 (IL-10). It also activates toll-like receptors that induce cathelicidin and β -defensin, which then start the autophagy activity of pathogens. Calciferol enhances the innate immune response that prevents

cytokine storms by reducing the production of inflammatory cytokines in patients with viral infections and sepsis (Chun et al. 2014, Kumar et al. 2021, Ao et al. 2021). In the cardiac myocardium, calciferol was reported to be beneficial as a cardioprotector in dilated cardiomyopathy and heart failure. There was a significant correlation between low calciferol and heart failure. Another study also reports the role of these vitamins in improving B-natriuretic peptide levels and the quality of life in heart failure patients (Priya et al. 2016, Moretti et al. 2017).

Hypovitaminosis D, or vitamin D deficiency, is indicated by a concentration of <50 nmol/L (<20 ng/mL). Severe vitamin D deficiency with a 25-hydroxyvitamin D (25-OHD) concentration of <30 nmol/L (12 ng/mL) dramatically increases the risk of infection, mortality, and other diseases (Yeşiltepe Mutlu & Hatun 2018, Wei et al. 2018, Amrein et al. 2020). Previous studies also showed that calciferol deficiency status has been associated with critical conditions in children receiving intensive care. There was some evidence of severe vitamin D deficiency associated with septic shock, longer mechanical ventilation, and longer treatment in the intensive care unit (ICU). Conditions of severe respiratory tract infection, sepsis, and significant mortality risk were also associated with findings of 25-OHD deficiency status (<50 nmol/L) (Cariolou et al. 2019, Sankar et al. 2019).

Vitamin D supplementation in doses of 400 IU per day is recommended during infancy. The average needs of older children and adolescents (400–600 IU per day) are usually met from food and natural sources such as sunlight. However, in conditions of severe calciferol deficiency and rickets, oral cholecalciferol at a daily dose of 2,000 IU for children under 1 year old and 3,000 IU for older children can be given for 3 months. High doses of vitamin D supplements are not associated with an increased risk of severe side effects in children aged 0–6 years. Vitamin D supplementation for children in the dosage range of 1,200 to 10,000 IU/day and bolus doses up to 600,000 IU are also well tolerated (Gupta et al. 2022, Brustad et al. 2022). A single dose of vitamin D (150,000 IU) may increase 25-OHD levels and lower the incidence of septic shock in children with critical sepsis. Vitamin D supplementation also improves the concentrations of various sepsis-related cytokines, e.g., angiotensin II (Ang-II), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α). In a previous study, the cardiovascular sequential organ failure assessment (CV-SOFA) scores (1.76 ± 0.8 vs. 2.3 ± 1.1) and septic shock incidence (7% vs. 20%) were lower in the group with vitamin D supplementation compared to the control group, although the duration of mechanical ventilation and mortality were the same

between the two groups (Wang et al. 2020).

Clinically, pediatric patients with CHD will experience critical conditions due to anomalies that interfere with heart function. Some CHD patients experience heart failure and are in critical condition after undergoing cardiac surgery with cardiopulmonary bypass, affecting the outcome of the procedure. Earlier studies had reported on changes in vitamin D status before and after pediatric heart surgery, but the benefits of vitamin D supplementation in pediatric heart surgery were not widely explored (Sankar et al. 2019, Wang et al. 2020). Our study objectively aimed to report the changes in vitamin D status in children with CHD undergoing heart surgery and the benefits of vitamin D supplementation to assist in the clinical evaluation of shock events, additional fluid resuscitation volumes, inotropic vasopressor support, and other conditions that influence patients' outcomes.

MATERIALS AND METHODS

A search for literature was conducted on the medical databases, including PubMed, Elsevier, and Cochrane, with the keywords "calciferol", "vitamin D", "child heart surgery", and "child cardiac surgery outcome". The selected studies were journal articles

published in English between January 2013 and December 2022. The inclusion criteria were open-access research publications, including observational studies, cohort studies, and clinical trials in humans with patients aged <18 years undergoing cardiac surgery with cardiopulmonary bypass due to CHD. The selected studies must discuss the interventions and comparisons of calciferol administration as well as the significance of serum vitamin D (calcitriol) levels before and after cardiac surgery (Page et al. 2021). Figure 1 shows the selection of the studies using the PRISMA flowchart.

Initially, the identification of the studies was performed by filtering the titles and abstracts before obtaining the full-text articles. Afterwards, a screening of the interventions, comparisons, characteristics, and output results of each study was carried out (Gupta et al. 2018). There were 326 pieces of research, but 8 duplicates and 87 studies not meeting the inclusion criteria were excluded. There were 68 studies in the follow-up screening, but 48 were considered irrelevant. For the remaining 20 pieces of research, 6 studies lacked detail, and 6 studies were systematic reviews as well (Siddaway et al. 2019). Finally, there were 8 eligible studies for this systematic review. The results and flow of the literature search are presented in Table 1.

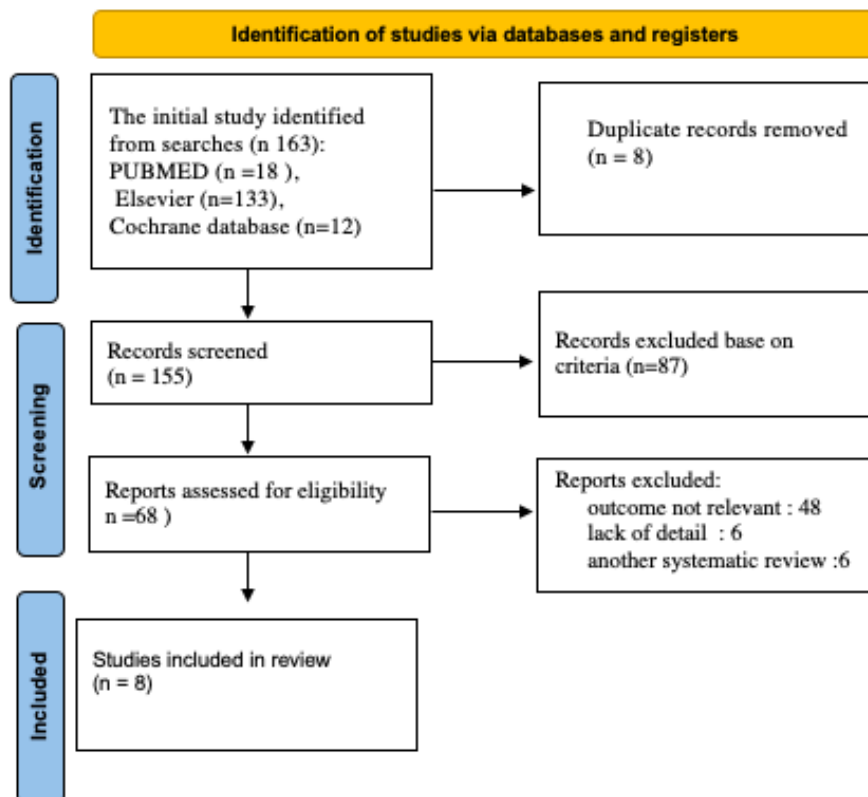


Figure 1. PRISMA flow diagram for the literature search.

Table 1. Characteristics and outcomes of the selected studies.

Authors, Year	Study Designs	Populations	Interventions/ Comparisons	Outcomes
McNally et al. (2013)	Prospective cohort	58 children aged <18 years with CHD who underwent elective and semi-elective cardiac surgery	Comparison of 25-OHD levels preoperatively, intraoperatively, and postoperatively; correlation of vitamin D status with clinical outcomes, including catecholamines, inotropic score, fluid boluses, total fluid intake, intubation duration, and PICU length of stay	CHD patients had low preoperative vitamin D levels and significant intraoperative decline. Low levels of 25-OHD were associated with higher fluid volumes and longer intubation.
Graham et al. (2013)	RCT	900 children with CHD who underwent cardiac surgery	Comparison of 25-OHD levels prior to surgery, during CPB, and 24 hours postoperatively; association of vitamin D status with clinical outcomes	Vitamin D deficiency was common in CHD patients, and lower postoperative vitamin D levels were associated with higher inotropic support in neonates after cardiac surgery.
Abou Zahr et al. (2017)	Prospective observational	20 CHD child patients aged between 2 months and 17 years who underwent CPB	Evaluation of serum 25OHD levels before, immediately after surgery, and 24 hours after surgery	CPB decreased the 25-OHD level by reducing the free fraction.
Acharya et al. (2018)	Cohort	56 children with CHD who underwent surgery and calcitriol evaluation preoperatively and postoperatively	Comparison of calcitriol levels preoperatively, postoperatively, and 48 hours after surgery	CHD patients had low levels of calcitriol intraoperatively and experienced a challenge in increasing the levels. Cholecalciferol reduced the severity of postoperative illness.
Ye et al. (2021)	Cohort	900 children with CHD who underwent cardiac surgery	Vasoactive inotropic score comparison of 25-OHD levels at 20–30 ng/mL and <20 ng/mL 24 hours after surgery	Vitamin D levels in child patients before cardiac surgery were associated with postoperative inotropic support 24 hours after the surgery.
Dohain et al. (2020)	Prospective cohort	69 children with CHD who underwent elective cardiac surgery with CPB	Comparison of vitamin D deficiency with levels of <20 ng/mL	Low levels of vitamin D after heart surgery were associated with inotropic support.
Sahu et al. (2019)	RCT	60 children with a TOF diagnosis and vitamin D levels of <20ng/dL	Children with CHD who underwent cardiac surgery and received vitamin D supplementation of 10,000 units/kgbw	TOF was highly associated with vitamin D deficiency after CPB. Vitamin D supplementation was useful to raise serum levels before and after surgery.
McNally et al. (2020)	RCT	41 children aged between 36 weeks and 17 years with CHD who underwent cardiac surgery, i.e., 21 received high doses of vitamin D vs. 20 received standard care	Comparison of preoperative cholecalciferol treatment with lower doses (400 IU/day for children aged <1 year; 600 IU/day for children aged >1 year) and higher doses (1,600 IU/day for children aged <1 year; 2,400 IU/day for children aged >1 year)	Daily vitamin D supplementation in high doses improved 15-OHD status before and after surgery in the PICU.

CPB: Cardiopulmonary bypass; CHD: Congenital heart disease; 25-OHD: 25-hydroxy-vitamin D; RCT: Randomized controlled trial; TOF: Tetralogy of Fallot; PICU: pediatric intensive care unit

RESULTS

Children with CHD and the calciferol status

There were 163 studies obtained from the literature search. After screening and excluding ineligible studies, eight studies were suitable to be reviewed in this study. There were five observational cohort studies and three randomized controlled trials (RCTs) that reported calciferol status in children with CHD who underwent open cardiac surgery (Figure 1).

Cardiac surgery performed on children aged <18 years with CHD significantly lowered calciferol

levels over time until post-surgery (Table 1). A study observed the calciferol status of 58 children with CHD before surgery, during ICU admission, and over 4 hours to 2 days after surgery. There was a significant decrease in vitamin D levels after the heart surgery. There was a significant decrease in vitamin D levels after the heart surgery. In the study, the average preoperative calciferol measured with serum 25-OHD was 58 ± 22.4 preoperatively. The average level changes from 34.2 ± 14.5 nm when the patients entered the pediatric intensive care unit (PICU) to 34.2 ± 14.5 four hours post-surgery, 33.9 ± 13.6 one day later, and 36.5 ± 12.2 after two days. The comparison of 25-OHD levels before and after surgery was significantly different (58.0 vs.

34.2 nm, $p < 0.001$) (McNally et al. 2013).

Another study conducted on neonates with CHD also found that calciferol deficiency was present in 84% of the neonates who underwent cardiac surgery. Most neonates had low calciferol levels of $< 20 \text{ ng/dL}$ (Graham et al. 2013). A study by Abou Zahr et al. (2017) reported similar findings. Cardiopulmonary bypass decreased the 25-OHD levels of pediatric patients. The average levels of 25-OHD were measured before, during, and 24 hours after the cardiopulmonary bypass, with mean levels of $26.8 \pm 4.2 \text{ ng/mL}$, $21.5 \pm 5.7 \text{ ng/mL}$, and $23.0 \pm 4.9 \text{ ng/mL}$ ($p < 0.001$), respectively. In the group of patients with initial vitamin D deficiency, there was also a significant decrease, with an average of $21.3 \pm 8 \text{ ng/mL}$ preoperatively, $19 \pm 5.8 \text{ ng/mL}$ during surgery, and $19.5 \pm 6.6 \text{ ng/mL}$ postoperatively.

Comparison of calciferol status and clinical outcomes in children with CHD who underwent cardiac surgery

Several studies on the calciferol status and clinical outcomes after pediatric heart surgery described the various hemodynamic parameters, the need for a ventilator, and the duration of treatment in the PICU (Table 1). McNally et al. (2013) reported that pediatric patients with lower calciferol levels of $< 25 \text{ nm/dL}$ required more catecholamine, postoperative fluid boluses, and fluid intake, had a prolonged intubation duration, and had a higher inotropic score compared to children with higher calciferol levels. After pediatric heart surgery, there were changes in calciferol levels according to a prospective observation by (Acharya et al. 2018). There was a significant decrease in intraoperative levels of 25-OHD (calcitriol) and a challenge to increase the levels postoperatively. The average calcitriol level was $122.3 \pm 69.1 \text{ pmol/L}$ preoperatively and dropped to $65.3 \pm 36.5 \text{ pmol/L}$ during PICU admission ($p < 0.0001$). The majority (61%, $n = 34$) of the patients were unable to increase their calcitriol levels within 48 hours after surgery. Postoperative predisposition from calcitriol deficiency was found to be inversely proportional to cardiovascular dysfunction, fluid requirements, ventilation support, and duration of PICU treatment ($p < 0.01$).

A secondary analysis in the study by Acharya et al. (2018) showed the negative effects of CHD surgery on the calciferol axis. There was a strong association between a downward trend in calcitriol levels and the severity of the postoperative condition. In another study, calciferol levels were significantly related to the vasoactive inotropic score at a maximum of 24 hours after surgery and a longer cardiopulmonary bypass duration. Calciferol levels of $< 30 \text{ ng/mL}$ were more likely to result in a

vasoactive inotropic score of > 15 compared to higher calciferol levels. Longer cardiopulmonary bypass duration was also found to be more prevalent among children with calciferol levels of $< 20 \text{ ng/mL}$. The association between calciferol status and clinical outcomes was still unclear. However, a study suggested that calciferol status was related to a patient's myocardial and inflammatory status (Ye et al. 2021).

In a study by Dohain et al. (2020), calciferol deficiency was common in pediatric patients with CHD. Most patients had calciferol deficiency after surgery, with an acute decrease in serum 25-OHD following a cardiopulmonary bypass. Lower levels of calciferol in children after heart surgery were associated with the need to improve inotropic support. Patients with calciferol deficiency postoperatively, with 25-OHD levels of $< 20 \text{ ng/mL}$, were more likely to need higher inotropic support. In the postoperative follow-ups, it was discovered that patients with calciferol deficiency were more susceptible to surgical wound infections, required extracorporeal membrane oxygenation (ECMO) support, and had a higher mortality rate before being discharged from the hospital (Dohain et al. 2020).

Consideration of calciferol doses in children with CHD who underwent cardiac surgery

Calciferol deficiency status before and after child heart surgery had an association with clinical outcomes in pediatric patients. In terms of maintaining the calciferol status, calciferol supplementation was given to achieve perioperative success. A randomized controlled trial conducted by Sahu et al. (2019) studied 60 children under 18 years of age with a tetralogy of Fallot diagnosis. Most patients had serum calciferol levels of $< 20 \text{ ng/dL}$, which decreased further after undergoing intracardiac surgical correction and cardiopulmonary bypass. The calciferol levels in children with tetralogy of Fallot berries were below the baseline ($< 20 \text{ ng/dL}$) preoperatively up to one day postoperatively. The group that received calciferol therapy in a single megadose of $10,000\text{--}400,000 \text{ units/kg}$ showed calciferol levels of $> 20 \text{ ng/dL}$ both during surgery and six hours up to one day after surgery compared to the control group. No significant difference was found in the laboratory parameters (e.g., parathyroid hormone, serum calcium, and urinary calcium creatinine ratio), clinical outcomes of inotropic support duration, ventilation duration, or ICU treatment duration. However, calciferol therapy significantly improved the postoperative calciferol status of the pediatric patients' hearts (Sahu et al. 2019).

Another randomized controlled trial conducted by McNally et al. (2013) reported that high-dose

supplementation of calciferol improved vitamin D status before surgery and reduced treatment time in the ICU. In the study, D3-calciferol was administered regularly at doses of 400 IU/day for children aged <1 year and 600 IU/day for children aged >1 year. In addition, higher doses of 1,600 IU/day for children aged <1 year and 2,400 IU/day for children aged >1 year were administered for comparison. The higher doses resulted in higher intraoperative calciferol levels (81.5 ± 36.5) compared to the lower doses in the control group (55.5 ± 13.8). There were no side effects of hypercalcemia or postoperative hypercalciuria. The pediatric clinical outcomes also showed that patients who received high-dose calciferol therapy required less mechanical ventilation and dialysis when they had acute renal failure. These results supported a high-dose regimen capable of reducing calciferol deficiency without additional side effects or toxicity, as well as improving clinical conditions. Vitamin D supplementation provided better clinical outcomes after pediatric heart surgery (McNally et al. 2020).

DISCUSSION

This systematic review showed that, generally, children with CHD had a calciferol deficiency. This condition might be related to the preceding malnutrition before surgery and the side effects of the disease. In this review, we also explained that there was a significant decrease in calciferol levels as an effect of cardiac surgery procedures and the hemodilution in cardiopulmonary bypass. Cardiac surgery poses risks to pediatric patients and can place them in a critical condition if monitoring in the ICU is inadequate (Morgan et al. 2013).

In a number of study reports, calciferol deficiency status in children and adults was associated with clinical outcomes, e.g., the need for longer mechanical ventilation, prolonged ICU treatment duration, infection, and respiratory failure. In this review, the postoperative calciferol status of pediatric patients with CHD was correlated with the need for inotropic support and mechanical ventilation. In critical conditions, calciferol supplementation can be administered to suppress various inflammatory responses that may occur during treatment (Cariolou et al. 2019, Kusumajaya et al. 2021).

The results of this review are still unable to confirm the role of calciferol in terms of improving the postoperative status of pediatric patients' hearts. The reasons were that many other factors affect a patient's external outcomes, such as heart failure that accompanies pediatric anomalies or abnormalities, the duration of surgery, the duration of cardiopulmonary bypass, bleeding, postoperative

hemodynamic disorders, and the risk of sepsis (Darren et al. 2022). In the end, various efforts must be made to maintain a good clinical condition. Previous studies showed quite positive benefits of supplementation in improving calciferol status preoperatively and postoperatively. A number of studies agreed to the administration of vitamin D therapy if a child's 25-OHD level is <20 ng/dL, with a recommended dose of 400–2,000 IU/day to increase the 25-OHD level to 30–50 ng/dL. This therapy should be carried out while monitoring potential side effects, such as hypercalcemia and hypercalciuria, which usually result from taking very high doses of calciferol over an extended period of time (Bouillon 2017, Pludowski et al. 2018, de la Guía-Galipienso et al. 2021).

Vitamin D supplementation can maintain optimal serum calciferol status before and after surgical correction, particularly in critical conditions due to CHD. Supportive results from the reviewed studies revealed the benefits of high doses of calciferol on the clinical outcomes of CHD patients. The findings indicated no incidence of severe side effects after pediatric heart surgery (Sahu et al. 2019, McNally et al. 2020). We suggest that further research may study calciferol administration with large doses and various timings of administration in correlation with other parameters, including pro-inflammatory cytokines, immune response, hemodynamics, side effects, and the postoperative clinical status of the child's heart.

Strength and limitations

Several research reports have discussed the role of calciferol in critical conditions, but not much has been described about pediatric cardiac surgery. This systematic review provides additional information regarding the role of calciferol in pediatric heart surgery. Other research reported that several factors also affect the outcomes of pediatric heart surgery, including previous heart failure, nutritional status, co-infection, intraoperative problems (e.g., surgery duration, bleeding, and the complexity of congenital heart anomalies), inflammation, and several other factors associated with mortality in the ICU. However, the information presented in this systematic review is quite useful, as the sources cited are relatively recent and pediatric cardiac surgery will continue to develop in the future.

CONCLUSION

Most pediatric congenital heart disease (CHD) patients had low levels of calciferol below normal, which further decreased following cardiac surgery and cardiopulmonary bypass. Calciferol deficiency is associated with increased inotropic requirements

and prolonged intensive care unit (ICU) stays compared to sufficient levels of calciferol. Preoperative calciferol administration can enhance serum calciferol levels above normal and potentially reduce the use of mechanical ventilation following heart surgery.

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Conflict of interest

None.

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Author contribution

ZE, A, FM, H, and RP contributed to the conception and design of the study. ZE, FM, H, TR, FZ, and HK drafted the manuscript. ZE, TR, FZ, and HK contributed to the critical revisions and final approval. ZE, A, FM, H, and RP collected, assembled, and analyzed the data. All authors also contributed to the revisions of the manuscript.

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