

## Review Article

# Association between Laboratory Markers and Complications in Pediatric Cardiac Surgery

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**Abstract**

Inflammatory changes compromise the adequate immune and metabolic functions in the postoperative period of pediatric patients submitted to surgery and may cause and/or aggravate clinical problems. Our aim was to investigate the association between intra and postoperative complications with laboratory markers in pediatric patients with congenital heart disease submitted to surgical correction. This was a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocol. The studies demonstrated an association between parameters such as glycemia, lactate, interleukins 6, 8 and 10, and surgical complications, all of which presented results with a statistical significance. There was evidence that associated inflammatory parameters as predictors of postoperative complications in children submitted to cardiac surgery. PROSPERO Registration: CRD 42018111409.

**ABBREVIATIONS**

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**INTRODUCTION**

Congenital heart diseases (CHDs) constitute a broad clinical spectrum, from asymptomatic defects, to those with high mortality rates [1]. They represent one of the most frequent malformations, the incidence of which varies from 8 to 10 per 1,000 live births and are a significant cause of mortality in the first year of life [2].

The intraoperative period is crucial in the evolution of children with heart disease. Volemic variations in body temperature, plasma composition and tissue blood flow are present and bring significant pathophysiological consequences. Additional aggressions, often unavoidable, such as cardiopulmonary bypass (CPB), contribute to aggravating an organic imbalance even further. The generated stress evokes defense mechanisms, defined as “neuroendocrine-immuno-metabolic response to injury”, for the initial harmful event [3].

The inflammatory response triggered by cardiac surgery is a process that is difficult to identify. Regardless of the triggering factor, the systemic response may have serious clinical implications

that compromise coagulation and the immune response; lead to vasodilation; a release of catecholamines in large quantities, changes in blood and electrolyte fluid; myocardial dysfunction, injury or necrosis and mild pulmonary dysfunction [4].

There is a consensus that tight preoperative control and strong efforts to guarantee intraoperative stability may guarantee patients a good postoperative evolution, even critically ill patients. However, poor preoperative preparation, associated with risk factors and periods of intraoperative hemodynamic instability aggravate the prognosis and may determine and/or trigger serious postoperative complications [5].

Inflammatory changes in congenital heart patients compromise adequate immunologic and metabolic functions during the postoperative period of cardiac surgery, and may cause and/or aggravate clinical problems. Thus, the probable existence of an association between inflammatory parameters and postoperative complications may assist in the control of pediatric cardiac patients, when previously assessing inflammatory markers. This study aimed to determine the association between inflammatory parameters and postoperative complications in pediatric patients submitted to cardiac surgical correction.

## METHOD

This was a systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocol [12]. The question in this review was: What is the relationship between inflammatory parameters and complications in pediatric cardiac surgery? Based on the strategy of the PICOS framework, studies were considered eligible if: 1 - the population was composed of cardiac patients submitted to cardiac surgery; 2 - they assessed the influence of inflammation markers in cardiac surgery, 3 - they compared outcomes between patients with inflammatory changes and complications in cardiac surgery; 4 - they presented complications and/or death; and 5 - they were clinical and/or observational studies.

The following databases were consulted until November 2019: *Cochrane Library*, *British Medical Journal (BMJ) Best Practice*, *National Library of Medicine National Institutes of Health (PubMed/MEDLINE)*, *Science Direct* and *Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS)*.

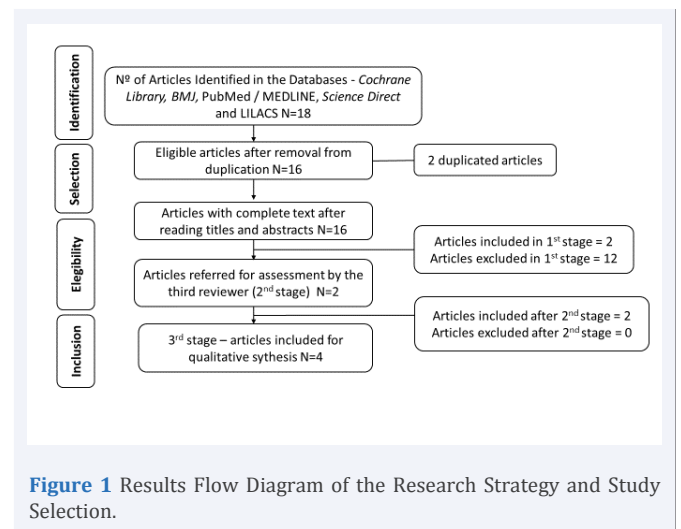
The search strategy was guided by the use of controlled vocabulary according to Health Sciences Descriptors (DeCs) as an expanded translation of Medical Subject Headings (MeSH). In the DeCs, research was conducted in Portuguese and the descriptors were obtained in English, and were combined using the Boolean operators “and” and “or”. The descriptors used for this study were: Child; Heart Disease; Inflammation; Postoperative Complications or Post-Surgical Complications; Clinical Studies; Observational Studies.

The search for the studies was guided by the research question and by the combination of descriptors in the databases aiming to locate the term in the title, abstract and keywords. There was no restriction on the period or language, other than the use of gray literature as long as they were clinical and/or observational studies. The descriptors were combined two by two on each base and, when necessary, a triple combination was chosen.

Initially, the titles and abstracts of the studies were read, and each researcher registered agreement or not on the assessed study (1st stage). Discordant cases were discussed and submitted for assessment by a third researcher with greater experience in the subject (2nd stage). Subsequently, the selected articles were read in full in order to seek an answer to the review question (3rd stage). Figure 1 describes the flow of identification, selection, eligibility and inclusion of the studies.

Data extraction was performed by two researchers independently with the help of an electronic form prepared with Microsoft Excel<sup>®</sup>, and a data compatibility assessment was conducted by a third researcher, in order to assess data consistency and cleanliness. The critical assessment of the quality of the study data was undertaken using the *Oxford Centre Evidence Based Medicine* method [8], in accordance with Table 1, as well as an assessment of the methodological quality of the studies according to the GRADE recommendations [9]. The data synthesis from this study was guided by PRISMA, followed by the IMRD structural logic - Introduction, Methods, Results and Discussion.

Aggregate data from the participating articles were used and a descriptive synthesis was developed. Assessments were conducted to determine whether there was an association between children with



inflammation submitted to cardiac surgery and the occurrence of complications.

The methods section was published in the form of a Protocol based on PROSPERO - *International Prospective Register of Systematic Reviews* affiliated to the University of York, according to the CRD Identification Code 42018111409 and available for free access at: [http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42018111409](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018111409) and following this, the other steps of this study were conducted.

## DISCUSSION & CONCLUSION

Four articles with a total of 838 participants met the inclusion criteria. The age of the included participants ranged from 1 (one) month to <18 years of age. All studies sought to demonstrate an association between inflammatory markers and the occurrence of complications in pediatric cardiac surgery. With regard to the language of the articles, 75.0% (n = 3) were published in English and 25.0% (n = 1) in Portuguese (Table 1).

The articles were analyzed in terms of quality and categorized by Grade of Recommendation and Level of Evidence, according to the classification developed by the *Oxford Centre for Evidence Based Medicine* [8]. It was found that 100% (n = 4) of the articles were classified as grade B of recommendation - Moderate. All were cohort studies, and of these, two were retrospective and two, prospective. All were classified with a level of evidence 2B (Table 1).

## POSTOPERATIVE COMPLICATIONS RELATED TO INFLAMMATION

Alves et al. (2011) [3], demonstrated that high intraoperative levels of glycemia were associated with: infectious complications in surgeries with CPB: OR 1.01 (1.00-1.02) p 0.048; infectious complications in surgeries without CPB: OR 1.02 (1.01-1.04) p 0.017; cardiovascular complications in surgeries with CPB: OR 1.01 (1.00-1.02) p 0.048; and hematological complications in surgeries without CPB: OR 1.02 (1.00-1.03) p 0.025.

Alves et al. (2012) [10], described the association of lactate with cardiovascular complications in surgeries with CPB: OR 1.60 (1.04–2.46), p 0.030; hematological complications in surgeries with CPB: OR 1.99 (1.20–3.33), p 0.008; respiratory complications in surgeries with

**Table 1:** Studies on inflammatory markers and their association with postoperative complications in pediatric patients submitted to cardiac surgery.

Study and Year of Publication	LE	Type of Study	Sample size and Age	Inflammatory Marker (s) Assessed	Postoperative Complications	OR (CI 95%) OR CI 95% and/or p-value	Conclusions
Alves et al., 2011 (3)	2B	Retrospective Cohort	160/8 months to 8 years	Glycemia	Infectious with CPB Infectious without CPB Cardiovascular with CPB Hematological without CPB	1.01 (1.00-1.02) p 0.048 1.02 (1.01-1.04) p 0.017 1.01 (1.00-1.02) p 0.048 1.02 (1.00-1.03) p 0.025	Higher intraoperative blood glucose levels are associated with greater morbidity in the postoperative period of pediatric cardiac surgery.
Alves et al., 2012 (10)	2B	Retrospective Cohort	160/< 16 years	Lactate	Cardiovascular with CPB Hematological with CPB Respiratory with CPB Kidney with CPB Kidney without CPB Death without CPB	1.60 (1.04–2.46) p 0.030 1.99 (1.20–3.33) p 0.008 1.56 (1.05–2.31) p 0.026 1.44 (1.02–2.02) p 0.036 1.89 (1.15–3.12) p 0.012 1.56 (1.03–2.36) p 0.033	Elevated intraoperative levels of arterial lactate are associated with higher morbidity and mortality in low and medium risk procedures, with or without CPB, in pediatric cardiac surgery.
Greenberg et al., 2015 (11)	2B	Prospective Cohort	106/1 month to 18 years	Interleukin-6 Interleukin-10	AKI	IL-6 = 6.41 (1.16–35.35) p 0.0001	The plasma concentration of preoperative IL-6 is associated with the development of stage 2/3 AKI and may be a prognosis for the use of resources
Fontnouvelle et al., 2017 (12)	2B	Prospective Cohort	412/1 to 18 years	Interleukin-8	AKI in those aged 2 years and over	IL-8 = 2.61 (1.05-6.46)	Preoperative IL-8 is significantly associated with a higher likelihood of AKI in children aged 2 years or older.

CPB: OR 1.56 (1.05–2.31), p 0.026; kidney complications in surgeries with CPB: OR 1.44 (1.02–2.02), p 0.036; kidney complications in surgeries without CPB: OR 1.89 (1.15–3.12), p 0.012; and deaths in surgeries without CPB: OR 1.56 (1.03–2.36), p 0.033.

Furthermore, Alves et al. (2012) [10], also demonstrated that complications were treated in subcategories. Cardiovascular complications: low cardiac output, OR 1.69 (1.12–2.53), p 0.011; prolonged use of vasopressors, OR 1.61 (1.11–2.35), p 0.012; prolonged use of inotropes, OR 1.54 (1.05–2.26), p 0.026. Respiratory complications: prolonged use of mechanical ventilation, OR 1.42 (1.01–2.00), p 0.046; and hematological complications: coagulopathies, OR 1.56 (1.04–2.34), p 0.029.

The results by Greenberg et al. (2015) [11], demonstrated an association between Interleukin-6 and the development of acute kidney injury (AKI), after cardiac surgery with CPB, OR 6.41 (1.16–35.35), p 0.0001. In a similar study, although assessing Interleukin-8, Fontnouvelle et al., (2017) (12), reported an association of AKI in patients aged 2 years and over with preoperative IL-8, OR 2.61 (1.05–6.46).

This systematic review has demonstrated that there is evidence that associated laboratory variables, which indicate signs of inflammation in pediatric patients, with surgical complications during the postoperative period. Most of the studies were classified as being of moderate quality with a grade B of recommendation, which may be justified due to the scarcity of randomized controlled clinical trials. However, all those that used measures of association reported a statistical significance and, according to their samples and specific characteristics, were able to demonstrate that the variables related

to inflammation were associated with the presence of complications during the postoperative period, reflected in an increase in the morbidity and mortality of the pediatric population with congenital cardiovascular malformations submitted to surgical correction.

In order to associate inflammation with complications, the included studies opted for classic inflammation markers, such as glycemia, serum lactate and parameters which, although of valuable importance, are rarely used in clinical routine, such as interleukins 6, 8 and 10. However, it should be noted that due to the heterogeneity of these variables, it was not possible to group data and compare one study with another.

It was observed that there are few studies, which have demonstrated an association of parameters that were indicative of inflammatory status with complications in pediatric cardiac surgery. This fact is of concern, since the surgery itself may be triggering or potentiating a systemic inflammation with multiple involvement of the organ systems. We observed that glycemia and serum lactate were used for this purpose, however only two studies presented these variables in isolation [3,10-12]. The question is therefore raised as to whether there may be a clinical underestimation of these parameters? Thus, future research must be conducted in order to fill this gap.

In conclusion, the studies analyzed demonstrated an association of pre- and intra-surgical inflammatory parameters associated with complications in pediatric cardiac surgery.

## CONFLICT OF INTEREST

The authors, being responsible for the content of the work and declare that there are no possible ethical and interest conflicts.

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