# The beneficial role of simple inflammatory blood indices in pediatric cardiology

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## Abstract

Simple whole blood analysis can effectively demonstrate complex changes in inflammatory responses to cardiovascular disorders in adults and enable the prediction of adverse outcomes or diminished survival. Such inflammatory activation has also been detected in the pediatric population. Blood analysis results are repeatable and readily available, which gives the method an advantage over others. Inflammatory phenomena such as a high leukocyte count and an increased neutrophil-to-lymphocyte ratio (NLR) are related to a poor prognosis of advanced heart defects and worse outcomes after pediatric cardiac surgery in the advanced stages of the disease. Surgery-associated inflammation exacerbates these diseases, and the inflammatory response may further complicate the postoperative period. Simple blood cell counts and indices may be beneficial for evaluating cardiac surgery outcomes and cardiovascular disorder prognosis in infants and children. This review summarizes current knowledge on inflammatory markers in pediatric cardiovascular diseases and surgery.

**Key words:** surgery, inflammation, congenital heart disease, neutrophil-to-lymphocyte ratio

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# Introduction

Inflammation is a well-known causative factor in cardiovascular disorders in adults, and several studies have underlined the significant contribution of inflammation in the occurrence and progression of coronary artery disease.[1,2] Atherosclerotic plaque formation and enlargement are related to neutrophil and macrophage infiltration, pro-inflammatory cytokines and chemokines, lipid accumulation in the core, and thinning of the fibrous cap.[3,4] Moreover, inflammatory responses were reported in heart failure[5–7] and worsened with its advancement and complications, such as pulmonary hypertension.[8] Furthermore, the assessment of inflammatory activation demonstrated its value in the pediatric population.[9]

The assessment of cardiovascular disease prognosis and procedural outcomes highlighted several parameters and biomarkers.[10–15] Many of them, including interleukins, microribonucleic acids (microRNAs), tumor necrosis factor alpha (TNF-α), and platelet-leukocyte aggregates,[16,17] have high prognostic value. However, using such markers in clinical practice is not possible, as a profound analysis of inflammatory phenomena is challenging and not cost-effective.[18,19] Hence, simpler methods, such as whole blood analysis, were introduced and described as sufficient for demonstrating complex changes in the inflammatory response to cardiovascular disorders and predicting adverse outcomes or diminished survival. The results of whole blood analysis are readily available, and the method is repeatable, which gives it an advantage over other methods.

# Objectives

The objective of this review was to summarize current knowledge on inflammatory markers in pediatric cardiovascular diseases. The contemporary studies concerning the assessment of inflammatory activation using simple blood count analysis were collected and analyzed.

# Outline of the issue

The neutrophil-to-lymphocyte ratio (NLR) is the most commonly described biomarker that represents the relationship between neutrophils and lymphocytes in the blood. Other indices include the monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR). More complex indices, such as the systemic inflammatory index (SII), systemic inflammatory response index (SIRI) and aggregate index of systemic inflammation (AISI), combine even more morphological elements of blood.

Leukocytes are the primary cellular mediators of inflammation, and changes in their subpopulation counts may reflect the immune response to several inflammation-associated phenomena. Neutrophils are a marker of ongoing nonspecific inflammation, while lymphocytes signify the immune regulatory response.[20] At the same time, lymphocyte count indicates physiological stress but is inversely proportional to inflammation.[21] The NLR combines 2 leukocyte subtypes and may have high predictive value in several cardiovascular and noncardiac disorders.

Platelets are involved in inflammatory processes and secrete thromboxane, chemokines, proinflammatory cytokines, and growth factors, which play roles in vascular inflammation and thrombosis.[21] Mean platelet volume (MPV) is a marker of platelet activation associated with active rheumatic arthritis, bowel disease[20] and revascularization processes.[22]

# Inflammatory markers in cardiac disorders

Hematological count and index derangements, functioning as predictors of clinical outcomes, are presented in Table 1.

## Cardiac arrhythmias

Cardiac arrhythmias usually occur in children as paroxysmal supraventricular tachycardia (SVT).[23] There are 2 peaks of its incidence – the 1st in infancy and the 2nd between 8 and 12 years of age.[24] Some hypotheses explain the etiology of SVT with an inflammatory state as its trigger. The fact that viral infections in children, especially those promoting myocarditis, are commonly related to the prevalence of arrhythmias supports these hypotheses.[25] Furthermore, Aydin et al. emphasised that patients with SVT have higher NLR values.[26]

Frequent premature ventricular beats may be associated with chronic myocardial injury that is related to many inflammatory response factors.[27] Therefore, an early prediction of a higher risk of myocardial damage is crucial. Among the available laboratory tests, troponin and creatine kinase are established markers of myocardial injury in acute and chronic heart failure. Recently, leukocyte count and NLR correlated positively with troponin and perioperative damage.[27] Preoperative neutrophil count has been proposed as a predictive factor for postoperative atrioventricular block in pediatric cardiac surgery.[28]

## Kawasaki disease

Kawasaki disease is an acute febrile disorder characterized by systemic inflammation and vasculitis.[29,30] Characteristic hallmarks of the disease include coronary artery lesions (CALs), coronary dilatation, aneurysm, stenosis, myocardial infarction, and valvular lesions. Chang et al. underlined the critical role of simple markers in preventing CAL development by identifying at-risk children.[29] They proposed 4 independent risk factors for predicting CALs,

Table 1. Hematological count and index derangements as predictors of clinical outcomes

| Parameters | Outcome | Reference |
|---|---|---|
| Neutrophilia | longer hospital stay<br>need for postoperative mechanical circulatory support | 65 |
| Lymphopenia | longer hospital stay<br>longer mechanical ventilation time<br>postoperative nitric oxide use<br>increased mortality<br>postoperative sepsis<br>increased susceptibility to infections<br>postoperative effusion and edema<br>heart failure | 43, 44, 64, 65 |
| Thrombocytopenia | longer hospital stay<br>postoperative sepsis | 64 |
| NLR | longer mechanical ventilation time<br>increased length of ICU stay<br>increased hospital stay<br>increased mortality<br>higher vasoactive–inotrope score<br>low cardiac output syndrome<br>pleural effusion, chylothorax<br>Kawasaki disease – coronary artery lesions<br>IVIG resistance in Kawasaki disease<br>Kawasaki disease diagnostics in uncertain cases<br>necrotizing enterocolitis in PDA children<br>arterial hypertension<br>heart failure<br>acute kidney disease<br>pulmonary hypertension<br>neonatal sepsis exclusion<br>progression in pulmonary hypertension related to congenital heart defects<br>cyanotic congenital heart disease<br>Fontan patients, PLE<br>coronary artery lesions in Kawasaki disease<br>supraventricular tachyarrhythmia<br>frequent ventricular premature beats<br>lymphatic malformations and complications after Fontan surgery<br>ECMO use | 21, 27, 29, 30, 31, 32, 33, 41, 44, 45, 46, 55, 56, 57, 59, 60, 62, 63, 71 |
| Platelet count | Kawasaki disease – coronary artery aneurysms<br>acute rheumatic carditis<br>arterial hypertension | 20, 30, 41 |
| PLR | Fontan patients<br>neonatal sepsis<br>ECMO use<br>IVIG resistance in Kawasaki disease<br>arterial hypertension | 21, 41 |
| MLR | necrotizing enterocolitis in PDA children<br>severity of valvular involvement in acute rheumatic carditis | 33, 35] |

ECMO – extracorporeal membrane oxygenation; ICU – intensive care unit; IVIG – intravenous immunoglobulin; MLR – monocyte-to-lymphocyte ratio; NLR – neutrophil-to-lymphocyte ratio; PDA – patent ductus arteriosus; PLE – protein-losing enteropathy; PLR – platelet-to-lymphocyte ratio.

namely C-reactive protein (CRP) >103 mg/L, NLR > 3.5, male gender, and intravenous immunoglobulin (IVIG) resistance. High-dose IVIG effectively resolves inflammation and reduces the risk of CALs. However, 10% of patients are resistant to this therapy. Kanai et al. showed high NLR and PLR to be strong predictors of IVIG resistance.[31] Moreover, Smorczewska-Kiljan et al. showed that high platelet count is one of the most important predictors of coronary artery aneurysm occurrence.[30] In addition, Yan et al. proposed NLR and CRP as markers deserving special attention in patients suspected of Kawasaki disease who do not initially meet the diagnostic criteria.[32]

## Necrotizing enterocolitis and congenital heart disease

Infants diagnosed with necrotizing enterocolitis with patent ductus arteriosus (PDA) and congenital heart defects had significantly higher NLR and MLR than children without cardiac abnormalities.[33] Higher NLR and MLR resulted in very intense local inflammation involving infiltration of the intestines by neutrophils and circulating monocytes. The monocytes differentiated into macrophages in situ in infants with impaired intestinal perfusion and systemic circulation caused by cardiac anomalies.

## Acute rheumatic disease

Inflammation is fundamentally involved in the pathogenesis of acute rheumatic disease. The infiltration of several inflammatory cells into the myocardium and endocardium of valves is observed, including neutrophils, macrophages and subpopulations of lymphocytes. Neutrophils and macrophages influence atrial remodeling, and the actions of macrophages include the generation of oxygen free radicals.[34] The healing process results in fibrosis and changes in the vasculature and dimensions of atrial cells. Increased NLR, PLR and MLR, and decreased MPV are associated with the severity of valvular involvement in patients with acute rheumatic carditis (ARC).[20,35] In addition, NLR correlated with leukocyte count, erythrocyte sedimentation rate (ESR) and CRP.[20,35] In other studies, ESR, CRP and red blood cell distribution width (RDW) were higher in patients with ARC.[36–38] Moreover, an increase in platelet count is relevant and reflects the production of new reactive platelets through cytokine stimulation.[20] Interleukin 6 (IL-6) is a platelet effector, and its serum levels increase significantly in episodes of acute rheumatic fever.[39] In the presence of IL-6, inflammatory processes are activated and generate thrombogenicity.[40]

## Arterial hypertension

Arterial hypertension is an increasing problem in children due to obesity, sedentary lifestyle and excessive

salt intake.[41] Subclinical inflammation may contribute to the pathogenesis of primary hypertension. Skrzypczyk et al. analyzed simple blood morphology and found higher NLR, PLR and platelet counts in hypertensive patients than in healthy subjects, and NLR correlated with arterial stiffness.[41] Based on the different diagnostic methods used in the study, the authors concluded that the intramural inflammatory process affects multiple arteries in primary hypertension in children.

### Heart failure

Heart failure in children is a rare but serious complication of several cardiological disorders and may lead to death or the need for a heart transplant.[42] Several clinical, echocardiographic and laboratory parameters characterize its advance and severity. Although brain natriuretic peptide (BNP) and N-terminal BNP are commonly analyzed, simple blood morphology predicted worse survival or the need for a heart transplant.[43]

Lymphocytopenia is multifactorial and may reflect the degree of sympathetic activation.[43] Araújo et al. reported a worse prognosis and a higher risk of death or cardiac transplant in children with dilated cardiomyopathy and higher NLR (>5.2) and lymphopenia (<1000/μL) values.[44] Gursoy et al. correlated inflammatory markers, including NLR, with the progression of pulmonary hypertension related to congenital heart defects.[45] In addition, mean pulmonary artery pressure and NLR significantly increased during the postoperative period in patients with a pulmonary hypertensive crisis.

## Surgery in cardiac disorders in children

The surgery itself is related to a certain degree of inflammatory response. However, it can be unpredictably exaggerated in some congenital heart diseases.

### Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) use is usually associated with a systemic inflammatory response, a nonspecific inflammatory syndrome that may be similar to infection and lead to the unnecessary use of broad-spectrum antibiotics. The contact of blood with the surface of the CPB circuit results in a cascade of pro-inflammatory cytokines, complement activation, blood coagulation, and an increase in leukocytes, platelets and vascular endothelial cells. The neutrophils are essential components of the systemic inflammatory response to tissue and reperfusion injury.[46] Furthermore, ischemia–reperfusion injury and endotoxemia due to hypothermic perfusion lead to endothelial injury and the release of reactive oxygen species. Neither leukocytosis, nor neutrophil count, nor CRP can discriminate between infection and a nonspecific inflammatory syndrome,[47] as these markers reflect the inflammatory process. Fortunately, the biomarker procalcitonin enables differentiation between bacterial infection and noninfectious systemic inflammatory responses[48,49] after surgery with CPB. Indeed, an increase in procalcitonin above a proposed cutoff value of 2 ng/mL should lead to the commencement of antibiotic therapy.[48] However, the cutoff points are different on consecutive days due to the evolution of procalcitonin over time, and increase rates differ between infected and noninfected patients. Indeed, Haponiuk et al. pointed out the importance of changes and trends in values in the early postoperative hours rather than concentrating on single values of inflammatory markers.[50] Deviation from the typical kinetics of leukocyte count, CRP and procalcitonin should pique the attention of physicians.

Manuel et al. observed that children with cyanotic congenital heart diseases exhibited higher preoperative NLR than acyanotic patients.[51] Therefore, the authors assumed that cyanosis was related to a higher degree of preoperative inflammation. Similarly, more sophisticated methods, including the analysis of interleukins, showed their higher levels in cyanotic children.[52] A lower perioperative anti-inflammatory cytokine balance may contribute to postoperative mortality.[53] There are still some gaps in the literature and questions, such as why some patients with the same disease have a higher NLR than others, which extends to other biomarkers of the same lineage. Manuel et al. recently proposed a probable mechanism to explain this increase and the association with unfavorable outcomes in pediatric cardiac surgery patients (Fig. 1).[54] Cyanotic patients are continuously exposed to myocardial hypoxia, promoting myocardial stress, which causes a permanent inflammatory response characterized by high oxidative stress, reactive oxygen species and the recruitment of neutrophils.[54] The exacerbation of these phenomena may negatively influence postoperative outcomes, especially with CPB use.[51,55] The described mechanism causes cellular apoptosis and tissue injury.[54] In turn, increased blood flow to the lungs induces pulmonary vascular stress, vascular remodeling and endothelial dysfunction, followed by pulmonary hypertension and preceded by chronic inflammatory processes in the pulmonary tissue of acyanotic patients. Similarly, surgery under CPB is associated with an exacerbated inflammatory response and a negative impact on surgery outcomes.

Moosmann et al. recommended calculating NLR and PLR for univentricular patients during the course of total cavopulmonary connection and follow-up.[56] In their study, NLR and PLR correlated with the degree of lymphatic malformations, which are associated with early complications after Fontan surgery and Fontan failure, and may also occur after Glenn surgery despite a lack of clinical manifestation. The authors suggested that patients with higher

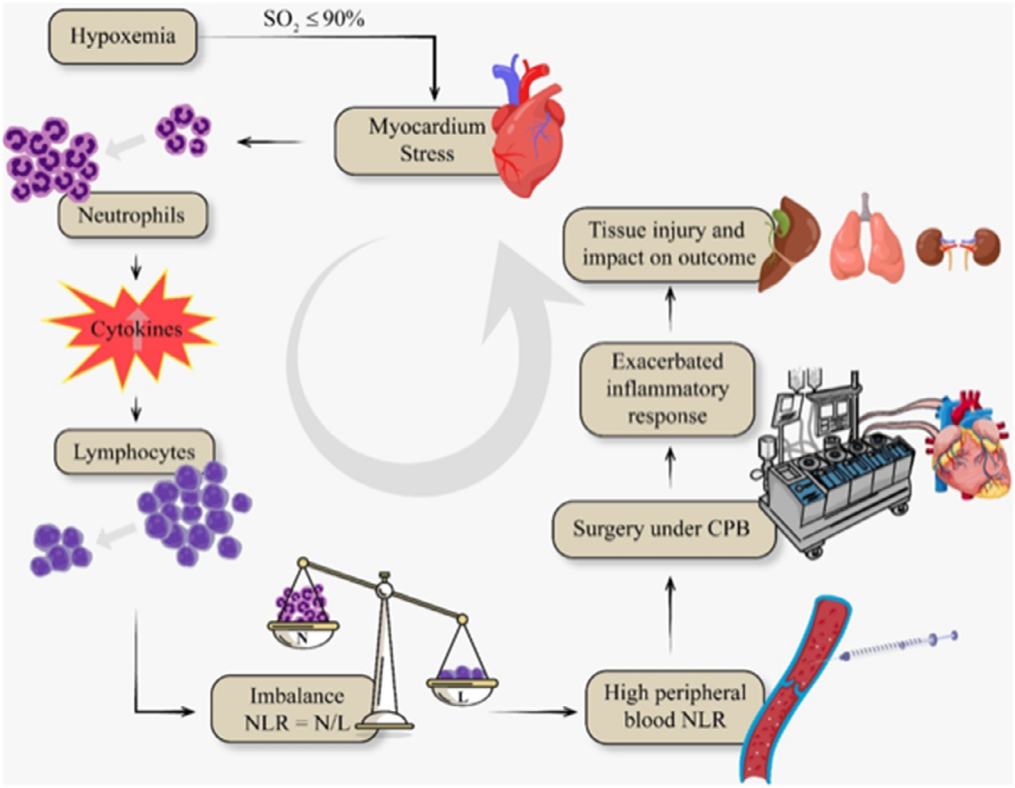


**Fig. 1.** Probable mechanism of high neutrophil-to-lymphocyte ratio (NLR) in cyanotic patients presenting with hypoxemia and myocardial stress linked with exaggerated inflammatory response and negative impact on postoperative outcomes. High pulmonary flow with pulmonary vascular stress seems to represent a comparable factor in acyanotic patients (see interpretation in the text). Adapted and modified, with permission, from Manuel V, Miana LA, Jatene MB. Neutrophil-lymphocyte ratio in congenital heart surgery: What is known and what is new? *World J Pediatr Congenit Heart Surg*. 2022;13(2):208–216. doi:10.1177/21501351211064143 [54]

CPB – cardiopulmonary bypass.

values require closer monitoring and evaluation for signs of Fontan complications, such as lymphatic malformations and protein-losing enteropathy (PLE). Lymphopenia in Fontan patients is associated with portal hypertension, PLE and lymphatic malformations. Lymphangiogenesis occurs during inflammation due to mediators released from inflammatory cells, including neutrophils. An increase in neutrophil and a decrease in lymphocyte count were described in Fontan patients.[56]

## Postoperative complications

Studies performed in acyanotic patients with co-existing pulmonary hypertension demonstrated a significant prognostic value of NLR and SII on a higher vasoactive–inotrope score (VIS), prolonged mechanical ventilation time, extended time in the intensive care unit (ICU), and the length of hospital stay.[57–59] The aforementioned inflammatory markers have been introduced in the assessment of prognosis in pediatric cardiac surgery.[46,54,60] In a study by Savluk et al., NLR varied between children with failed and successful extubation (following prolonged intubation).[61] Moreover, a high preoperative NLR was associated with acute kidney injury after tetralogy of Fallot repair.[62] Therefore, NLR may be used to identify patients at risk of postoperative complications.

Elevated preoperative NLR was associated with higher mortality in hypoplastic left heart syndrome patients.[63] Cabrera et al. reported preoperative lymphopenia as a predictor of adverse outcomes such as longer postoperative length of stay, mechanical ventilation, postoperative nitric oxide use, and mortality.[64] Other authors made similar observations.[65,66] Perioperative complications associated with abnormal blood cell counts include an increased risk of perioperative mortality (lymphopenia), longer postoperative length of stay (lymphopenia, thrombocytopenia and neutrophilia), increased occurrence of postoperative sepsis (lymphopenia and thrombocytopenia), and the need for postoperative mechanical circulatory support (neutrophilia). A decreased absolute lymphocyte count secondary to acquired or inherited deficiency resulted in an increased susceptibility to infections.[64] The causes are multifactorial, with increased destruction or loss secondary to sequestration and decreased production. The authors explained their results by the presence of pulmonary lymphatic dysplasia and lymphangiectasia. These lesions may be associated with cardiac disorders with pulmonary venous obstruction, such as hypoplastic left heart syndrome or total anomalous pulmonary venous return.

Postoperative pleural effusion is a common complication after CPB during cardiac surgery.[67] Prolonged accumulation may lead to the deterioration of postoperative recovery, extended hospital stay and a higher mortality rate due to malnutrition.[68] Yakuwa et al. found no significant differences in baseline characteristics, while NLR change had prognostic value in predicting prolonged pleural effusion, including chylothorax.[68] Besides several factors such as increased right-sided hydrostatic pressure, decreased collagen osmolarity, slow bleeding, warfarin use, longer

CPB time, and postoperative infection, enhanced permeability due to systemic inflammation is an important etiological factor.[68] Gupta-Malhotra et al. showed a weak correlation between pleural fluid volume and IL-6, and in their further study,[69] they demonstrated an association between total duration and the amount of pleural effusion and troponin.[67] Bocsi et al. recommended the evaluation of preoperative neutrophil count and percentage, as well as a decreased percentage of lymphocytes, as suitable for identifying patients at risk of postoperative effusions and edema.[70] Crucially, NLR includes both blood elements in its calculation.

## Extracorporeal membrane oxygenation

The use of extracorporeal membrane oxygenation (ECMO) in the postoperative period may be critical for pediatric patients with low output and pulmonary difficulties[21] to facilitate pulmonary or cardiac recovery. The therapeutic outcomes vary due to several factors, complications and comorbidities. Inflammation, infection and heart failure are common problems. Considering the interaction between blood flow and the foreign surfaces of ECMO, changes in the severity of inflammatory indices may show the degree of inflammation and provide information concerning prognosis. In a study by Arslanoğlu et al., NLR and PLR significantly increased compared to the preoperative period in patients who received ECMO, but its association with mortality was uncertain.[21] Iliopoulos et al. demonstrated a significant relationship between preoperative NLR and low cardiac output syndrome after cardiac surgery in children, particularly during the first 12 h.[71]

## Limitations

The limitation of the evaluated inflammatory indices casts doubt over their normal ranges in children, especially if multiple pathological conditions and comorbidities exist.

# Conclusions

The greatest advantages of using NLR and other indices are their accessibility in clinical practice and low evaluation costs. Several of the aforementioned reports highlighted their beneficial role in evaluating infants and children in terms of cardiac surgery outcomes and the prognosis of several cardiological disorders.

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