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ARTICLE

Prognostic Value of the Perioperative Neutrophil–Lymphocyte Ratio for Adverse Outcomes in Pediatric Congenital Heart Surgery: A Retrospective Cohort Study

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ABSTRACT: Background: The neutrophil–lymphocyte ratio (NLR) is a simple, cost-effective marker of systemic inflammation. This study aims to evaluate the association between perioperative NLR and postoperative outcomes in pediatric patients undergoing congenital heart surgery with cardiopulmonary bypass (CPB). **Methods:** We retrospectively reviewed 70 patients under 18 years of age who underwent surgery between 2018 and 2023. NLR was measured preoperatively and on postoperative days (POD) 0, 1, 2, 3, and 6. Receiver operating characteristic analysis identified optimal cutoffs, and associations with postoperative outcomes were assessed. **Results:** The preoperative NLR cutoff of 1.14 (AUC = 0.75) was associated with prolonged mechanical ventilation (>72 h) (p = 0.02), extended intensive care unit (ICU) stay (p = 0.004), and longer hospital stay (p = 0.006). NLR values on POD3 (AUC = 0.74) and POD6 (AUC = 0.78) also demonstrated strong predictive ability for these outcomes. **Conclusions:** Elevated perioperative NLR—particularly preoperative values ≥1.14—is associated with prolonged mechanical ventilation, longer ICU admission, and extended hospitalization in pediatric congenital heart surgery. NLR may serve as a practical biomarker for early risk stratification and postoperative management.

KEYWORDS: Congenital heart defects; neutrophil–lymphocyte ratio; inflammation; cardiopulmonary bypass

1 Introduction

Congenital heart diseases (CHDs) are cardiac anomalies that develop during the intrauterine formation of the heart. They include both major cardiovascular abnormalities and defects in intracardiac structures. CHDs are the leading cause of mortality in childhood [1].

Congenital heart surgery involves a broad spectrum of complexities and is notably associated with mortality, particularly in intricate cases [2]. These risks are often due to anatomical variations, prolonged operation times, and the experience level of the surgical center [3].

Although cardiopulmonary bypass (CPB) has made recovery possible for pediatric patients with CHD, the inflammatory response induced by CPB remains a significant contributor to in-hospital mortality [4].

Various studies have investigated the inflammatory effects caused by CPB on the human body. CPB induces an inflammatory response through the activation of neutrophils and the complement system, as well as endothelial adhesion. Consequently, pro-inflammatory cytokines are released, increasing capillary endothelial permeability and leading to capillary leakage. Uncontrolled tissue damage from multi-organ dysfunction can severely worsen postoperative outcomes.

Numerous biomarkers have been evaluated as prognostic indicators of uncontrolled inflammation. These include interleukins (ILs), suppression of tumorigenicity 2, insulin-like growth factor-binding proteins 1 and 7, amino-terminal propeptide of type III procollagen, delta-like 1 homolog, fatty acid-binding protein 4, microRNA, growth differentiation factor 15, N-terminus pro-B-type natriuretic peptide (NT-proBNP), galectin-3, matrix metalloproteinase 2, tumor necrosis factor-alpha, and von Willebrand factor [5].

The NLR has been established as a novel biomarker to assess inflammation levels in various disorders. Previous studies indicate that an increased preoperative NLR in pediatric patients undergoing open heart surgery is an independent risk factor for impaired cardiac function in the early postoperative period and is associated with both short-term and long-term mortality. While the NLR has been considered a relevant marker for measuring inflammation and clinical outcomes, evidence within the congenital heart surgery population remains limited [5]. The NLR offers several advantages over other inflammatory markers in the perioperative setting. It can be calculated easily from a standard complete blood count, which is routinely performed in all surgical patients, eliminating the need for additional, costly laboratory tests. The NLR reflects the balance between neutrophil-driven innate immune activation and lymphocyte-mediated adaptive immune regulation, thereby providing an integrated measure of systemic inflammation. In contrast, many cytokines and novel biomarkers—such as ILs, NT-proBNP, or galectin-3—require specialized assays, are more expensive, and are not universally available. The NLR can be measured at multiple perioperative time points without extra cost, allowing dynamic monitoring of the inflammatory trajectory. These practical, economic, and pathophysiological advantages make NLR an attractive candidate for perioperative risk assessment in pediatric congenital heart surgery. Several recent studies have begun to explore the prognostic utility of NLR in pediatric cardiac surgery. Serra et al. [6] reported that NLR measured on postoperative day (POD) 3 had strong predictive performance for adverse outcomes in infants undergoing cardiac surgery, with an optimal cutoff of 2.05. Manuel et al. [5] evaluated preoperative NLR in children undergoing congenital heart defect repairs and identified cutoff thresholds ranging from 0.80 to >2 associated with prolonged mechanical ventilation, intensive care unit (ICU) length of stay (LOS), and long-term mortality, particularly in cyanotic subgroups. More recently, Raharjo et al. [7] demonstrated that NLR in acyanotic pediatric CHD patients undergoing open heart surgery was significantly predictive of poor postoperative outcomes. Together, these findings support the potential role of NLR as an accessible inflammatory biomarker in pediatric congenital heart surgery—a summary that frames and motivates our current focus on both preoperative and perioperative NLR values.

This study aimed to examine the predictive value of the perioperative NLR in forecasting unfavorable clinical outcomes after congenital heart surgery in pediatric patients. Through the examination of NLR values recorded pre- and post-surgery, we aimed to determine definitive cutoff thresholds linked to prolonged mechanical ventilatory support, extended ICU and hospital LOS, and other significant postoperative sequelae. This work sought to enhance the sparse literature on

the significance of NLR as an economical, accessible biomarker for risk classification in congenital heart operations conducted under CPB.

2 Methods

2.1 Study Design

This retrospective study included 70 patients <18 years of age who underwent surgery for CHDs between November 2018 and June 2023 at Muğla Sıtkı Koçman University Medical Faculty, Cardiovascular Surgery Department. This study was reviewed and approved by Muğla Sıtkı Koçman University ethical board (approval number: 13/I, 15 June 2023). The study was conducted in accordance with the principles of the Declaration of Helsinki. Patient's data were collected retrospectively from the institutional database, hence informed consent was waived.

The inclusion criterion was treatment by congenital heart surgery with CPB for cyanotic or acyanotic heart diseases. The exclusion criteria were palliative procedures without CPB and preoperative cardiac arrest or infection.

2.2 Clinical Variables

Venous blood samples were obtained and sent to the laboratory preoperatively within 48 h, upon admission to ICU, 1 hour after the ICU admission (on the day of surgery) and each morning throughout the ICU stay. The NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count from the same blood test. The NLR measured 1 day prior to surgery was defined as the baseline NLR, with subsequent measurements taken on POD 0 (the day of surgery) and on POD 1, 2, 3, and 6.

The primary postoperative outcome was a composite poor outcome, defined as the occurrence of one or more of the following events within 30 days after surgery: mechanical ventilation >72 h, peritoneal dialysis, temporary or permanent pacemaker implantation, pulmonary infection, postoperative reintubation, reoperation for any cardiac complication, extracorporeal membrane oxygenation (ECMO) support, cardiopulmonary resuscitation (CPR), mortality within 30 days, or retention of an open sternum postoperatively. This composite definition is consistent with previously published pediatric congenital heart surgery studies and allows for standardized comparison across studies. Patients without any of these events were classified as having a good outcome.

For the primary analysis, the preoperative NLR—measured from the last blood sample obtained within 24 h before surgery—was used to evaluate its association with the composite poor outcome. Additional analyses were performed for each perioperative NLR measurement, including values obtained on the day of surgery (POD 0) and on POD's 1, 2, 3, and 6. Each time point was analyzed separately using receiver operating characteristic (ROC) curve analysis to determine its optimal cutoff value for predicting poor outcomes. Multiple NLR measurements were therefore treated as distinct variables in independent models rather than as repeated measures in a longitudinal analysis. The predictive performance of each time point was compared by examining the corresponding area under the curve (AUC), sensitivity, and specificity values.

2.3 Data Collection

Clinical information was retrospectively recorded, including patient demographics (sex, age, and weight). Intraoperative variables were the type of surgical procedure, CPB time, and aortic

cross-clamp (ACC) time. Postoperative variables included the duration of mechanical ventilation, ICU LOS, hospital LOS, need for reintubation, ECMO support, peritoneal dialysis, CPR, and mortality. These postoperative variables also served as the study's endpoints.

2.4 Complete Blood Count

Blood tests were conducted during the preoperative period and on POD's 0, 1, 2, 3, and 6 as part of routine monitoring. Preoperative peripheral venous blood samples were collected and dispatched to the hospital laboratory for complete blood count evaluation. Blood samples were drawn into ethylenediaminetetraacetic acid tubes and analyzed using a Sysmex XN1000 hematology analyzer (Sysmex, Kobe, Japan) for complete blood count. Postoperative venous blood samples were collected postoperative 1st hour on POD 0 (the day of surgery) and early in the morning on POD's 1, 2, 3, and 6. The NLR was calculated from the complete blood count test results as follows: NLR = absolute neutrophil count ($\times 10^9$/L) ÷ absolute lymphocyte count ($\times 10^9$/L).

Data completeness for NLR measurements was as follows: preoperative (100%, n = 70), POD 0 (100%, n = 70), POD 1 (100%, n = 70), POD 2 (100%, n = 70), POD 3 (100%, n = 70), and POD 6 (92.9%, n = 65). Missing values on POD 6 were due to patient discharge or death before the scheduled blood draw. No statistical imputation was applied; each time point was analyzed based on available data only.

2.5 Statistical Analysis

Mean and standard deviation, as well as median (Q1–Q3) values, were reported for numerical variables, while frequency and percentage values were provided for categorical variables. The chi-square test or Fisher's exact test was used to analyze categorical variables. Welch's *t*-test was applied for numerical variables. Spearman correlation coefficients were calculated to assess relationships between numerical variables. For the assessment of predictive ability, ROC analysis was performed to identify the optimal NLR cutoff value for predicting the composite poor outcome. The AUC was calculated. The derived cutoff value was subsequently used to stratify the cohort into two groups (NLR $\geq$ 1.14 and <1.14), and postoperative outcomes were compared accordingly. The optimal preoperative NLR cutoff for predicting the composite poor outcome was determined using ROC curve analysis in our study cohort. The cutoff value of 1.14 was identified as the point maximizing the sum of sensitivity and specificity. This value was used to stratify patients into two groups (NLR $\geq$ 1.14 and NLR < 1.14) for comparative analyses. In addition, a binary logistic regression model was constructed to evaluate whether preoperative NLR remained an independent predictor of the composite poor outcome after adjusting for selected covariates. All analyses were conducted using R 4.4.1 (R Core Team, 2024). For ROC analyses, we calculated and reported AUC with 95% confidence intervals, sensitivity and specifity. For correlation analyses, only preoperative NLR was used, in line with the primary aim of assessing its value as an early preoperative biomarker. A *p*-value of <0.05 was considered statistically significant.

3 Results

A ROC analysis was initially conducted to identify the optimal preoperative NLR cutoff value for predicting poor outcomes. The preoperative NLR yielded a cutoff value of 1.14, with an AUC of 0.75 (95% CI: 0.64–0.86), a sensitivity of 0.74, and specificity of 0.69. Based on this cutoff, patients

were stratified into two groups: NLR $\geq$ 1.14 and NLR < 1.14. Receiver operating characteristic analyses were also performed for postoperative NLR values (POD's 0, 1, 2, 3, and 6). Among these, NLR levels measured on POD 6 demonstrated the highest predictive accuracy, with an AUC of 0.78 (95% CI: 0.67–0.89), sensitivity of 0.83, and specificity of 0.66 (Table 1). Postoperative day 3 also showed high predictive capacity (AUC = 0.74). These findings support the prognostic value of perioperative NLR trends for adverse postoperative outcomes.

NLR data were complete for all patients at preoperative and early postoperative time points. On POD 6, values were available for 65 patients; missing data were due to early discharge or mortality prior to this time point.

Table 1: Receiver operating characteristic analysis results for predicting poor outcomes using NLR values measured at different perioperative time points*.

Variable	Cut Point	Accuracy	Sensitivity	Specificity	AUC (95% CI)
Preoperative day	1.14	0.71	0.74	0.69	0.75 (0.64–0.86)
POD 0		0.5	0.31	0.69	0.46 (0.34–0.60)
POD 1		0.57	0.26	0.89	0.49 (0.36–0.64)
POD 2	7.23	0.64	0.43	0.86	0.66 (0.53–0.78)
POD 3	4.16	0.69	0.63	0.74	0.74 (0.61–0.85)
POD 6	2.05	0.74	0.83	0.66	0.78 (0.67–0.89)

*Greater NLR value indicates poorer outcome. Poor outcome was defined as $\geq$1 of the following within 30 days postoperatively: mechanical ventilation >72 h, peritoneal dialysis, temporary/permanent pacemaker implantation, pulmonary infection, reintubation, reoperation for cardiac complication, ECMO support, CPR, mortality, or open sternum retention. Abbreviation: AUC: Area under the curve; POD: Postoperative day, NLR: Neutrophil-lymphocyte ratio, ECMO: Extracorporeal membrane oxygenation; CPR: Cardiopulmonary resusitation.

Based on the preoperative NLR cutoff of 1.14, patients were stratified into two groups (NLR $\geq$ 1.14 and NLR < 1.14) for comparison of baseline characteristics and postoperative outcomes. Comparative analysis between these two groups revealed that patients in the NLR $\geq$ 1.14 group had significantly longer durations of mechanical ventilation (p = 0.02), ICU LOS (p = 0.004), and hospital LOS (p = 0.006). Additionally, the proportion of patients with poor outcomes was markedly higher in the high-NLR group (p < 0.001) (Table 2). When stratified by outcome, patients in the poor outcome group demonstrated higher NLR values at all perioperative time points compared to the good outcome group. Median preoperative NLR was 1.73 [1.11–3.53] in the poor outcome group versus 0.80 [0.50–1.46] in the good outcome group. The difference persisted through POD 6, where values remained elevated in the poor outcome group (4.47 [2.49–6.20] vs. 1.68 [1.13–2.70]). These findings suggest that both baseline inflammatory status and sustained postoperative elevation of NLR are associated with adverse outcomes.

Tables 3 and 4 summarize the spectrum of congenital heart defects observed in the poor and good outcome groups, respectively. In the poor outcome group, complex and high-risk lesions such as tetralogy of Fallot (TOF) with absent pulmonary valve syndrome (APVS), transposition of the great arteries (TGA) with ventricular septal defect (VSD) and pulmonary stenosis (PS), unbalanced atrioventricular septal defect (AVSD), and truncus arteriosus were more prevalent. These conditions often required multi-stage or technically demanding repairs. In contrast, the good outcome group predominantly included simpler lesions, such as isolated VSD, atrial septal defect (ASD), and partial anomalous pulmonary venous return (PAPVR), which typically involve shorter CPB times and lower perioperative risk. This distribution suggests that the anatomical complexity of the congenital heart defect may contribute to the likelihood of adverse postoperative outcomes.

Table 2: Baseline characteristics of patients based of cut-off value of NLR.

	NLR $\geq$ 1.14, n = 37	NLR < 1.14, n = 33	*p*
Age (month)	7.50 (1.00–48.00)	17.00 (7.00–42.00)	0.6
Gender (male)	18 (48.65%)	12 (36.36%)	0.3
Poor outcome	12.93 $\pm$ 3.38	14.33 $\pm$ 3.13	0.077
Good outcome	11(29.73%)	24(72.73%)	<0.001
Weight (kg)	10.07 $\pm$ 8.99	10.04 $\pm$ 6.12	>0.9
BMI	12.93 $\pm$ 3.38	14.33 $\pm$ 3.13	0.077
CPB duration (minute)	171.43 $\pm$ 83.93	150.88 $\pm$ 74.75	0.3
ACC duration (minute)	110.16 $\pm$ 47.40	97.12 $\pm$ 58.97	0.3
Duration of intubation (days)	2.00 (0.38–7.00)	0.75 (0.42–2.00)	0.02
Re-intubation	3 (8.11%)	2 (6.06%)	>0.9
ECMO	1 (2.70%)	2 (6.06%)	0.6
Peritoneal dialysis	8 (21.62%)	4 (12.12%)	0.3
ICU LOS	8.00 (5.00–15.00)	4.00 (3.00–7.00)	0.004
Hospital LOS	12.00 (8.00–19.00)	8.00 (7.00–10.00)	0.006
CPR	10 (27.03%)	4 (12.12%)	0.12
Exitus	10 (27.03%)	4 (12.12%)	0.12

Abbreviations: NLR: Neutrophil–lymphocyte ratio; BMI: Body mass index; CPB: Cardio-pulmonary bypass; ACC: Aortic clamping time; ECMO: Extracorporeal membrane oxygenator; ICU: Intensive care unit; LOS: Length of stay; CPR: Cardiopulmonary resuscitation.

Table 3: Congenital heart pathologies which were presented in poor outcome group.

Congenital Heart Defect	Operation	Number (n = 37)
VSD	VSD repair	1
VSD-p. banding	Debanding-VSD repair	1
VSD-MI	VSD repair-mitral annuloplasty	1
VSD-tricuspid chordal straddling	VSD repair-chordal transfer	1
VSD-PA	Rastelli conduit revision	1
VSD-PA-previously separated DAA and previously performed m BT shunt	Rastelli operation-shunt division	1
VSD-PA-m BT shunt	Central shunt-RPA & LPA augmentation	1
PA-IVS	Central shunt-RVOT augmentation-atrial septectomy	2
DORV-unbalanced ventricles	P. banding-atrial septectomy	1
DORV-m BT shunt	Rastelli operation—shunt division	1
DORV-Rastelli operation-subaortic ridge	Subaortic ridge resection-aortic valve repair	1
DILV-Glenn shunt	Fontan operation	1
TGA	Jatene operation	2
TGA-VSD-PS-m BT shunt	Jatene operation-VSD repair-shunt division	1
TGA-VSD	Jatene operation-VSD repair	2
TOF	Total correction	1
TOF-APVS	TOF correction-pulmonary conduit interposition	3
TOF-PA	m BT shunt	3
AVSD	Total correction	2
AVSD-PS-cor triatriatum sinister	Total correction	1
AVSD-MS-PS	Total correction	1
AVSD-p. banding	Debanding-AVSD repair	1
Corrected AVSD-MI	MVR	1
Unbalanced AVSD-Glenn shunt	Fontan operation	1
Truncus arteriosus	Rastelli operation	1
Truncus arteriosus-Rastelli	Rastelli conduit revision	1
Aortic arch hypoplasia	Arch repair	1
Aortic arch hypoplasia-VSD	Arch and VSD repair	1
IAA-VSD	Total correction	1

Abbreviations: VSD: Ventricular septal defect; P. banding: Pulmonary banding; MI: Mitral insufficiency; PA: Pulmonary atresia; DAA: Double aortic arch; m BT shunt: Modified Blalock–Taussig shunt; IVS: Intact ventricular septum; RPA: Right pulmonary artery; LPA: Left pulmonary artery; RVOT: Right ventricle outflow tract; DORV: Double outlet right ventricle; DILV: Double inlet left ventricle; TGA: Transposition of great arteries; PS: Pulmonary stenosis; TOF: Tetralogy of Fallot; APVS: Absent pulmonary valve syndrome; AVSD: Atrioventricular septal defect; MS: Mitral stenosis; MVR: Mitral valve replacement; IAA: Interrupted aortic arch.

Table 4: Congenital heart pathologies which were presented in good outcome group.

Congenital Heart Defect	Operation	Number (n = 33)
ASD	ASD repair	1
ASD-PAPVR	Total correction	1
VSD	VSD repair	8
VSD-PS	VSD repair, enlargement of PS	2
VSD-p. banding	Debanding-VSD repair	4
VSD-MI	VSD repair-mitral annuloplasty	1
VSD-TI	VSD repair-tricuspid annuloplasty and raphe repair	1
VSD-PI-AI	VSD repair-resection of prolapsus of aortic and pulmonary cusps—repair with autologous pericardium	1
VSD-tricuspid chordal straddling	VSD repair-chordal transfer	1
VSD-PA	Rastelli conduit revision	1
VSD-PA	m BT shunt-enlargement of pulmonary confluence	1
TOF	Total correction	3
TOF-PA	m BT shunt	1
AVSD	Total correction	3
Truncus arteriosus-Rastelli	Rastelli conduit revision	1
TGA-aortic arch hypoplasia-VSD-TA	Glenn shunt	1
TA-previous Glenn shunt	Extracardiac Fontan	1
TA-AVSD-PS	m BT shunt	1

Abbreviations: ASD: Atrial septal defect; PAPVR: Partial anomalous pulmonary venous return; VSD: Ventricular septal defect; PS: Pulmonary stenosis; P. banding: Pulmonary banding; MI: Mitral insufficiency; TI: Tricuspid insufficiency; PI: Pulmonary insufficiency; AI: Aortic insufficiency; PA: Pulmonary atresia; m BT shunt: Modified Blalock–Taussig shunt; TOF: Tetralogy of Fallot; AVSD: Atrioventricular septal defect; TGA: Transposition of great arteries; TA: Tricuspid atresia.

A Spearman correlation analysis was also performed to examine the relationship between the preoperative NLR and key clinical endpoints. The preoperative NLR showed a strong positive correlation with ICU LOS (r = 0.53, $p < 0.001$), and moderate correlations with hospital LOS (r = 0.32, $p < 0.01$) and duration of mechanical ventilatory support (r = 0.32, $p < 0.01$) (Table 5).

Table 5: Spearman correlation analysis between preoperative NLR and clinical outcomes (ICU stay, hospital stay, and mechanical ventilatory support).

	ICU LOS	Hospital LOS	Mechanical Ventilatory Support (Days)
Preoperative NLR	0.53***	0.32**	0.32**
Hospital LOS	0.74***	-	0.28*
Mechanical ventilatory support (days)	0.56***	0.28*	-

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$. Abbreviations: NLR: Neutrophil-lymphocyte ratio; ICU: Intensive care unit; LOS: Length of stay.

A binary logistic regression model was constructed using preoperative NLR ($\geq$1.14) as the independent variable and the composite poor outcome as the dependent variable. The model did not reach statistical significance ($p > 0.05$), suggesting that preoperative NLR alone may not be an independent predictor of composite adverse outcomes when confounding variables are considered. However, its significant associations with secondary endpoints (ICU LOS, duration of mechanical ventilatory support, and hospital LOS) were maintained in univariate analyses. Given the limited

number of events, the model included a restricted set of covariates to mitigate overfitting; under these constraints, NLR $\geq$ 1.14 was not independently associated with the composite outcome.

4 Discussion

This study established that preoperative NLR values, as well as those measured on POD's 3 and 6, possess significant predictive significance for forecasting unfavorable outcomes in pediatric patients having congenital heart surgery. The established cutoff values for NLR ($\geq$1.14 preoperatively, $\geq$4.16 on POD 3, and $\geq$2.05 on POD 6) were substantially correlated with prolonged mechanical ventilatory support, extended ICU, and further postoperative problems ($p < 0.05$; AUC = 0.75). A robust positive link was identified between preoperative NLR and ICU time, whereas substantial yet moderate correlations were detected with hospital LOS and duration of mechanical ventilatory support. The data indicate that the systemic inflammatory response is pivotal in the postoperative trajectory and that a higher NLR may signify a dysregulated or exacerbated inflammatory condition.

Several studies have reported a higher incidence of systemic inflammatory response syndrome in younger children or those with lower body weight following CPB [7,8]. The discrepancy between the patient's blood volume and the priming volume of the CPB circuit results in an exacerbated inflammatory response. Pediatric patients, owing to their restricted physiological reserves, are especially vulnerable to problems arising from this response [9].

Several studies have explored the etiological factors contributing to poor outcomes in CHD [5]. For instance, Iliopoulos et al. [10] and Laila et al. [11] found that a higher NLR was predictive of low cardiac output syndrome. Afari et al. [12] examined the NLR in adults in relation to cardiac valvular surgery, acute coronary syndrome, and atrial fibrillation. Pediatric patients undergoing CPB exhibit a more severe inflammatory response than adults [13]. Olasińska-Wiśniewska et al. [14] proposed that the inflammatory response during CPB is driven by endotoxemia, and injury triggered by ischemia–reperfusion, both resulting from hypothermic perfusion, which leads to endothelial damage and the release of reactive oxygen species. The acute inflammatory response following CPB and the postoperative stress reaction can lead to an increase in postoperative NLR and other biochemical markers [15,16]. Iliopoulos et al. [10] and Manuel et al. [17] suggested that an increase in the NLR is likely driven by the stress response and neurohormonal activity during CPB, which functions to minimize hemorrhage, maintain homeostasis, and facilitate injury repair. However, this system can become exaggerated and dysregulated [10].

Lymphocytes that produce IL-10 play an important role in maintaining the equilibrium between inflammatory and anti-inflammatory states, functioning as "regulatory cells" [5]. Equilibrium among white blood cell helps reduce inflammation, and within the vascular bed, IL-10 can inhibit the production of pro-inflammatory cytokines [5]. IL-10 also suppresses neutrophil recruitment, thereby preventing tissue damage, including in the myocardium [5]. Conversely, insufficient IL-10 leads to neutrophil dominance, resulting in an altered NLR and increased inflammation [5]. Moreover, CPB initiates neutrophil activation within the complement cascade. This activation triggers the secretion of polymorphonuclear elastase ethylate (PMN-E). Unregulated PMN-E activation can directly cause cellular damage and indirectly amplify the inflammatory response by increasing the production and secretion of IL-8 and IL-1 [5].

The preoperative NLR has been linked to adverse outcomes in pediatric patients undergoing congenital heart surgery [6,10,18–21]. In our study, we identified a preoperative NLR cutoff value of 1.14. Contrary to the findings of Serra et al. [6], our data indicate that the preoperative NLR is not an independent risk factor to predict adverse outcomes. However, when comparing NLR values across different preoperative and postoperative days, we found that the preoperative NLR demonstrated the strongest predictive capability for adverse outcomes, serving as an independent risk factor. Manuel et al. [21] conducted a retrospective analysis of 141 univentricular patients, showing that a preoperative NLR of >2 was linked to an extended hospital stay, extended mechanical ventilation, longer ICU stays, and higher mortality within 24 months postoperatively. Building on prior research, Manuel et al. [19] also validated the link between preoperative cytokine levels and adverse outcomes, establishing an NLR cutoff value of 0.80. Our findings suggest that elevated preoperative NLR levels may predispose patients to a compromised postoperative neurohumoral response.

Furthermore, Yin et al. [20] identified a strong correlation between the preoperative NLR and pulmonary artery hypertension in children with acyanotic congenital heart pathologies accompanied by pulmonary artery hypertension.

Serra et al. [6] investigated the cutoff value of the NLR and found that the NLR on POD 3 had the highest predictive performance, with a cutoff value of 2.05. Similarly, Raharjo et al. [7] found that the most valuable predictive NLR cutoff for poor outcomes in pediatric patients occurred on POD 3. Although the highest predictive accuracy was observed for NLR values on POD 6 (AUC = 0.78), and to a lesser extent on POD 3 (AUC = 0.74), our primary focus on the preoperative NLR was guided by its practical clinical relevance. Preoperative markers offer the advantage of early risk stratification before surgery, enabling timely planning and perioperative optimization. In contrast, postoperative NLR values, although informative, are only available after significant events may have occurred. Nonetheless, our findings align with previous studies, including Serra et al. [6], which highlighted POD 3 NLR as a strong predictor of poor outcomes. This suggests that dynamic perioperative trends in NLR deserve further attention and could be valuable in future predictive modeling. Although no statistically significant difference was observed in the composite "poor outcome" variable between NLR groups, several individual clinical endpoints—particularly prolonged mechanical ventilation, extended ICU stay, and prolonged hospitalization—were significantly associated with elevated preoperative NLR. This finding suggests that while the composite endpoint may lack sensitivity due to its heterogeneous components and low-frequency events, the NLR may still reflect meaningful inflammatory risk in specific domains of postoperative recovery.

From a mechanistic perspective, the NLR reflects the balance between innate and adaptive immune responses. Elevated values may indicate either heightened systemic inflammation or an impaired ability to resolve inflammation. In our study, the prognostic associations of preoperative NLR are less likely to be explained by postoperative inflammatory failure, as measurements were taken prior to surgical insult. By contrast, postoperative NLR elevations, particularly on POD 3 and POD 6, may represent a sustained or uncontrolled inflammatory state in patients with adverse outcomes. While these findings support the use of preoperative NLR as a risk stratification tool, they do not establish causality. Distinguishing predictive from reactive NLR changes will require prospective studies with serial perioperative measurements and concurrent assessment of other immune-resolution markers.

We found that the preoperative NLR demonstrated the strongest univariate predictive signal for adverse outcomes; however, its independent association with the composite endpoint was not confirmed in our multivariable model.

Although our correlation analyses showed significant relationships between preoperative NLR and clinical outcomes such as ICU LOS and duration of mechanic ventilatory support, these analyses did not account for potential confounding factors such as age, weight, or surgical complexity. Due to the limited sample size and low event rates, the study was underpowered for robust multivariable modeling. A logistic regression model including preoperative NLR failed to identify it as an independent predictor of the composite outcome, highlighting the need for larger, prospective studies to assess the independent prognostic value of NLR using adjusted multivariable frameworks.

Although preoperative NLR demonstrated significant associations with several postoperative outcomes in univariate analyses, it was not independently associated with the composite poor outcome in our multivariable model after adjusting for selected covariates. The limited sample size and low number of events restricted the inclusion of multiple confounders in the model, highlighting the need for larger prospective studies to more rigorously assess the independent prognostic value of NLR.

Among the pediatric population undergoing congenital heart surgery, Manuel et al. [21] evaluated both cyanotic and acyanotic patients and found that preoperative NLR levels were higher in the cyanotic group. They hypothesized that cyanotic patients produce more pro-inflammatory cytokines, leading to worse postoperative outcomes. Their investigation suggested that cyanotic and acyanotic patients may respond differently to the inflammatory process induced by CPB. Their study involved patients who underwent surgery for VSD and TOF, and showed that those with TOF exhibited reduced lymphocyte concentrations. Their investigation suggested that cyanotic and acyanotic patients may respond differently to the inflammatory process induced by CPB, as evidenced by reduced lymphocyte concentrations in TOF patients compared to those undergoing surgery for VSD. They concluded that this may result in a less intense inflammatory response and reduced tissue damage, particularly in the myocardium. Building on their previous study, Manuel et al. [19] validated the association between preoperative cytokine levels and adverse outcomes, determining a cutoff value of 0.80 for the NLR. Their comparison of two cyanotic patient groups revealed that a NLR of >0.80 was significantly linked to poor outcomes in patients diagnosed with cyanotic heart disease. Prolonged mechanical ventilation following pediatric cardiac surgery has also consistently been linked to longer CPB durations in other studies [22]. The exclusive focus on single-ventricle patients in those studies may have contributed to a higher preoperative NLR cutoff value than in our analysis. Similarly, our study identified a significant relationship between a lower preoperative NLR and the duration of ventilator weaning.

Laila et al. [11] examined the correlation between the NLR and postoperative poor cardiac output syndrome following CPB. The study found that NLR values measured preoperatively and at postoperative 0, 4, and 8 h exhibited strong predictive capability for identifying decreased cardiac output. The NLR cutoff values identified were $\geq$0.88 preoperatively, $\geq$4.73 at 0 h, $\geq$6.19 at 4 h, and $\geq$6.78 at 8 h postoperatively ($p = 0.027$, $p < 0.0001$, $p < 0.0001$, and $p < 0.0001$).

Yakuwa et al. [23] evaluated the relationship between the postoperative NLR and prolonged pleural effusion in pediatric heart surgery. They proposed using the NLR change ratio to predict the timing of chest tube removal (NLR change ratio = NLR before medical treatment divided by the

preoperative NLR) and concluded that this ratio could serve as a predictor for chest tube removal within 10 days postoperatively [23].

Our results should be interpreted with caution, as several potential confounding factors may have influenced the observed associations between NLR and postoperative outcomes. Variables such as patient age, body weight, cyanotic versus acyanotic status, and surgical complexity are known to affect both the inflammatory response and clinical recovery after congenital heart surgery. Although we performed logistic regression including selected covariates, the small sample size and low number of adverse events limited the number of variables that could be incorporated into the model. Consequently, the observed associations between NLR and certain outcomes in univariate analyses may reflect, at least in part, the influence of unmeasured or residual confounding factors.

The current study has numerous significant strengths. This study primarily targets the pediatric population having congenital heart surgery, a demographic where prognostic biomarkers like the NLR remain under investigated. The study offers a thorough perioperative assessment of NLR values at several time points, including on preoperative and POD's 0, 1, 2, 3, and 6, facilitating an in-depth temporal examination of inflammatory processes. The utilization of a well-defined composite endpoint that includes many postoperative problems enhances the clinical significance of the results. The determination of a practical NLR cutoff value improves its usability at the bedside and facilitates risk classification in actual clinical environments.

5 Limitations

This investigation was conducted retrospectively, which entails inherent limitations. The patient cohort was relatively small, and the single-center design further limits the generalizability of the study. The range of patient's age was 1 to 48 months which includes patients with different physiological NLR values and response. The study included only individuals who underwent congenital heart surgery under CPB; and the range of CHD was broad that means different degree of difficulty in surgical procedures. Because of the limited sample size, we were unable to compare outcomes between cyanotic and acyanotic patients. Additionally, this study does not clarify the underlying mechanisms behind an elevated NLR and other postoperative biochemical changes, despite our findings. The severity of adverse outcomes is likely influenced by a combination of biochemical and hematological factors beyond the NLR alone. Nevertheless, our findings provide a foundation for future research and raise important questions for further investigation. Multi-center studies and larger sample sizes for futher researches are required. Another significant limitation is the absence of age stratification or adjustment for age as a covariate in the analysis. NLR values vary physiologically with age, particularly in the neonatal and infant periods, where relatively elevated NLR levels may still represent normal immune development. The use of a uniform NLR cutoff value (1.14) across a heterogeneous pediatric population—from neonates to adolescents—may reduce the reliability and generalizability of our findings. Future studies should include age-specific reference intervals and stratified analyses to better determine clinically meaningful thresholds. Additionally, although NLR values on POD 3 and 6 demonstrated strong predictive ability, our analysis did not include stratified risk modeling based on these time points due to sample size constraints and a focus on preoperative planning. Future prospective studies should explore the utility of dynamic NLR changes in postoperative risk classification. In addition, the composite primary endpoint may have been underpowered due to the low frequency of some adverse events,

such as ECMO support or mortality. This may have limited our ability to detect a statistically significant association between NLR and the overall composite outcome. Additionally, the influence of perioperative medications—such as antibiotics and corticosteroids—on NLR levels could not be fully accounted for due to the retrospective design. Although preoperative infections were excluded and institutional antibiotic protocols were standardized, residual confounding from unmeasured medication effects remains possible. The study was underpowered for multivariable modeling due to sample size constraints and the low number of events for some endpoints. As such, we could not fully isolate the independent effect of NLR after adjusting for covariates such as age or surgical complexity. Accordingly, our findings should be interpreted as hypothesis-generating regarding NLR's independent prognostic role. Furthermore, potential confounding variables—including age, weight, cyanotic status, and surgical complexity—could not be fully accounted for in the analysis due to the limited sample size and low event rates. Although we adjusted for selected covariates in a logistic regression model, the possibility of residual confounding remains. This limitation underscores the need for larger, prospective, multicenter studies with robust multivariable modeling to isolate the independent prognostic value of NLR. The study was underpowered for comprehensive multivariable adjustment. While we included a limited set of covariates in a logistic regression model to reduce overfitting, this approach could not fully control for confounding by important clinical variables such as age, comorbidities, and surgical complexity.

6 Conclusions

This study demonstrated that elevated preoperative NLR values were associated with extended mechanical ventilation, prolonged ICU stay, and longer hospitalization in pediatric patients undergoing congenital heart surgery. Although NLR values measured on POD's 3 and 6 showed even higher predictive performance, we focused on the preoperative NLR due to its potential for early risk assessment and clinical decision-making. Overall, the NLR appears to be a cost-effective, readily accessible biomarker with meaningful prognostic value throughout the perioperative period. Future studies should further examine the dynamic trajectory of NLR in the postoperative phase.

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Availability of Data and Materials: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval: This study was reviewed and approved by Muğla Sıtkı Koçman University ethical board (approval number: 13/I, 15 June 2023), and conducted in accordance with the principles of the Declaration of Helsinki. Patient's data were collected retrospectively from the institutional database, hence informed consent was waived.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

Abbreviations

CHD	Congenital heart disease
CPB	Cardiopulmonary bypass
IL	Interleukin
NT-proBNP	N-terminus pro-B-type natriuretic peptide
NLR	Neutrophil–lymphocyte ratio
POD	Postoperative day
ICU	Intensive care unit
LOS	Length of stay
ECMO	Extracorporeal membrane oxygenation
CPR	Cardiopulmonary resuscitation
ROC	Receiver operating characteristic
AUC	Area under the curve
ACC	Aortic cross-clamp
CI	Confidential interval
BMI	Body mass index
TOF	Tetralogy of Fallot
APVS	Absent pulmonary valve syndrome
TGA	Transposition of the great arteries
VSD	Ventricular septal defect
PS	Pulmonary stenosis
AVSD	Atrioventricular septal defect
ASD	Atrial septal defect
PAPVR	Partial anomalous pulmonary venous return
P. banding	Pulmonary banding
MI	Mitral insufficiency
PA	Pulmonary atresia
DAA	Double aortic arch
M BT shunt	Modified Blalock-Taussig shunt
IVS	Intact ventricular septum
RPA	Right pulmonary artery
LPA	Left pulmonary artery
RVOT	Right ventricle outflow tract
DORV	Double outlet right ventricle
DILV	Double inlet left ventricle
MS	Mitral stenosis
MVR	Mitral valve replacement
IAA	Interrupted aortic arch
TI	Tricuspid insufficiency
PI	Pulmonary insufficiency
AI	Aortic insufficiency
TA	Tricuspid atresia
PMN-E	Polymorphonuclear elastase ethylate

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