

## Clinical Value of Neutrophil Lymphocyte Ratio as a Prognostic Biomarker in Congenital Heart Surgery

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### Abstract:

**Background:** Congenital heart disease (CHD) is the most common birth defect and a leading cause of infant mortality. The neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation, is emerging as a simple, cost-effective prognostic tool in cardiac surgery. **Aim:** To assess the prognostic value of preoperative and postoperative NLR in predicting complications and mortality in pediatric CHD surgeries and compare outcomes between cyanotic and acyanotic patients. **Methods:** This retrospective cohort study included fifty pediatric CHD patients (1 month–8 years) undergoing surgery at Benha University Hospital and Baheim Hospital. Patients were divided into cyanotic (n = 10) and acyanotic (n = 40) groups. Preoperative labs, including NLR, were recorded. Postoperative data included complications, ICU/hospital stay, and 30-day mortality. **Results:** Postoperative NLR was significantly higher in patients with complications in both groups (p = 0.001 acyanotic; p = 0.018 cyanotic). In acyanotic cases, post-NLR correlated with ICU stay (r = 0.489, p = 0.003) and predicted complications (AUC = 1, p = 0.011). In cyanotic patients, post-NLR correlated with longer hospital stay (r = 0.798, p = 0.008), and predicted complications and mortality (AUC = 0.917, p = 0.007). Preoperative NLR had no significant predictive value. **Conclusion:** Postoperative NLR is a valuable prognostic marker for complications and mortality, especially in cyanotic CHD, and may aid in early risk stratification.

**Keywords:** congenital heart disease, cyanotic, acyanotic, neutrophil lymphocyte ratio

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## Introduction

Congenital heart disease (CHD) represents the most generic form of congenital malformation worldwide, posing a significant clinical and surgical challenge in the pediatric population <sup>(1)</sup>. Advances in surgical techniques and perioperative care have substantially improved outcomes; however, postoperative complications and variable prognoses remain prevalent concerns. Identifying reliable, cost-effective prognostic biomarkers is crucial for risk stratification and optimizing patient management in congenital heart surgery <sup>(2)</sup>.

Systemic inflammation plays a pivotal role in the pathophysiology of postoperative complications following cardiac surgery, particularly when cardiopulmonary bypass is employed <sup>(3)</sup>. Among emerging inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR)—derived from a routine complete blood count—has gained attention for its prognostic significance in various cardiovascular and surgical settings. NLR reflects the balance between innate (neutrophil) and adaptive (lymphocyte) immune responses and serves as a surrogate marker of systemic inflammatory burden <sup>(4)</sup>.

Previous studies have demonstrated the prognostic value of NLR in adult cardiac surgery, acute coronary syndromes, and heart failure. However, data regarding its predictive utility in the pediatric population undergoing congenital heart surgery remain limited. Given the simplicity, availability, and low cost of NLR assessment, its clinical application in this setting warrants further investigation <sup>(5,6)</sup>.

The current study aimed to investigate the role of preoperative and postoperative NLR level as a prognostic biomarker to assess the mortality and morbidity of cardiac surgery and compare between cyanotic and acyanotic heart diseases.

## Methods

The current prospective cohort study was conducted in the Pediatric Intensive Care

Unit (PICU) of Benha University Hospital and Bahteim Hospital for cardiothoracic surgery over one year (October 2023–October 2024). The study enrolled 50 pediatric patients with CHD, categorized into cyanotic (n = 10) and acyanotic (n = 40) groups based on echocardiographic findings.

Inclusion criteria comprised children aged 1 month–8 years with confirmed CHD scheduled for cardiac surgery. Exclusion criteria included prior cardiac surgery, preoperative hemodynamic instability, active infections, or comorbidities affecting immune function. Ethical approval was obtained from Benha Faculty of Medicine (Ref: Ms. 10-12-2023), with informed consent from all parents.

A detailed history (maternal/perinatal/neonatal records, cardiac symptoms) and physical examination (anthropometrics, vital signs, cardiac/abdominal/neurological exams) were performed.

Pre- and postoperative CBC (for NLR calculation), liver/kidney function tests, and echocardiography (e.g., ejection fraction, pulmonary pressure) were analyzed.

Operative and postoperative monitoring including intraoperative data as surgical duration, cardiopulmonary bypass (CPB) time, lactate levels, and vasoactive-inotropic score (VIS). Postoperative outcomes tracked complications (e.g., acute kidney injury, sepsis), ICU/hospital stays, and 30-day mortality.

**Approval code:** MS 10-12-2023

## Statistical analysis

Data were analyzed using IBM SPSS Statistics Version 25 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Kolmogorov-Smirnov test. Descriptive statistics included mean  $\pm$  SD for parametric data, and median (range) for non-parametric data. Categorical variables were presented as frequencies and percentages. For group comparisons, the student's *t*-test and Mann-Whitney U test were used for

parametric and non-parametric data, respectively. The Kruskal-Wallis's test was applied for multiple group comparisons. Categorical associations were evaluated using Chi-square or Fisher's exact test. Correlation analysis assessed relationships between quantitative variables. ROC curve analysis determined diagnostic accuracy via AUC. Linear regression identified predictors and estimated odds ratios with 95% CIs. Statistical significance was set at  $p \leq 0.05$  (7).

## Results

Regarding personal history, the mean age was higher in the acyanotic group ( $31.1 \pm 33$  months) than in the cyanotic group ( $12.7 \pm 6.6$  months), although not statistically significant ( $p = 0.087$ ). A significant sex disparity was observed, with all cyanotic patients being male (100%) versus 47.5% in the acyanotic group ( $p = 0.003$ ). No significant differences were found in consanguinity ( $p = 0.463$ ) or family history of congenital heart disease ( $p = 1.000$ ) (Table 1).

**Table 1:** Personal history among the studied groups

Variable	Acyanotic group (N=40)		Cyanotic group (N=10)		t-test	P-value
<b>Age (m):</b>						
• Mean ± SD!	31.1 ± 33		12.7 ± 6.6		1.7	0.087
• Median	11		12		(MW)	
• Range	0-96		1-24			
Variable	N	%	N	%	χ <sup>2</sup>	P-value
<b>Sex:</b>						
• Male	19	47.5	10	100	Fisher	<b>0.003*</b>
• Female	21	52.5	0	0		
<b>Consanguinity:</b>						
• Negative	27	67.5	5	50	Fisher	0.463
• Positive	13	32.5	5	50		
<b>Family history:</b>						
• Free	37	92.5	9	90	Fisher	1
• Brother with CHD	3	7.5	1	10		

Both cyanotic and acyanotic groups demonstrated comparable gestational ages, with a mean of  $37.5 \pm 1.2$  weeks and  $37.5 \pm 0.7$  weeks, respectively, indicating no statistically significant difference ( $p = 0.952$ ). However, the duration of neonatal intensive care unit (NICU) admission was significantly longer in the cyanotic group, with a mean of  $25 \pm 6.9$  days compared to  $9.1 \pm 8.3$  days in the acyanotic group ( $p = 0.000$ ). Although all patients in the cyanotic group were delivered via cesarean section compared to 82.5% in the acyanotic group, this difference did not reach statistical significance ( $p = 0.319$ ). Maternal risk factors, including diabetes and advanced maternal age, were more frequent in the cyanotic group but showed

no significant difference between the two groups ( $p = 0.258$ ).

Regarding the type of CHD, Ventricular Septal Defect (VSD) was the most common lesion, comprising 40% of cases. Atrial Septal Defect (ASD) followed at 18%, and Tetralogy of Fallot (TOF) at 16%. Less common conditions included ASD with Pulmonary Stenosis (PS), Patent Ductus Arteriosus (PDA), Aortic Regurgitation (AR), Partial Atrioventricular Canal (PAVC), and Vascular ring, each at 4%. Total Anomalous Pulmonary Venous Drainage (TAPVD) also accounted for 4% of cases (Table 2).

**Table 2:** Type of CHD among the studied groups:

Variable	N (50)	% (100)
<b>CHD:</b>		
• <i>VSD</i>	20	40
• <i>ASD</i>	9	18
• <i>ASD, PS</i>	3	6
• <i>PDA</i>	2	4
• <i>AR</i>	2	4
• <i>PAVC</i>	2	4
• <i>Vascular ring</i>	2	4
• <i>TOF</i>	8	16
• <i>TAPVD</i>	2	4

There were no significant differences between the acyanotic and cyanotic groups regarding pre-operative neutrophil count ( $p = 0.369$ ), lymphocyte count ( $p = 0.397$ ), or neutrophil-to-lymphocyte (N/L) ratio ( $p = 0.204$ ). However, the cyanotic group showed significantly higher hemoglobin levels ( $p = 0.000$ ), hematocrit ( $p = 0.000$ ), and RBC count ( $p = 0.000$ ), reflecting the expected compensatory polycythemia in cyanotic heart disease (Table 3).

**Table 3:** Pre-operative investigations among the studied groups:

Variable	Acyanotic group (N=40)	Cyanotic group (N=10)	t-test	P-value
<b>Neutrophil:</b>				
• <i>Mean <math>\pm</math> SD.</i>	5.1 $\pm$ 4.1	4.8 $\pm$ 2.7	0.908	0.369
• <i>Median</i>	6.1	4.1	(MW)	
• <i>Range</i>	1.4-15.1	1.5-8.2		
<b>Lymphocytes:</b>				
• <i>Mean <math>\pm</math> SD.</i>	5.6 $\pm$ 3.1	6.7 $\pm$ 2.3	-0.991	0.397
• <i>Median</i>	4.4	7.8	(MW)	
• <i>Range</i>	1.2-12	4-9.5		
<b>N/L ratio:</b>				
• <i>Mean <math>\pm</math> SD.</i>	0.88 $\pm$ 0.65	1.9 $\pm$ 2.7	1.3	0.204
• <i>Median</i>	0.91	1.3	(MW)	
• <i>Range</i>	0.16-1.9	0.19-9.7		
<b>Hg:</b>				
• <i>Mean <math>\pm</math> SD.</i>	11.2 $\pm$ 1.3	13.3 $\pm$ 2.3	-3.7	<b>0.000</b>
• <i>Range</i>	9.3-14.9	11.1-17.2		<b>(HS)</b>
<b>HTC:</b>				
• <i>Mean <math>\pm</math> SD.</i>	30.3 $\pm$ 6.2	39.1 $\pm$ 6.5	-3.9	<b>0.000</b>
• <i>Range</i>	15.7-39.5	31.3-48.4		<b>(HS)</b>
<b>RBC count:</b>				
• <i>Mean <math>\pm</math> SD.</i>	4.4 $\pm$ 0.5	5.2 $\pm$ 0.9	-3.8	<b>0.000</b>
• <i>Range</i>	3.5-5.3	4-6.05		<b>(HS)</b>

Post-operative neutrophil, lymphocyte counts, and N/L ratio were higher in the cyanotic group than in the acyanotic group, but the differences did not reach statistical significance ( $p > 0.05$ ). However, the cyanotic group had

significantly higher hemoglobin ( $p = 0.001$ ), hematocrit ( $p = 0.000$ ), and RBC count ( $p = 0.000$ ), indicating persistent polycythemic adaptation post-surgery (Table 4).

**Table 4:** Post-Operative investigations among the studied groups:

Variable	Acyanotic group (N=40)	Cyanotic group (N=10)	t-test	P-value
<b>Neutrophil:</b>				
• Mean $\pm$ SD.	11.3 $\pm$ 3.1	12.5 $\pm$ 3.3	-1.1	0.264
• Range	7-18.5	6.3-15		
<b>Lymphocytes:</b>				
• Mean $\pm$ SD.	3.2 $\pm$ 2.7	4.4 $\pm$ 1.4	-1.3	0.200
• Median	2.2	4.4	(MW)	
• Range	0.8-10.2	2.1-6.2		
<b>N\L ratio:</b>				
• Mean $\pm$ SD.	3.5 $\pm$ 2.1	6.4 $\pm$ 5.2	-1.8	0.084
• Median	3	4.6	(MW)	
• Range	1.02-7.1	1.3-19.9		
<b>Hg:</b>				
• Mean $\pm$ SD.	11.3 $\pm$ 1.3	12.9 $\pm$ 0.95	-3.7	<b>0.001</b>
• Range	8.7-13.5	12-14.3		<b>(HS)</b>
<b>HTC:</b>				
• Mean $\pm$ SD.	31.5 $\pm$ 3.6	37.3 $\pm$ 2.3	-4.8	<b>0.000</b>
• Range	24-37.5	34.4-40.3		<b>(HS)</b>
<b>RBC count:</b>				
• Mean $\pm$ SD.	4.4 $\pm$ 0.35	5 $\pm$ 0.28	-5.1	<b>0.000</b>
• Range	3.5-4.9	4.5-5.3		<b>(HS)</b>

There was a statistically significant difference in 30-day mortality between the acyanotic and cyanotic groups ( $p=0.014$ ). The acyanotic group exhibited a low mortality rate of 2.5%, whereas the

cyanotic group demonstrated a higher mortality rate of 30%. This finding underscores the more severe clinical outcomes associated with cyanotic congenital heart disease (Table 5).

**Table 5:** Mortality at day thirty among the studied groups:

Variable	Acyanotic group (N=40)		Cyanotic group (N=10)		$\chi^2$	P-value
	N	%	N	%		
<b>Mortality:</b>						
• No	39	97.5	7	70	Fisher	0.014 (S)
• Died	1	2.5	3	30		

In the acyanotic group, pre-operative neutrophil-to-lymphocyte ratio (pre-NLR) demonstrated a significant positive correlation between the pre-NLR and operation time ( $r = 0.638$ ,  $p = 0.000$ ). However, no significant correlations were found between the pre-NLR and MV duration, ICU stay, or hospital stays.

Post-operative NLR (post-NLR), however, was significantly associated with ICU stay ( $r = 0.489$ ,  $p = 0.001$ ) and showed a borderline correlation with hospital stay ( $r = 0.331$ ,  $p = 0.050$ ), indicating its potential role in predicting prolonged recovery in the ICU.

Regarding post-operative complications in the acyanotic group, patients who developed post-operative complications had significantly higher post-operative NLR compared to those without complications ( $p=0.001$ ). Moreover, the operation time was significantly shorter in patients who developed complications ( $p=0.027$ ). In contrast, pre-operative NLR

and pulmonary pressure did not show significant associations with complications (Table 6). When evaluating the predictive value of NLR, pre-NLR demonstrated no predictive value ( $AUC = 0.5$ ,  $p = 1$ ) (Table 10), while post-NLR showed excellent predictive validity ( $AUC = 1$ ,  $p = 0.011$ ), with perfect sensitivity and specificity for detecting complications.

**Table 6:** Association between different variables and post-operative complications among the acyanotic group:

Variable	Post-operative complications		MW-test	P-value
	No (N=32)	Yes (N=8)		
<b>Pre-operative NLR:</b>				
• <i>Mean <math>\pm</math> SD.</i>	0.77 $\pm$ 0.33	0.82 $\pm$ 0.3	0.390	0.699
• <i>Median</i>	0.91	1		
• <i>Range</i>	0.36-1.05	0.16-1.9		
<b>Post-operative NLR:</b>				
• <i>Mean <math>\pm</math> SD.</i>	2.3 $\pm$ 1	4.5 $\pm$ 1.2	5.4	0.001
• <i>Median</i>	2.5	4.5		(1)
• <i>Range</i>	1.02-3	3.3-7.1		
<b>Operation time:</b>				
• <i>Mean <math>\pm</math> SD.</i>	126.3 $\pm$ 52.4	950.9	0.745	0.027
• <i>Median</i>	132.5	95		(S)
• <i>Range</i>	60-210	85-105		
<b>Pul. pressure:</b>				
• <i>Mean <math>\pm</math> SD.</i>	47.3 $\pm$ 16.7	50 $\pm$ 2.1	0.838	0.366
• <i>Median</i>	45	50		
• <i>Range</i>	30-85	45-55		

In the cyanotic group, pre-NLR showed no statistically significant correlations with operation time, MV duration, ICU stay, or hospital stay. Conversely, post-NLR displayed a strong negative correlation with operation time ( $r = -0.691$ ,  $p = 0.028$ ) and a strong positive correlation with hospital stay ( $r = 0.798$ ,  $p = 0.008$ ), suggesting its potential utility as a prognostic marker. Moreover, post-NLR was significantly lower in patients who died, ( $p = 0.018$ ), further supporting its role as a predictor of mortality. Additionally, operation time was significantly longer in the mortality group with a  $p$ -value of 0.035. Post-NLR demonstrated perfect discriminatory power

for predicting complications ( $AUC = 1$ ,  $p = 0.011$ ), with perfect sensitivity and specificity.

Finally, pulmonary hypertension showed a significant positive correlation with post-operative complications ( $r = 0.28$ ,  $p = 0.049$ ) across all cases, indicating that higher pulmonary pressures may increase the risk of adverse events. However, its association with mortality was not statistically significant ( $r = 0.219$ ,  $p = 0.127$ ).

## Discussion

Congenital heart disease (CHD), defined as a macroscopic structural abnormality of the heart or great vessels with significant

physiological impact, remains the most common congenital malformation and a leading cause of early childhood mortality worldwide, with a prevalence ranging from 0.8% to 5%<sup>(8)</sup>. Advances such as CPB have drastically improved surgical outcomes, reducing mortality to less than 3% in specialized centers<sup>(9,10)</sup>.

The prognostic utility of biomarkers, including NLR, has been explored extensively in cardiac surgery, especially in coronary artery bypass grafting (CABG). NLR, easily derived from routine blood counts, has emerged as a promising marker for predicting outcomes; however, normative pediatric values and clinical thresholds remain under investigation<sup>(11)</sup>.

In our study of fifty children with CHD (40 acyanotic, 10 cyanotic), a significant male predominance was noted in the cyanotic group (100% male), consistent with previous reports associating certain CHD subtypes, such as left ventricular outflow tract obstruction, with male sex<sup>(12-14)</sup>. Consanguinity rates were higher in the cyanotic group but not significantly different between groups, aligning with prior observations linking consanguinity to increased CHD risk<sup>(13, 15)</sup>. Family history prevalence was low and similar across groups, reflecting variable findings in the literature<sup>(13, 16)</sup>.

In the current study, cyanotic patients experienced longer NICU stays, consistent with the complexity of their conditions<sup>(17)</sup>. Feeding methods differed significantly; all cyanotic infants were bottle-fed, likely due to feeding fatigue and higher energy demands<sup>(18)</sup>.

Our study reveals that post-operative NLR (post-NLR) is a robust prognostic marker in both acyanotic and cyanotic CHD cases, whereas pre-operative NLR (pre-NLR) lacked consistent predictive value.

Studies of infants undergoing congenital cardiac surgery consistently highlight the predictive value of elevated post-NLR for adverse outcomes. For instance, one large retrospective cohort in infants reported that day-3 post-operative NLR  $\geq 2.05$  yielded

an AUC of 0.763 (95% CI 0.700–0.826), and was independently associated (OR  $\approx 3.72$ ,  $p < 0.001$ ) with poor postoperative events, including longer ICU/hospital stays and mechanical ventilation duration<sup>(19)</sup>. Similarly, a broader pediatric CHD-PAH study found pre-NLR correlated with ventilation time and ICU stays, but post-NLR was more strongly associated with early complications and prolonged ventilation beyond 24–72 h<sup>(20)</sup>.

In adult cardiac surgery, elevated POD-1 NLR (e.g.,  $>7.28$ ) has been linked to increased short-term and long-term mortality, prolonged ICU/hospital stay, and renal replacement therapy<sup>(21)</sup>. Our findings of perfect sensitivity and specificity (AUC = 1.0) for post-NLR predicting complications and mortality in acyanotic CHD, and AUC = 0.917 (sensitivity 100%, specificity 90%) in cyanotic patients, although unusually high, align with the trend that early post-operative systemic inflammation—as reflected by NLR—is a strong outcome mediator.

While some earlier pediatric studies reported high pre-NLR as independently predictive of adverse outcomes (including mortality and low cardiac output syndrome)<sup>(20, 22)</sup>, our current data did not show pre-NLR as a reliable predictor in either group (acyanotic: AUC = 0.5,  $p = 1$ ; cyanotic: no significant correlation with outcomes). This discrepancy may be due to age distribution, cohort size, or timing of measurement, consistent with discussions in Xu et al. that early perioperative NLR may show weaker or inconsistent associations depending on surgical timing and endpoints<sup>(23)</sup>.

NLR reflects systemic inflammation and immune stress: CPB triggers the release of pro-inflammatory cytokines and neutrophil activation, while lymphocyte counts often decline under stress. Sustained post-operative elevation—the persistence of high NLR rather than a transient spike—may be a surrogate for ongoing SIRS, predicting prolonged ICU stay,

complications, and mortality <sup>(24)</sup>. our findings (post-NLR correlated with ICU and hospital stay) are consistent with this mechanistic understanding.

The positive correlation between pulmonary hypertension and post-operative complications ( $r = 0.28$ ,  $p = 0.049$ ) suggests that elevated baseline pulmonary pressures may contribute to inflammatory burden and amplify post-surgical risk. This resonates with data indicating that CHD-PAH patients tend to have higher perioperative NLR and poorer outcomes <sup>(25, 26)</sup>.

## Conclusion

Post-operative neutrophil-to-lymphocyte ratio (NLR) proved to be a reliable predictor of complications and mortality in children undergoing surgery for congenital heart disease, especially in cyanotic cases. In contrast, pre-operative NLR showed no significant prognostic value. Given its simplicity and accessibility, post-NLR may serve as a useful biomarker for early risk stratification and post-operative management in pediatric cardiac surgery.

## Recommendations

Our findings suggest that NLR is a simple, cost-effective marker valuable for postoperative risk stratification. However, further research is needed to establish standardized pediatric reference values and validate NLR's predictive accuracy in larger, multicenter cohorts.

## Conflict of interest

None declared any conflict of interest.

## Abbreviations Full Term

CHD	Congenital Heart Disease
NLR	Neutrophil-to-Lymphocyte Ratio
ICU	Intensive Care Unit
MV	Mechanical Ventilation
VSD	Ventricular Septal Defect
ASD	Atrial Septal Defect
PDA	Patent Ductus Arteriosus
PS	Pulmonary Stenosis
TOF	Tetralogy of Fallot

## Abbreviations Full Term

TAPVD	Total Anomalous Pulmonary Venous Drainage
PAVC	Partial Atrioventricular Canal
RBC	Red Blood Cell
Hg	Hemoglobin
HCT	Hematocrit
CS	Cesarean Section

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