The Association Between Neutrophil-Lymphocyte Ratio and Poor Outcomes Following Infant Cardiac Surgery

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Abstract

Background: Neutrophil-lymphocyte ratio (NLR) is a valuable indicator for evaluating inflammation and adverse outcomes after cardiac surgery. The objective of this study was to evaluate the association of perioperative NLR with clinical outcomes in infants undergoing congenital heart surgery with cardiopulmonary bypass.

Methods: We performed a retrospective review of 424 consecutive infants (≤ 1 year) undergoing cardiac surgery between January 2019 and September 2019. Neonates (≤ 28 days) and patients with incomplete NLR data were excluded. The study endpoint was a composite of poor outcomes after surgery. We assess the correlation between perioperative NLR and clinical outcomes. A receiver operating characteristic curve and multivariable logistic regression were applied to identify the prognosis performance of postoperative NLR for poor outcomes.

Results: A total of 68 (16%) infants experienced at least one of the poor outcomes. Postoperative NLR on the third day after the surgery showed the best prognostic significance (AUC = 0.763, 95%CI 0.700-0.826) among perioperative period, with a cut-off value of 2.05. Postoperative NLR was also strongly correlated with mechanical ventilation time, length of ICU and hospital stay (p < 0.001). Multivariable logistic regression revealed that elevated postoperative NLR (OR 3.722, 95%CI 1.895-7.309, p < 0.001) was an independent risk factor for poor outcomes in infants after cardiac surgery.

Conclusions: Postoperative NLR was correlated with increased mechanical ventilation time, length of ICU and hospital stay. Elevated postoperative NLR was an independent predictor for poor outcomes after cardiac surgery in infants.

Background

Cardiopulmonary bypass (CPB) initiates systemic inflammatory response syndrome (SIRS), which is associated with adverse outcomes in pediatric cardiac surgery [1,2]. However, few inflammatory biomarkers could be conveniently used to evaluate outcomes in current clinical practice. Neutrophil-lymphocyte ratio (NLR) has been reported as a useful marker of system inflammation in sepsis, chronic obstructive pulmonary disease, and abdominal operations [3-5], as a simple and readily available biomarker that was calculated from blood routine examination. Moreover, increased perioperative NLR was shown to be associated with poor outcomes after cardiac surgery in adult patients [6]. Recent studies showed that the higher preoperative NLR in children undergoing cardiac surgery was not only an independent risk factor for low cardiac output in the early postoperative period but also correlated with short-term and long-term mortality [7,8]. Besides, postoperative NLR in pediatric patients with cardiopulmonary bypass was significantly higher than those before the operation, which was consistent with increased duration of mechanical ventilation and ICU stay [9]. Although NLR is a valuable indicator for evaluating inflammation and clinical outcomes, limited evidence in the population of infants has been shown. We hypothesized that elevated NLR is relevant to poor outcomes after pediatric cardiac surgery.
The objective of the present study was to evaluate the association of perioperative NLR with clinical outcomes in infants, thereby providing an underlying predictor for clinical prognosis.

Patients And Methods

Patients

This is a retrospective observational study conducted at Fuwai Hospital (Beijing, China). From January 2019 to September 2019, a total of 497 infants (≤1 year) undergoing cardiac surgery with CPB were consecutively included. Excluded were patients utilizing preoperative extracorporeal life support, without cardioplegic arrest, emergent surgery, or incomplete data of perioperative NLR. Neonates (≤28 days) were also excluded because they have a special pathophysiological condition. The study was approved by Fuwai hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

Definitions

For each pediatric patient, the data were retrospectively collected through the electronic database of the hospital information system. Peripheral venous blood was taken and sent to the laboratory for blood routine examination at the admission in pediatric intensive care unit (PICU) and every morning during PICU stay. NLR is the quotient of the absolute value of neutrophils and lymphocytes from the same blood routine examination. NLR on one day before the surgery was defined as Baseline NLR, the operation day as Day0 and 1, 2, 3, 6 days after surgery respectively named as Day1, Day2, Day3, Day6.

Poor outcomes were limited to the postoperative duration of hospitalization, defined as patients undergoing at least one of death, pulmonary or incision infection, need for peritoneal dialysis, postoperative re-intubation or re-operation, the requirement of extracorporeal membrane oxygenation (ECMO), prolonged ICU stay ≥ 11 days (90th percentile) and prolonged mechanical ventilation ≥ 100 hours (90th percentile).

Statistical Analyses

Categorical variables were presented as frequencies with percentages, continuous variables as mean ± standard deviation, or median with interquartile ranges (IQR) 25–75th percentile. The normality of distribution was tested with the Shapiro-Wilk test. Chi-square or Fisher’s exact test was used for categorical variables, and the t-test or Mann–Whitney U test for continuous variables. As for the relationship between poor outcomes and NLR on different days, cut-off values were identified using a receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was used to determine the accuracy of the diagnostic prediction. Select the NLR with the best diagnostic performance as the
postoperative NLR. We performed a Spearman rank correlation test (r) to assess the unadjusted relationships between preoperative and postoperative NLR with clinical outcomes (mechanical ventilation time, length of ICU and hospital stay).

To evaluate if postoperative NLR predicts poor outcomes, we built multivariable logistic regression modeling, adjusting for factors that were evaluable in the prediction of clinical outcome of pediatric heart surgery: age, gender, weight, Risk Adjustment for Congenital Heart Surgery (RACHS) score, and CPB duration [10]. The NLR model added postoperative NLR to the basic model included age, gender, weight, RACHS score, and CPB duration. ROC comparisons were performed between models to check discriminative ability. For each cut-off value, the sensitivity and specificity were measured.

For all the statistical tests, a $p$-value $<0.05$ was considered significant. The data were analyzed using statistical software SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and R 4.1.0 (Institute for Statistics and Mathematics, Vienna, Austria).

**Results**

**Patient characteristics**

During the study period (January 2019 to September 2019), 497 pediatric patients were consecutively included. Due to incomplete NLR data, only 424 infants (219 male and 205 female) were included in the final analysis. The number of patients with poor outcomes was 68/424 (16.0%). Comparisons of the patient-related variables and surgery-related variables between patients with and without poor outcomes are presented in Table 1. Differences were apparent in the following variables: age, gender, previous cardiac surgery, cyanotic heart disease, height, weight, complex procedure (RACHS score $\geq$ 3), CPB duration, clamping time, lower body circulatory arrest, lowest nasopharyngeal temperature, and maximum lactate during surgery.

| Table 1 |
| The characteristics of patients with poor outcomes and non-poor outcomes. |
| Variable                                      | Poor outcomes n=68  | Non-poor outcomes n=356 | p-value |
|----------------------------------------------|---------------------|--------------------------|---------|
| **Patient-related variables**                |                     |                          |         |
| Age (months)                                 | 5.66 ± 3.24         | 6.95 ± 2.70              | 0.001a  |
| Female                                       | 23 (33.8%)          | 182 (51.1%)              | 0.009b  |
| Previous cardiac surgery                     | 5 (7.4%)            | 3 (0.8%)                 | 0.004b  |
| Birth weight (kg)                            | 3.13 ± 0.62         | 3.17 ± 0.62              | 0.77a   |
| Pulmonary arterial hypertension              | 33 (48.5%)          | 164 (46.1%)              | 0.709b  |
| Cyanotic heart disease                       | 30 (44.1%)          | 109 (30.6%)              | 0.03b   |
| Height (cm)                                  | 62.76 ± 7.19        | 66.06 ± 6.11             | <0.001a |
| Weight (kg)                                  | 6.19 ± 1.73         | 6.93 ± 1.49              | <0.001a |
| Preoperative hemoglobin (g/L)                | 122.0 ± 26.63       | 114.42 ± 16.09           | 0.083a  |
| Preoperative LVEF (%)                        | 64.72 ± 10.04       | 67.35 ± 5.74             | 0.133a  |
| **Surgery-related variables**                |                     |                          |         |
| Complex procedure (RACHS score ≥ 3)          | 33 (48.5%)          | 113 (31.7%)              | 0.008b  |
| CPB duration (min)                           | 119.46 ± 58.34      | 85.07 ± 34.62            | <0.001a |
| Clamping time (min)                          | 73.15 ± 39.0        | 55.81 ± 28.71            | <0.001a |
| Repeated CPB                                 | 4 (5.9%)            | 9 (2.5%)                 | 0.135b  |
| Lower body circulatory arrest                | 5 (7.4%)            | 6 (1.7%)                 | 0.019b  |
| lowest nasopharyngeal temperature (℃)        | 29.47 ± 2.46        | 30.89 ± 3.0              | <0.001a |
| Lowest hematocrit during CPB (%)             | 23.88 ± 3.33        | 23.77 ± 2.85             | 0.74a   |
| Maximum lactate during surgery (mmol/L)      | 2.22 ± 1.22         | 1.69 ± 0.76              | 0.013a  |

LVEF, left ventricular ejection fraction; RACHS, Risk Adjustment for Congenital Heart Surgery; CPB: cardiopulmonary bypass; a Mann-Whitney U test; b χ² test

**Perioperative NLR and clinical outcomes**
NLR variation among different days between infants with poor outcomes and non-poor outcomes is illustrated in Figure 1. A definite trend is evident that perioperative NLR increased from baseline due to the operation and CPB. NLR in patients without poor outcomes increased to a peak one day after the surgery and then decreased gradually. However, postoperative NLR in patients with poor outcomes maintained at a high level within 3 days after the surgery and still higher until Day6.

Baseline, Day0, Day2, Day3, and Day6 NLR showed statistical significance between the two groups. Repeated measurement analysis of variance showed that NLR was different in two groups, including both single NLR (F = 330.529\( p < 0.001 \)), an interaction term between NLR and poor outcomes (F = 19.416\( p < 0.001 \)). To explore the predictive value of NLR on different days, ROC curve analysis with NLR and poor outcomes was applied, results are shown in Table 2. According to AUC and \( p \)-value, Baseline, Day2, Day3, and Day6 NLR have a predictive diagnostic effect, with cutoff values of 0.37, 5.24 2.05, and 1.38 respectively, and Day3 NLR (AUC = 0.763, 95%CI 0.700-0.826) showed the best prognostic significance (Table 2).

### Table 2

| Variable     | \( p \) value | AUC    | 95% CI         | Cut-off Value |
|--------------|---------------|--------|----------------|--------------|
| Baseline NLR | 0.018         | 0.591  | 0.516-0.666    | 0.37         |
| Day0 NLR     | 0.098         | 0.563  | 0.491-0.636    | -            |
| Day1 NLR     | 0.717         | 0.514  | 0.436-0.592    | -            |
| Day2 NLR     | <0.001        | 0.719  | 0.658-0.781    | 5.24         |
| Day3 NLR     | <0.001        | 0.763  | 0.700-0.826    | 2.05         |
| Day6 NLR     | <0.001        | 0.748  | 0.679-0.817    | 1.38         |

ROC, receiver operating characteristic; NLR, neutrophil-lymphocyte ratio

Since Day3 NLR showed a larger AUC than other days, we choose it as postoperative NLR in the following analysis. As presented in Table 3, preoperative NLR was significantly correlated with mechanical ventilation time (\( p = 0.002 \)) and ICU length of stay (\( p = 0.023 \)) but had no obvious correlation with hospital length of stay (\( p = 0.081 \)). Postoperative NLR was closely related to mechanical ventilation time (\( p < 0.001 \)), length of ICU (\( p < 0.001 \)) and hospital stay (\( p < 0.001 \)).

### Table 3

Correlation between perioperative NLR and clinical outcomes.
| Variable     | Preoperative NLR | Postoperative NLR |
|-------------|------------------|-------------------|
|             | Coefficient     | p-value           | Coefficient   | p-value          |
| MV time     | 0.148            | 0.002             | 0.554         | <0.001          |
| ICU LOS     | 0.110            | 0.023             | 0.469         | <0.001          |
| Hospital LOS| 0.081            | 0.094             | 0.421         | <0.001          |

NLR, neutrophil-lymphocyte ratio; MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay

The Predictive Effect of NLR on Poor Outcomes

According to postoperative NLR cutoff thresholds (2.05), 424 infants were grouped to evaluate the relationship between postoperative NLR and poor outcomes. 54/195 (27.7%) of elevated postoperative NLR (≥2.05) patients experienced at least one of the poor outcomes compared to only 6.1% (14/229) without elevated postoperative NLR (p < 0.001). Infants in the elevated NLR group had a higher incidence of comorbidity: postoperative re-intubation (9.2% vs 1.3%, p <0.001), re-operation (7.7% vs 1.7%, p = 0.003), need for peritoneal dialysis (3.6% vs 0%, p = 0.004), pulmonary infection (25.1% vs 8.1%, p < 0.001), prolonged ICU stay (20.5% vs 3.5%, p < 0.001), and prolonged mechanical ventilation time (20.5% vs 3.9%, p < 0.001). However, differences in death (1.5% vs 0.9%, p = 0.665), incision infection (0% vs 0.9%, p = 0.502) and requirement of ECMO (1.0% vs 0%, p = 0.211) were not significant between the two groups. Median mechanical ventilation time, length of ICU and hospital stay were 26 hours, 5 days and 17 days in elevated NLR patients, respectively, but only 9 hours, 3 days, and 12 days in non-elevated NLR patients (p < 0.001). Results are shown in Table 4.

Table 4

Comparison of poor outcomes between the elevated postoperative NLR and non-elevated postoperative NLR patients
As presented in Table 5, the multivariable logistic regression model showed that postoperative NLR (OR 1.298, 95%CI 1.153-1.461, \( p < 0.001 \)) predicted a composite of poor outcomes, after adjusting for basic clinical predictions (age, gender, weight, RACHS score, and CPB duration). When NLR was analyzed as a categorical variable, elevated postoperative NLR (\( \geq 2.05 \)) (OR 3.722, 95%CI 1.895-7.309, \( p < 0.001 \)) was also an independent risk factor for poor outcomes. However, preoperative NLR showed no prognostic significance for poor outcomes (\( p = 0.097 \)).
| Variable                               | Wald  | p-value | OR     | 95%CI            |
|----------------------------------------|-------|---------|--------|-----------------|
| NLR Model 1                            |       |         |        |                 |
| Gender                                 | 5.185 | 0.023   | 2.062  | 1.106-3.844     |
| Weight                                 | 9.964 | 0.002   | 0.716  | 0.581-0.881     |
| CPB duration                           | 13.025| <0.001  | 1.016  | 1.006-1.021     |
| Postoperative NLR                      | 18.620| <0.001  | 1.298  | 1.153-1.461     |
| NLR Model 2                            |       |         |        |                 |
| Gender                                 | 8.662 | 0.003   | 2.488  | 1.356-4.565     |
| Weight                                 | 11.378| 0.001   | 0.708  | 0.580-0.865     |
| CPB duration                           | 13.816| <0.001  | 1.012  | 1.006-1.019     |
| Elevated postoperative NLR             | 14.561| <0.001  | 3.722  | 1.895-7.309     |
| NLR Model 3                            |       |         |        |                 |
| Gender                                 | 4.353 | 0.037   | 1.861  | 1.038-3.334     |
| Age                                    | 9.960 | 0.002   | 0.849  | 0.767-0.940     |
| CPB duration                           | 27.261| <0.001  | 1.017  | 1.011-1.023     |
| Preoperative NLR                       | 2.759 | 0.097   | 1.739  | 0.905-3.341     |

NLR, neutrophil-lymphocyte ratio; CPB: cardiopulmonary bypass;

The basic model included age, gender, weight, RACHS score, and CPB duration demonstrated good predictive power (AUC 0.759, 95%CI 0.693-0.826), with better discrimination in the NLR Model 1 (AUC 0.813, 95%CI 0.754-0.872) and NLR Model 2 (AUC 0.797, 95%CI 0.739-0.855) containing postoperative NLR as a categorical variable. Results are shown in Table 6. The NLR Model 1 and NLR Model 2 demonstrated improvement on the basic model as measured by the absolute difference in AUC, respectively ($\Delta$AUC = 0.0538, $p = 0.0043$) and ($\Delta$AUC = 0.0378, $p = 0.0436$). The NLR Model 1 had the best predictive performance among the three models (sensitivity 82.35%, specificity 71.63%). ROC comparison between the NLR model and basic model is illustrated in Figure 2.
| Variables      | AUC (95%CI)       | Sensitivity | Specificity | Youden index | p-value |
|---------------|------------------|-------------|-------------|--------------|---------|
| Basic Model   | 0.759 (0.693-0.826) | 79.41       | 65.17       | 0.4458       | <0.001  |
| NLR Model 1   | 0.813 (0.754-0.872) | 82.35       | 71.63       | 0.5398       | <0.001  |
| NLR Model 2   | 0.797 (0.739-0.855) | 75.00       | 73.60       | 0.4860       | <0.001  |

ROC, receiver operating characteristic; NLR, neutrophil-lymphocyte ratio

Comment

The main findings of this study were that postoperative NLR showed an obvious increase as a result of cardiac surgery and CPB. Postoperative NLR was associated with poor outcomes in infants undergoing congenital heart surgery, and NLR on the third day after surgery had the best predictive performance with a cut-off value of 2.05. After adjustment for other risk factors, the elevated postoperative NLR still emerged as an independent predictor of poor outcomes. In addition, postoperative NLR was significantly correlated with mechanical ventilation time, length of ICU and hospital stay. The result suggests that postoperative NLR could be a predictor for poor outcomes in infants undergoing CPB.

Systemic inflammatory response syndrome is frequently observed after cardiac surgery, which plays an important role in the pathogenesis of adverse clinical outcomes related to cardiopulmonary bypass and surgical trauma [11, 12]. The comprehensive contact of blood with the surface of the cardiopulmonary bypass circuit causes an inflammatory cascade of body fluid (pro-inflammatory cytokines, complement, and blood coagulation system), as well as cells (leukocytes, platelets, and vascular endothelial cells) [13]. These inflammatory pathways are complicated and interconnected in multiple ways with each other, exaggerating their mutual effect. Meanwhile, ischemia-reperfusion injury and endotoxemia, as a result of hypothermic advection perfusion or even circulatory arrest, leads to vascular endothelial injury by release of reactive oxygen species and variations of the microcirculation [2]. Compared with adult patients, the inflammatory response is more severe in pediatric patients undergoing CPB [14]. Many studies have indicated a higher incidence of SIRS in children with younger age or lower body weight after CPB [15, 16]. Due to the lower body weight, the pediatric patient’s total blood volume is seriously mismatched with the surface area of the cardiopulmonary bypass circuit and priming volume, leading to greater activation of the inflammatory response and theoretically higher risk of SIRS [17]. What’s more, younger children may experience a greater risk of SIRS for their immature organ function and a higher metabolic rate [1, 17].

Although a variety of biomarkers of inflammatory response have been determined in the prediction and diagnosis of adverse outcomes, few could readily and conveniently use in current clinical practice. NLR has been paid more attention for its significant features of low price, immediate access, direct and repeatable detection. Various evidence regards NLR as a novel marker, which can reflect the level of systematic inflammation [18, 19] and a good indicator for predicting and diagnosing prognostic outcomes in several diseases [20–22]. The neutrophil is an essential component of the systemic inflammatory response to tissue injury and reperfusion injury [23]. Converted WBC subtypes, specifically
elevated neutrophils with reduced lymphocytes represent an inflammatory process that has been associated with increased risk of death and myocardial infarction in patients with coronary artery disease [24]. Recent studies indicated NLR was an independent predictor of adverse outcomes and harmed long-term survival after open-heart surgery in adult patients [25].

In adult patients, an increase in perioperative NLR was associated with raised mortality and morbidity in patients undergoing cardiac surgery [26], which may guide perioperative management and risk-stratification of patients. Many investigators have also proposed and proved the application of NLR in pediatric heart surgery. Xu et al [9] found that postoperative NLR increased significantly after open-heart surgery with cardiopulmonary bypass, which was consistent with prolonged mechanical ventilation time and ICU length of stay. Manuel et al [27] retrospectively analyzed 141 univentricular patients, results showed preoperative NLR was associated with an increase in prolonged total hospital length of stay, duration of mechanical ventilation, and ICU length of stay, and these pediatric patients had higher mortality in 24 months after the operation. Moreover, a recent study [28] also reported NLR could predict prolonged mechanical ventilation as a novel indicator, which was closely related to early postoperative clinical outcomes. Savluk and colleagues [8] evaluated the impact of preoperative NLR in Norwood stage I operations. They demonstrated a correlation between high preoperative NLR with an increased risk of death in 53 patients. Besides, Iliopoulos et al [7] indicated that elevated preoperative neutrophil-lymphocyte ratio had almost three times more risk to develop low cardiac output in children after congenital heart surgery.

In the current study, preoperative NLR was not an independent risk factor for predicting postoperative adverse outcomes, which was different from the conclusions of previous studies [8, 27, 29]. Although preoperative NLR was associated with mechanical ventilation time and length of ICU stay like other studies, the small coefficient indicated a weak correlation. Meanwhile, postoperative NLR on the first day after surgery showed no prognostic significance. The disparate results limit the application of NLR in predicting clinical outcomes during early postoperative period in infants after CPB. Most subjects in previous studies were older than infants and the endpoints varied from each other, which may help explain the difference in results. In addition, NLR on different days in pediatric heart surgery was not shown before. By comparing NLR on different perioperative days, we found that the NLR on the third day after surgery has the best predictive performance for poor outcomes, which was an independent risk factor at the same time. Furthermore, it has a strong correlation with mechanical ventilation time, length of ICU and hospital stay.

Our data exhibited that perioperative NLR rose to a peak on the first day after surgery in infants undergoing cardiac surgery. Compared with the infants without poor outcomes, whose NLR gradually decreased after surgery, patients with poor outcomes maintained a high level of postoperative NLR for a week or even longer, which indicates a sustained high level of inflammatory response. This might be the potential performance of the poor outcomes rather than the cause, however, postoperative NLR did have a significant correlation with poor prognosis and clinical outcomes. Our results suggest the importance to pay attention to the inflammatory response in the pediatric population. Thus, we speculate that active
prevention of systemic inflammatory response may protect immature organs from injury, furthermore reduce postoperative mortality and morbidity.

There are a few limitations to our study. Firstly, as a retrospective study conducted in our hospital, it would inevitably be affected by systematic errors and bias. Secondly, 73 patients were excluded due to incomplete data, and most of them didn't have postoperative daily blood routine examination for their fast recovery from surgery, which may have a slight impact on the results. Finally, the specific relationship between NLR and inflammatory response remains unclear, because well-established inflammatory biomarkers such as inflammatory factors and C-reactive protein are not daily available. More further researches are needed before we fully understand this phenomenon.

**Conclusion**

This study demonstrated postoperative NLR was correlated with increased mechanical ventilation time, length of ICU and hospital stay. Elevated postoperative NLR ($\geq 2.05$) was an independent predictor for poor outcomes following congenital heart surgery in infants. NLR was a good biomarker that showed satisfying prognostic significance and could be utilized as a convenient and low-cost indicator for postoperative care after pediatric cardiac surgery.

**Abbreviations**

NLR: neutrophil-lymphocyte ratio; CPB: cardiopulmonary bypass; SIRS: systemic inflammatory response syndrome; PICU: pediatric intensive care unit; RACHS: risk adjustment for congenital heart surgery.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Medical Ethics Committee of Fuwai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences (approval number: 2021-1483). Written informed consent was provided by all participants' legal guardians.

**Consent for publication**

Not applicable.

**Availability of data and materials**
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare no competing interests.

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**Authors' contributions**

Study design, data analysis, interpretation of results, drafting of manuscript: GP. Interpretation of results, reviewing the manuscript: WX. Data collection, database design, reviewing the manuscript: ZPY, JY, BLT, LYX. Study design, interpretation of results, critical reviewing the manuscript: LJP. All authors read and approved the final manuscript.

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Figures
Figure 1

Perioperative NLR variation in infants with poor outcomes and non-poor outcomes (* indicates a p-value at 0.05-0.01, ** indicates a p-value at 0.01-0.001, *** indicates a p-value <0.001)
Figure 2

ROC comparison between the NLR model and basic model.