Postoperative Neutrophil-to-Lymphocyte Ratio Is Associated with Mortality in Adult Patients After Cardiopulmonary Bypass Surgery: A Cohort Study

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Background: Cardiopulmonary bypass (CPB) contributes to the development of systemic inflammatory response after cardiothoracic surgery. As a measure of inflammation and immune reaction, the neutrophil-to-lymphocyte ratio (NLR) has been linked to poor outcomes in a variety of diseases. However, it remains to be seen whether postoperative NLR is associated with CPB patient mortality. The purpose of this research was to explore the prognostic role of the postoperative NLR in adult patients undergoing cardiothoracic surgery with cardiopulmonary bypass.

Material/Methods: This study incorporates data from the MIMIC III database, which includes more than 50,000 critically ill patients. The variable of interest was postoperative NLR. The primary outcome was 30-day mortality and the secondary outcomes were 90-day mortality, length of intensive care unit stay, and length of hospital stay.

Results: We enrolled 575 CPB patients. The ROC curve for the postoperative NLR to estimate mortality was 0.741 (95% confidence interval [CI]: 0.636-0.847, \(P<0.001\)), and the critical value was 7.48. There was a significant difference between different postoperative NLR levels in the Kaplan-Meier curve (\(P=0.045\)). Furthermore, elevated postoperative NLR was associated with increased hospital mortality (hazard ratio [HR]: 1.1, 95% CI: 1.0-1.1, \(P=0.021\)). However, there was no important relationship in these patients between the postoperative NLR levels and 90-day mortality (HR: 1.1, 95% CI: 1.0-1.5, \(P=0.465\)).

Conclusions: Our findings suggest that higher postoperative NLR is associated with greater hospital mortality in adult patients undergoing cardiopulmonary bypass surgery.

Keywords: Cardiopulmonary Bypass • Hospital Mortality • Outcome Assessment, Health Care

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Background

Cardiovascular disease and its associated risk factors are the leading cause of death worldwide [1]. Cardiothoracic surgery with cardiopulmonary bypass (CPB) is the criterion standard treatment for various serious heart diseases, and many studies have shown that CPB contributes to the development of systemic inflammatory response after cardiothoracic surgery [2-4]. Numerous studies have confirmed increased inflammatory mediators among several patients following CPB [5-8]. However, in clinical practice, there are no inflammatory biomarkers for outcome evaluation. Therefore, it is critical to identify early postoperative clinical factors associated with an increased risk of poor outcomes.

The neutrophil-to-lymphocyte ratio (NLR) is an innovative inflammatory biomarker derived from combined neutrophil and lymphocyte counts [9]. Non-specific inflammation triggers neutrophils, whereas a decreased lymphocyte count suggests that the body is under stress or has poor immunity. The NLR integrates these 2 opposing immune pathways [10]. Additionally, as an innovative inflammatory marker, the NLR has been associated with the severity and prognosis of various cardiovascular problems [11,12]. Moreover, prior to heart surgery, an elevated NLR is associated with decreased survival [13-15]. Despite this, the association between increased postoperative NLR and worse prognosis in adult patients after cardiothoracic surgery with CPB remains unclear. Therefore, the purpose of this study was to explore the prognostic role of postoperative NLR in adult patients undergoing cardiothoracic surgery with CPB.

Material and Methods

Data Source

The Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC III, V.1.4) database maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology's Laboratory has extensive data on over 50 000 patients admitted to the critical care unit at Beth Israel Deaconess Medical Center over the years 2001 to 2012 [16]. For the purpose of applying for access to the database, we took the National Institutes of Health’s web-based course “Protecting Human Research Participants”.

Institutional review boards at both the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) gave their approval for the creation of the database. The data for this study were collected by the author Jiang after completing an online training course offered by the National Institutes of Health (certification number: 9322422).

Population Selection Criteria

The MIMIC III database had information on 58 976 intensive care unit (ICU) patients in total. In these people, we included patients who underwent cardiac surgery utilizing cardiopulmonary bypass, were older than 18 years, and stayed in the ICU for at least 2 days. Patients were excluded if they had a missing neutrophil or lymphocyte count to calculate the NLR, had >1% missing data, or had been diagnosed with hematological disorders such as leukemia or lymphoma. Only data of the first ICU admission of the first hospitalization were used.

Data Extraction

Data were extracted from the database using Structure query language (SQL). It included white blood cell (WBC) count, neutrophil, lymphocyte, and platelet count, hemoglobin, hematocrit, serum lactate, serum bicarbonate, anion gap, serum chloride, serum sodium, serum potassium, and serum glucose. NLR was calculated using complete neutrophil and lymphocyte counts. Since the patients had several measurements available, the arithmetic mean between the highest and the lowest value in the first 24 h postoperatively was used. The NLR in the first 24 h of the postoperative period was chosen because during this time as systemic inflammatory response is usually the most severe then.

Demographic parameters included age, sex, ethnicity (white, black, or other), height, weight, vital signs, comorbidities, and disease severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] III) [17]. Measurements of vital signs, comorbidities, and disease severity scores were collected on the first day of ICU admission. The follow-up began on the day of admission to the ICU. The primary outcome was 30-day mortality and the secondary outcomes included 90-day mortality, length of intensive care unit stay (ICU LOS), and length of hospital stay (hospital LOS).

Statistical Analyses

The mean and standard deviation (SD) or median and interquartile ranges are presented in the tables for continuous variables. The t test, Wilcoxon test, or Kruskal-Wallis test were performed, as appropriate. The diagnostic efficiency was shown by the receiver operating characteristic (ROC) curve, and Youden indexes were computed. The optimal NLR cut-off value was determined using the highest Youden Index. All study participants were separated into 2 groups based on the NLR cut-off value. For categorical variables expressed as percentages, the chi-square or Fisher’s exact test was utilized. To estimate the association between postoperative NLR and all-cause mortality, Kaplan-Meier curve and log rank method were used. To classify predictors of death, multivariate Cox regression analysis...
was performed. Relevant covariates known to predict outcome were entered into the model, including age, sex, ethnicity, BMI, heart rate, MAP, SpO\textsubscript{2}, temperature, comorbidities, laboratory tests, and APACHE III score. These variables were selected due to their clinical relevance. The final models were built using a stepwise backward elimination method with a significance level of 0.05. SPSS software was used for all statistical analysis (SPSS-22.0; IBM Corp., Armonk, NY, USA). A two-sided \( P < 0.05 \) was used to indicate statistical significance.

### Results

Finally, 575 patients met the study’s criteria. Figure 1 depicts the data selection approach and data exclusion criteria. The demographic features of survivors and non-survivors are summarized in Table 1. NLR was significantly lower for survivors (9.1±9.2) than non-survivors (24.3±26.4) (\( P < 0.001 \)). Additionally, non-survivors appeared to be more likely to have a higher respiratory rate, lower blood pressure and SPO\textsubscript{2}, higher BUN, SCr, serum lactate, and APS III scores, and a history of CHF, AF, chronic renal disease, and pneumonia (\( P < 0.05 \)).

According to the ROC of the NLR (Figure 2), the critical value was 7.48, with an AUC of 0.741 (95% CI: 0.636-0.847, \( P < 0.001 \)), corresponding to an 80.0% predictive sensitivity and a 58.0% predictive specificity.

According to the cut-off value, all patients were divided into 2 groups. Table 2 summarizes the postoperative outcomes for the 2 NLR categories. Observed hospital mortality and 90-day mortality were higher in the elevated NLR group compared with the non-elevated NLR group (\( P < 0.001 \), all). Additionally, the elevated NLR group had longer hospital stay and ICU stay (\( P < 0.001 \), both).

The Kaplan-Meier curve analysis revealed that all-cause mortality was significantly different between the different NLR levels.

### Table 1. Comparisons of demographics between survivors and non-survivors.

| Characteristics | Survivors (n=550) | Non-survivors (n=25) | \( p \) Value |
|-----------------|-------------------|----------------------|---------------|
| Age (year)      | 67.1±12.29        | 70.6±15.9            | 0.182         |
| Sex, n (%)      |                   |                      | 0.317         |
| Male            | 382 (69.5%)       | 15 (60.0%)           |               |
| Female          | 168 (30.5%)       | 10 (40.0%)           |               |
| BMI (Kg/m\textsuperscript{2}) | 29.0±6.3       | 30.9±8.0             | 0.144         |
| Ethnicity, n (%)|                   |                      | 0.973         |
| White           | 431 (78.4%)       | 20 (80.0%)           |               |
| Black           | 21 (3.8%)         | 1 (4.0%)             |               |
| Other           | 98 (17.8%)        | 4 (16.0%)            |               |
| Vital signs     |                   |                      |               |
| HR (beats/min)  | 83.9±11.6         | 88.2±17.5            | 0.077         |
| RR (beats/min)  | 14.5±4.2          | 16.5±5.2             | 0.020         |
| SBP, mmHg       | 114.1±17.5        | 102.8±13.5           | 0.002         |
| DBP, mmHg       | 60.2±11.5         | 54.1±14.4            | 0.010         |
| MBP, mmHg       | 78.0±12.4         | 70.7±10.1            | 0.004         |
Table 1 continued. Comparisons of demographics between survivors and non-survivors.

| Characteristics                             | Survivors (n=550) | Non-survivors (n=25) | p Value |
|---------------------------------------------|-------------------|----------------------|---------|
| **SPO2, %**                                 | 98.8±2.4          | 97.3±3.8             | 0.005   |
| **Laboratory parameters**                   |                   |                      |         |
| Hemoglobin, g/dL                            | 9.9±2.3           | 9.8±2.4              | 0.879   |
| Hematocrit, %                               | 28.5±6.7          | 29.6±6.8             | 0.933   |
| WBC count, 10^9/L                           | 12.9±5.0          | 13.4±4.9             | 0.659   |
| Neutrophil, (%)                             | 80.0±8.0          | 82.7±5.8             | 0.107   |
| Lymphocyte, (%)                             | 14.2±7.1          | 10.6±5.1             | 0.014   |
| NLR                                         | 9.1±9.2           | 24.3±26.4            | <0.001  |
| Platelet count, 10^9/L                      | 176±67.6          | 191.7±87.5           | 0.262   |
| Serum sodium, mmol/l                        | 136.3±3.1         | 136.3±3.5            | 0.986   |
| Serum potassium, mmol/l                     | 4.7±0.8           | 4.9±1.2              | 0.100   |
| Serum chloride, mmol/l                      | 105.7±4.4         | 106.2±6.1            | 0.593   |
| Anion gap, mmol/l                           | 11.5±2.9          | 14.3±3.5             | <0.001  |
| Serum bicarbonate, mmol/l                   | 24.0±2.6          | 21.3±3.5             | <0.001  |
| BUN, mg/dL                                  | 20.2±11.5         | 32.1±17.7            | <0.001  |
| SCr, mg/dl                                  | 1.1±0.7           | 1.9±1.3              | <0.001  |
| Serum glucose, mg/dl                        | 141.0±43.1        | 153.6±58.0           | 0.159   |
| Serum lactate, mmol/l                       | 2.4±1.3           | 3.3±2.1              | 0.001   |
| Vasoactive drug use, n (%)                  | 543 (98.7%)       | 25 (100%)            | 0.731   |
| **Comorbidities, n (%)**                    |                   |                      |         |
| Endocarditis                                | 17 (3.1%)         | 3 (12.0%)            | 0.051   |
| CHF                                         | 171 (31.1%)       | 13 (52.0%)           | 0.028   |
| AF                                          | 271 (49.3%)       | 17 (68.0%)           | 0.067   |
| Chronic renal disease                       | 14 (2.5%)         | 3 (12.0%)            | 0.033   |
| Chronic liver disease                       | 5 (0.9%)          | 0 (0)                | 0.800   |
| COPD                                        | 5 (0.9%)          | 1 (4.0%)             | 0.235   |
| CAD                                         | 396 (72.0%)       | 16 (64.0%)           | 0.385   |
| Stroke                                      | 27 (4.9%)         | 3 (12.0%)            | 0.136   |
| Malignancy                                  | 12 (2.2%)         | 0 (0)                | 0.584   |
| Pneumonia                                   | 53 (9.6%)         | 9 (36.0%)            | 0.001   |
| APS III                                     | 36 (28.49)        | 50 (40.73)           | <0.001  |

Data are presented as the mean±SD and n (%). BMI – body mass index; HR – heart rate; RR – respiratory rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; MBP – mean blood pressure; SPO2 – percutaneous oxygen saturation; WBC – white blood cell; NLR – neutrophil-to-lymphocyte ratio; SCR – serum creatinine; BUN – blood urea nitrogen; CHF – congestive heart failure; AF – atrial fibrillation; COPD – chronic obstructive pulmonary disease; CAD – coronary artery disease; APS III – acute physiology score III.
In contrast to patients with NLR lower than 7.48, those with NLR higher than 7.48 had higher mortality \((P=0.045)\).

To determine potential predictors of hospital mortality and 90-day mortality in the study population, multivariate analysis was used (Table 3). The analysis showed that after adjusting for covariates, higher NLR was associated with higher hospital mortality \((\text{HR}=1.1, \; 95\% \; \text{CI} \; 1.0-1.1, \; P=0.021)\). However, after adjusting for covariates, no association was observed between NLR levels and 90-day mortality in those patients \((\text{HR}=1.1, \; 95\% \; \text{CI} \; 1.0-1.5, \; P=0.465)\).

**Discussion**

Our study revealed that elevated postoperative NLR was an independent predictor of hospital mortality in adult patients undergoing cardiothoracic surgery with CPB. Hospital mortality increased with an increase in the NLR \((\text{HR}=1.1, \; P=0.021)\). According to the ROC of the NLR, the critical value was 7.48, with an area under the curve of 0.741 \((95\% \; \text{CI} \; 0.636-0.847, \; P<0.001)\), corresponding to 80.0% predictive sensitivity and 58.0% predictive specificity.

Numerous studies have shown that CPB induces a systemic inflammatory response, likely due to blood components coming into contact with the artificial surface of the extracorporeal circuit. This contributes to the high mortality associated with heart surgery [3,18-20]. White blood cell count is a marker of systemic inflammation [21,22] and has also been associated with mortality after heart surgery [23,24]. However, the potential function of the absolute white blood cell count is limited by apparent confounding variables, and the association between increased white blood cell count and outcomes is non-linear [22,24]. Neutrophils are the most abundant type of white blood cell, and they respond rapidly to acute inflammation while being...
Table 3. Multivariate Cox hazard model NLR (adjusted HRs) for the possible predictors of outcomes in the study population.

| Variable          | HR    | 95% CI       | p Value |
|-------------------|-------|--------------|---------|
| Hospital mortality|       |              |         |
| Elevated NLR      | 1.1   | 1.0-1.1      | 0.021   |
| MBP               | 0.9   | 0.9-1.0      | 0.009   |
| SCr               | 1.6   | 1.1-2.4      | 0.009   |
| Serum lactate     | 1.4   | 1.1-1.9      | 0.014   |
| 90-day mortality  |       |              |         |
| Elevated NLR      | 1.1   | 1.0-1.1      | 0.465   |
| Ethnicity         |       |              |         |
| White             |       |              |         |
| Black             | 1.6   | 0.2-12.7     | 0.66    |
| Other             | 3.7   | 1.4-9.6      | 0.008   |
| SCr               | 2.2   | 1.4-3.6      | 0.001   |
| Serum lactate     | 1.3   | 1.1-1.6      | 0.007   |

Multivariate Cox proportional hazards regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

capable of killing invading pathogens [25]. Inflammation caused by CPB is primarily mediated by activated neutrophils, leading to systemic inflammation [26,27]. CPB initiates the complement cascade by activating neutrophils and inducing the secretion of polymorphonuclear elastase (PMN-E). The overactivation of PMN-E leads to cell damage and promotes the synthesis and release of IL-8 by IL-1 signaling, which indirectly enhances inflammatory reactions [28]. Furthermore, tissue and endothelial dysfunction are caused by neutrophil-driven enzymes such as elastase, myeloperoxidase, and reactive oxygen species, rendering patients vulnerable to organ damage. Activated neutrophils also directly stimulate endothelial cells, increasing perivascular edema and leukocyte migration to the extracellular matrix [29]. The development of cortisol and neuroendocrine stress was linked to lymphopenia after major operations [30], indicating that the body was stressed and the immune system was compromised. Therefore, the NLR reflects these 2 diametrically opposed immune pathways. One reflects unrestrained inflammation, while the other reflects a potential immune pathway. Furthermore, NLR is determined during a routine full blood count following surgery. Additional inspections are not necessary, and it is an inexpensive and readily available marker. Several studies have previously sought to link NLR with cardiac surgery mortality. The NLR levels were correlated with the outcomes of patients undergoing cardiac surgery with CPB [13-15,31,32]. Although most studies examined the relationship between preoperative or perioperative NLR and outcomes, few studies have examined the prognostic significance of postoperative NLR in patients undergoing cardiac surgery with CPB. In children with CPB, Xu et al [33] discovered a significant and positive association between early outcomes and postoperative NLR. Adult patients undergoing CPB had a weaker inflammatory response than pediatric patients [2]. According to our study, postoperative NLR was also associated with early prognosis in adult patients undergoing CPB.

Contrary to our study, the findings of a recent meta-analysis [31] and a study by Silberman et al (2018), in which 3027 adult patients who underwent CPB surgery were evaluated [15], the preoperative NLR and long-term mortality (>90 days) were strongly and positively associated. We propose a possible explanation for this finding. Elevated preoperative NLR reflects chronic background inflammation caused by chronic cardiovascular disease. Neutrophils are associated with the hypercoagulable state of coronary artery disease and the unstable atherosclerotic plaque state. These indicate patients with high cardiovascular risk [34]. The elevated postoperative NLR demonstrates the extent of myocardial injury and the degree of hypoperfusion caused by decreased cardiac output and ischemia-reperfusion syndrome [35]. However, these are temporary. Therefore, the association between postoperative NLR and long-term mortality (90-day mortality) was not significant. Additionally, a study by Wang et al [36] showed that the postoperative NLR with a cut-off value of 7.28 is an independent predictor of short survival. This finding is consistent with our results. However, they also found that postoperative NLR is positively associated with long-term mortality (90 days). This is in contrast to our results. We propose possible explanations for this finding. First, the NLR selected was different. Although NLR was determined in the first 24 h postoperatively, we used the arithmetic mean between the highest and lowest values. Wang et al [36] might have used the highest NLR.
value. Second, as this was a retrospective study, to process missing data, the analysis of the primary outcome was replicated after multiple imputations. This gave rise to an inevitable bias. Further investigations (including clinical trials) are necessary to explore the relationship between postoperative NLR and mortality in the future.

Our study has some limitations. First, we selected patients who stayed in the intensive care unit (ICU) for at least 2 days, as we aimed to select patients with severe illness and inflammatory reactions. However, the current findings cannot be applied to patients who were transferred from the ICU or those who died within the first 48 h. Second, as the datasets utilized in this analysis were from publicly available data, intraoperative variables such as CPB time, DHCA time, cross-clamping time, and the use of a balloon pump were not collected.

Conclusions
Elevated postoperative NLR is associated with increased hospital mortality, hospital length of stay (LOS), and ICU LOS in adult patients after CPB surgery. Owing to the simplicity of determining the NLR using complete blood count values, monitoring the postoperative NLR can predict the early outcome of adult patients undergoing CPB surgery.

Conflicts of Interest
None.

Declaration of Figures Authenticity
All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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