

## Association between Postoperative Neutrophil/Lymphocyte Ratio, Neutrophil/Platelet Ratio with Mortality after Off-Pump Cardiac Surgery in Premature Newborns

Prematüre Yenidoğanlarda Pompasız Kalp Cerrahisi Sonrası Postoperatif Nötrofil/Lenfosit Oranı, Nötrofil/Trombosit Oranı ile Mortalite Arasındaki İlişki

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### ABSTRACT

**Objective:** Each year nearly 15 million premature babies are born and their survival rates around the world vary dramatically. Neutrophil-lymphocyte ratio (NLR) is not only a novel marker of systemic inflammation but also a reliable predictor of poor prognosis, response to surgical or medical therapy. Neutrophil-platelet ratio (NPR) is also gaining importance in some emerging studies as an effective screening tool for inflammatory process. The objective of the present study was to evaluate the association of postoperative NLR and NPR with clinical outcomes in prematures undergoing off-pump cardiac surgery, thereby providing an underlying predictor for clinical prognosis.

**Methods:** Records of 14 premature infants were retrospectively evaluated. These patients' PDAs were closed surgically without cardiopulmonary bypass. The association of postoperative NLR and NPR with post-operative outcomes such as postoperative length of stay, hospital length of stay, postoperative mechanical ventilation time and hospital mortality was evaluated.

**Results:** This study was conducted with fourteen premature infants with a mean ( $\pm$ SD) gestational age of 25.7( $\pm$ 2.0) weeks and a mean weight of 1191( $\pm$ 553) g at the time of operation. A positive correlation was detected between postoperative NPR and both postoperative NLR ( $r=0.704, P=0.005$ ) and mortality ( $r=0.598, P=0.024$ ). However, there was no statistically significant relationship between both postoperative NLR, NPR and mean postoperative length of stay, mean hospital stay and mean postoperative mechanical ventilation time. Also there was no statistically significant relationship between NLR and mortality. However, when the patients were divided into 2 groups as alive and dead NLR and NPR were significantly higher in dead group compared to alive group.

**Conclusions:** There is a positive correlation between postoperative NPR and both postoperative NLR and mortality. Both NLR and NPR are easily obtained and inexpensive markers that can offer an additional means of risk stratification in this vulnerable premature population undergoing off-pump cardiac surgery.

**Keywords:** Neutrophil/lymphocyte ratio (NLR), Neutrophil/platelet ratio (NPR), Premature

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### ÖZET

**Amaç:** Her yıl yaklaşık 15 milyon prematüre bebek doğuyor ve dünya çapında hayatta kalma oranları önemli ölçüde değişiyor. Nötrofil-lenfosit oranı (NLR) sadece sistemik enflamasyonun yeni bir belirteci değil, aynı zamanda kötü prognoz, cerrahi veya medikal tedaviye yanıtın güvenilir bir göstergesidir. Nötrofil-trombosit oranı (NPR), yeni ortaya çıkan bazı çalışmalarda inflamatuvar süreç için etkili bir tarama aracı olarak da önem kazanmaktadır. Bu çalışmanın amacı, pompasız kalp ameliyatı geçiren prematürelere postoperatif NLR ve NPR'nin klinik sonuçlarla ilişkisini değerlendirmek ve böylece klinik prognoz için altta yatan bir belirteç sağlamaktır.

**Yöntem:** On dört prematüre bebeğin kayıtları retrospektif olarak incelendi. Bu hastaların PDA'ları kardiyopulmoner baypas yapılmadan cerrahi olarak kapatıldı. Postoperatif NLR ve NPR'nin postoperatif kalış süresi, hastanede kalış süresi, postoperatif mekanik ventilasyon süresi ve hastane mortalitesi gibi postoperatif sonuçlarla ilişkisi değerlendirildi.

**Bulgular:** Bu çalışma, ortalama ( $\pm$ SS) gebelik yaşı 25,7( $\pm$ 2,0) hafta ve ortalama ameliyat ağırlığı 1191( $\pm$ 553) g olan 14 prematüre bebek ile gerçekleştirildi. Postoperatif NPR ile hem postoperatif NLR ( $r=0.704, P=0.005$ ) hem de mortalite ( $r=0.598, P=0.024$ ) arasında pozitif korelasyon saptandı. Ancak hem postoperatif NLR, NPR hem de ortalama postoperatif kalış süresi, ortalama hastanede kalış süresi ve ortalama postoperatif mekanik ventilasyon süresi arasında istatistiksel olarak anlamlı bir ilişki yoktu. Ayrıca NLR ile mortalite arasında istatistiksel olarak anlamlı bir ilişki yoktu. Ancak hastalar sağ kalan ve sağ kalmayan olarak 2 gruba ayrıldığında NLR ve NPR sağ kalmayan grupta sağ kalan gruba göre anlamlı olarak yüksekti.

**Sonuç:** Postoperatif NPR ile hem postoperatif NLR hem de mortalite arasında pozitif bir korelasyon vardır. Hem NLR hem de NPR, pompasız kalp ameliyatı geçiren prematüre popülasyonda ek bir risk sınıflandırma aracı sunabilen kolayca elde edilen ve ucuz belirteçlerdir.

**Anahtar Sözcükler:** Nötrofil/lenfosit oranı (NLR), Nötrofil/trombosit oranı (NPR), Prematüre

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## INTRODUCTION

Each year nearly 15 million premature babies are born and their survival rates around the world vary dramatically. Most premature babies (>80%) are between 32 and 37 weeks of gestation and due to advances in neonatal care many die simply the lack of basic care like immediate and exclusive breastfeeding, thermal care and hygienic cord and skin care (1). This basic care gains even more importance in the postoperative period in cardiac surgery patients.

Neutrophil-lymphocyte ratio (NLR) is not only a novel marker of systemic inflammation but also a reliable predictor of poor prognosis, response to surgical or medical therapy(2-4). There are also several studies claiming NLR is also a good prognostic factor of cardiovascular diseases and some malignancies like breast, kidney, esophagus, and lung cancers(5,6). NLR, as a simple parameter related to systemic inflammation, was first used by cardiologists to determine mortality risk after major cardiac events in adults(7). However, it is gaining importance in some emerging studies as a marker for low cardiac output, ductal patency, prognosis after cardiac surgery, and NEC(necrotizing enterocolitis) risk in premature babies and infants(8-11).

Neutrophil-platelet ratio (NPR) is also a marker for prognosis in patients with ST-elevated myocardial infarction (12). He et al. (13) reported NPR is associated with hemorrhagic transformation in patients with acute ischemic stroke and has a potential to predict the prognosis of acute ischemic stroke. NPR is also found to be an effective screening tool for inflammatory process and related with increased mortality in patients with infective endocarditis(14). Jin et al.(15) reported high NPR in patients with acute ischemic stroke was associated with poor prognosis.

Hypothesis was that there is a correlation between elevated postoperative NLR, NPR and poor outcomes in premature patients after pediatric cardiac surgery. However, to the best of our knowledge, there is no study in the literature designed to explore whether high NLR and NPR was associated with poor prognosis especially in premature infants undergoing cardiac surgery. The objective of the present study was to evaluate the association of postoperative NLR and NPR with clinical outcomes in prematures undergoing off-pump cardiac surgery, thereby providing an underlying predictor for clinical prognosis.

## MATERIALS and METHODS

Records of premature infants (gestational age < 37 weeks) were retrospectively evaluated. These infants were diagnosed as hemodynamically significant patent ductus arteriosus (PDA) unresponsive to medical therapy in the neonatal intensive care unit (NICU) of Diyarbakir Dr. Gazi Yasargil Training and Research Hospital between October 2020 and May 2022. Hemodynamically significant PDA was defined as one with an internal ductal diameter of  $\geq 1.5$  mm and/or with a left atrium/aortic root ratio  $\geq 1.5$  echocardiographically. These patients' PDAs were closed surgically without cardiopulmonary bypass (CPB). The only exclusion criteria was being transferred to another hospital after the operation. For each premature patient, the data were retrospectively collected through the electronic database of the hospital information system. NLR and NPR ratio were determined using neutrophil, lymphocyte, platelet counts from postoperative blood tests. The association of postoperative NLR and NPR with post-operative outcomes such as postoperative length of stay, hospital length of stay, postoperative mechanical ventilation time and hospital mortality sought to be evaluated. The study was undertaken in compliance with the guidelines of the Declaration of Helsinki, and it was approved by the local Ethics Committee (19.96.2022/97).

## Statistical analysis

The SPSS statistics software (SPSS, Inc., Chicago, IL, United States of America) was used to perform the statistical analysis (version 25 for Windows). Continuous data were presented as a mean  $\pm$  standard deviation together with its ranges in brackets and nominal variables were presented as counts and/or percentages. A p-value of 0.05 was used to determine the statistical significance of differences and correlations. Correlation analyses have been performed using Pearson's r.

## RESULTS

This study was conducted with fourteen premature infants with a mean ( $\pm$ SD) gestational age of 25.7 ( $\pm$ 2.0) weeks and a mean weight of 1191 ( $\pm$ 553) g at the time of operation. They were all PDA ligated by the same surgeon and the clinical data and postoperative outcomes of the whole cohort are shown in Table 1. Eight were females (57.1%), 6 were males (42.9%). The patients' mean NLR was 2.22 ( $\pm$ 3.67), mean NPR was 106.1 ( $\pm$ 66.6), postoperative mean mechanical ventilatory support time was 29.5 ( $\pm$ 42.63) days, mean hospital stay was 71.5 ( $\pm$ 56.08) days and the mean postoperative length of stay was 47.4 ( $\pm$ 44.2) days. There were 7 mortalities after the operation (50%) (Table 1). Causes of death were sepsis in four patients, necrotizing enterocolitis in one patient, hydrops fetalis in one patient and renal failure with hepatoblastoma in one patient. There was no intraoperative or surgery related mortality. Complications such as bleeding, pneumothorax were not seen.

Table 1: Clinical data and postoperative outcomes

	Mean $\pm$ SD (minimum– maximum)
Gestational age (week)	25.7 $\pm$ 2.0
Mean weight at surgery (g)	1191 $\pm$ 553
Mean postoperative LOS	47.4 $\pm$ 44.2
Mean hospital stay	71.5 $\pm$ 56.08
Mean postoperative MV time	29.5 $\pm$ 42.63
Mean NLR	2.22 $\pm$ 3.67
Mean NPR	106.1 $\pm$ 66.6

MV: Mechanical ventilation, LOS: Length of stay, NLR: Neutrophil-lymphocyte ratio, NPR: Neutrophil-platelet ratio.

A positive correlation was detected between postoperative NPR and both postoperative NLR ( $r = 0.704$ ,  $P = 0.005$ ) and mortality ( $r = 0.598$ ,  $P = 0.024$ ). However, there was no statistically significant relationship between both postoperative NLR, NPR and mean postoperative length of stay (LOS), mean hospital stay and mean postoperative mechanical ventilation (MV) time. Also there was no statistically significant relationship between NLR and mortality. However, when the patients were divided into 2 groups as alive and dead NLR and NPR were significantly higher in dead group compared to alive group (Table 2).

Table 2: Features of alive and dead cases

	Alive (n = 7)	Dead (n = 7)	p Value
Sex (male/female)	4/3	2/5	N/A
NLR	0.54 $\pm$ 0.4	3.91 $\pm$ 4.74	0.004*
NPR	67.7 $\pm$ 24.7	144.6 $\pm$ 74.6	0.028*
Mean postoperative LOS	56 $\pm$ 29.9	38.9 $\pm$ 56.8	0.124
Mean hospital stay	83.7 $\pm$ 51.3	59.3 $\pm$ 62	0.224
Mean postoperative MV time	20.1 $\pm$ 23.8	38.9.7 $\pm$ 56.3	0.337

MV: Mechanical ventilation, LOS: Length of stay, NLR: Neutrophil-lymphocyte ratio, NPR: Neutrophil-platelet ratio, N/A: not available.

## DISCUSSION

This study documented a significant relationship between postoperative NPR and mortality after cardiac surgery without CPB in prematures. In particular, elevated NLR(although it is not statistically significant) and NPR were associated with mortality. This is the first study to document the prognostic significance of especially postoperative NPR in prematures after cardiac surgery without CPB.

There are a number of studies demonstrating the importance of NLR after cardiac surgery and NLR's relationship with mortality in adults(16,17). Aldemir et al. studied the changes of NLR in patients undergoing on-pump and off-pump coronary artery bypass graft surgery(18). Iliopoulos et al(8). reported that pre-operative NLR may be a useful prognostic marker in children undergoing congenital heart surgery but they couldn't find any association between postoperative NLR and postoperative outcomes of the patients. In the current study, although there was a positive correlation between postoperative NPR and both postoperative NLR and mortality, there was no statistically significant relationship between NLR and mortality similar to the previous study. Manuel et al. (10) also reached similar results in their study group of 116 Tetralogy of Fallot (TOF) patients undergoing surgical repair. They reported that higher preoperative NLR was associated with long intensive care unit and hospital length of stay in patients undergoing TOF repair. Although there are studies emphasizing the importance of NLR on prognostic role and clinical course in preterm newborns, to the best of our knowledge there is no study in the literature investigating the relationship between postoperative NLR and mortality, clinical course in premature babies after off-pump cardiac surgery(9,19).

The clinical importance of NPR is increasing day by day. He et al. (13) reported that high NPR was associated with the increased risk of hemorrhagic transformation after acute ischemic stroke. Also NPR was found to have adequate diagnostic utility to identify ulcerative colitis patients(20). Kubat et al. (21) reported that NPR was successful to differentiate complicated acute appendicitis. Yildirim et al. (22) observed that NLR and NPR values were significant in determining the need for intensive care unit and mortality rate in patients diagnosed with Covid-19. Although NPR was found to be an important diagnostic and prognostic factor in previous studies, there was no study in the literature investigating its relationship with the postoperative outcomes of premature patients. However, in this study postoperative NPR was also found to be associated with mortality in premature patients after off-pump cardiac surgery.

The literature linking the NLR with outcomes in pediatric patients undergoing cardiac surgery continues to grow and this growth may accelerate with NPR. Neutrophils play a key role in inflammatory-mediated tissue injury and hypercoagulability. Over activation of the inflammatory processes can lead to myocardial dysfunction(23). This may even lead to more serious adverse outcomes even mortality in premature infants.

Inevitably, the following question comes to mind: Can we modify the postoperative outcomes of the patients with prophylactic postoperative anti-inflammatory treatment? This was not the subject of this research; but there are some studies claiming by reducing the level of cytokines using anti-inflammatory therapies a positive impact may be accomplished on outcomes of heart failure patients(24,25). As NLR and NPR gains importance as a marker of mortality in premature cardiac patients, using anti-inflammatory therapies for these patients may be an interesting future research.

This study, of course, has limitations. First of all this is a single center, retrospective study. It is small sample sized with 14 patients and a randomized, prospective trial could not be performed. Secondly, all the patients were operated by the same surgeon and although there was no surgery related mortality predominantly sepsis was the main cause of the death. One goal of future research is to perform a large prospective multicenter study with longterm, close follow-up of premature newborns and increase precautions for sepsis.

In conclusion, there is a positive correlation between postoperative NPR and both postoperative NLR and mortality. Both NLR and NPR are easily obtained and inexpensive markers that can offer an additional means of risk stratification in this vulnerable premature population undergoing off-pump cardiac surgery. Further studies in large multi-center cohorts are required to confirm validity and generalisability of these preliminary findings.

## Conflict of interest

No conflict of interest was declared by the authors.

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