

The Effect of Variations in the Neutrophil/Lymphocyte Ratio on The Length of Post-Operative ICU Stay in Cases Diagnosed with Transposition of the Great Arteries

Büyük Arterlerin Transpozisyonu Tanılı Olgularda Nötrofil/Lenfosit Oranı Değişikliklerinin Operasyon Sonrası Yoğun Bakımda Kalış Süresine Etkisi

🔟 Hatice Dilek Özcanoğlu, 1 🖻 Erkut Öztürk, 2 🖻 Şerife Özalp, 1 🖻 Selin Sağlam, 1 🗊 İncila Ali Kahraman, 1 D Berra Tan Recep, 3 ២ Behzat Tüzün, 3 🖻 Cansaran Tanıdır, 2 ២ Funda Gümüş Özcan, 1 ២ Ali Can Hatemi 3

¹Department of Anaesthesiology and Reanimation, İstanbul Basaksehir Çam and Sakura City Hospital, İstanbul, Türkiye İstanbul Başakşehir Çam ve Sakura Şehir Hastanesi, Anestezi ve Reaminasyon Anabilim Dalı, İstanbul, Türkiye ²Department of Pediatric Cardiology, İstanbul Basaksehir Çam and Sakura City Hospital, İstanbul, Türkiye İstanbul Başakşehir Çam ve Sakura Şehir Hastanesi, Çocuk Kardiyolojisi Anabilim Dalı, İstanbul, Türkiye **3Department of Pediatric Cardiovascular Surgery, İstanbul Basaksehir Çam and Sakura City Hospital, İstanbul, Türkiye** İstanbul Başakşehir Çam ve Sakura Şehir Hastanesi, Çocuk Kardiyolojisi Anabilim Dalı, İstanbul, Türkiye **3Department of Pediatric Cardiovascular Surgery, İstanbul Basaksehir Çam and Sakura City Hospital, İstanbul, Türkiye** İstanbul Başakşehir Çam ve Sakura Şehir Hastanesi, Çocuk Kalp Cerrahisi Anabilim Dalı, İstanbul, Türkiye

ABSTRACT

Objectives: In this context, the objective of this study is to investigate the effect of variations in the neutrophil/lymphocyte ratio on the length of post-operative intensive care unit (ICU) stay in cases that were diagnosed with transposition of the great arteries (TGA) and who subsequently underwent arterial switch operation (ASO).

Methods: This study was conducted with newborns that were diagnosed with TGA, followed up in the pediatric cardiac ICU, and who underwent ASO between January 1, 2021 and December 31, 2021. Variations in neutrophil-lymphocyte ratio (NLR) were recorded before and after the operation (day 1, 2, and 3). The primary endpoint was deemed as the prolonged post-operative ICU stay. For the purposes of this study, a prolonged post-operative ICU stay (PCILOS) was defined as a post-operative ICU stay that falls within the 25th percentile of the lengths of stay with the most extended durations.

Results: The patient group comprised 45 patients. The median age of the patients was 3 (interquartile range [IQR] 2-7) days, and the median operation weight was 3000 (IQR 2800-3100) grams. Of the patients included in the study, 51% were male, and 49% were female. Median duration on a mechanical ventilator, the median length of ICU stay, and median length of hospital stay were 48 (IQR 24-96) hours, 6 (IQR 5-12) days, and 12 (IQR 10-16) days, respectively. PCILOS duration was determined

ÖΖ

Amaç: Büyük arterlerin transpozisyonu yenidoğanlarda siyanotik kalp hastalığının önemli nedenlerinden biridir ve yaşamın ilk dönemlerinde cerrahi olarak tedavi edilmelidir. Son dönemlerde nötrofil/lenfosit oranı konjenital kalp hastalarında mortalite ve morbidite öngörüsü şeklinde yeni bir belirteç olarak kullanılmaktadır. Bu çalışmada, arteryel switch operasyonu yapılan büyük arterlerin transpozisyonu tanılı olgularda nötrofil/lenfosit oranı değişikliklerinin yoğun bakımda kalış süresine etkisi araştırıldı.

Yöntem: Çalışma 1 Ocak 2021-31 Aralık 2021 tarihleri arasında pediatrik kardiyak yoğun bakım ünitesinde izlenen ve arteryel switch operasyonu gerçekleştirilen büyük arterlerin transpozisyonu tanılı yenidoğanlar üzerinde yapıldı. Operasyon öncesi ve sonrası (birinci, ikinci, üçüncü gün) nötrofil/lenfosit oranı değişiklikleri kaydedildi. Primer sonlanım noktası uzun yoğun bakım ünitesi süresi (pediatrik kardiyak yoğun bakım ünitesinde kalış süresi, süre olarak en uzun yüzde 25'lik dilimde olması) olarak kaydedildi. Nötrofil/lenfosit oranı değişikliklerinin pediatrik kardiyak yoğun bakım ünitesinde kalış süresi üzerine etkileri incelendi.

Bulgular: Çalışma döneminde 45 olgu mevcuttu. Medyan yaş 3 gün (IQR 2-7 gün) ve medyan operasyon ağırlığı 3000 gram (IQR 2800-3100) idi. Olguların %51'i erkek, %49'u kızdı. Medyan mekanik ventilatörde kalış süresi, yoğun bakımda kalış süresi ve hastanede kalış süreleri sırasıyla 48 saat (IQR 24-96 saat), 6 gün (IQR 5-12) ve 12 gün (IQR 10-16) idi. Pediatrik kardiyak yoğun bakım ünitesinde kalış süresi >8 gün olarak saptandı. Dört (%8,8) hasta erken dönemde kaybedildi. Preoperatif nötrofil/lenfo-

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Address for correspondence: Hatice Dilek Özcanoğlu, MD. İstanbul Başakşehir Çam ve Sakura Şehir Hastanesi, Anestezi ve Reaminasyon Anabilim Dalı, İstanbul, Türkiye

Phone: +90 533 367 52 02 E-mail: dilekmersin@hotmail.com

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as >8 days. Four (8.8%) patients died in the early period. Pre-operative NLR values of >1.5 and post-operative day-3 NLR values of >2.1 were found to be strong predictors of PCILOS.

Conclusion: The findings of this study suggest that high NLR values in the pre-operative and early post-operative period in patients that were diagnosed with TGA and who underwent ASO were good predictors of prolonged ICU stays.

Keywords: Intensive care, neutrophil-lymphocyte ratio, newborn, transposition of the great arteries

Introduction

Transposition of the great arteries (TGA) is one of the most common congenital heart diseases in the neonatal period and is an important cause of hospitalization of newborns in the pediatric cardiac intensive care unit (ICU) in the first 2 weeks of life.^[1] The first option in TGA treatment is arterial switch operation (ASO). Prostaglandin E1 infusion or balloon atrial septostomy procedures may be applied preoperatively to prevent the adverse effects of hypoxemia during the period till the time of operation.^[2,3]

Cardiopulmonary bypass (CPB) is utilized in a majority of cases during congenital heart surgery. However, CPB has the potential to trigger an inflammatory response, particularly in newborns, which may adversely affect the post-operative morbidity and mortality rates.^[4,5]

Biomarkers such as galectin-3, N-Terminal prohormone B-type natriuretic peptide, lymphopenia, thrombocytopenia, and C-reactive protein have been used to evaluate the effects of inflammation on the outcome of congenital heart surgery.^[6] The neutrophil-lymphocyte ratio (NLR), which has been commonly used as an inflammation marker in sepsis, bowel operations, and chronic lung disease, has started to be used as a new biomarker in heart disease cases in recent years.^[7] The most important advantage of NLR over other biomarkers is that it is easy to apply and is also inexpensive.

The use of NLR as a predictor of low cardiac output, mortality, and morbidity has been studied in a limited number of studies involving cases with different diagnoses of congenital heart disease.^[8,9] In this context, the objective of this study is to investigate the effect of variations in the neutrophil/lymphocyte ratio measured in the pre-operative and early post-operative periods on the length of post-operative ICU stay in cases that were diagnosed with TGA and underwent ASO.

Methods

Population and Sample

The population of this retrospective study comprised newborns that were diagnosed with TGA, followed up in the pediatric cardiac ICU, and who underwent ASO, between sit oranı değerinin >1,5 olması ve postoperatif üçüncü gün nötrofil/lenfosit oranı >2,1 olması pediatrik kardiyak yoğun bakım ünitesinde kalış süresini tahmin etmede güçlü belirteçlerdi.

Sonuç: Arteryel switch operasyonu yapılan büyük arterlerin transpozisyonu tanılı olgularda ameliyat öncesi ve postoperatif erken dönemdeki yüksek nötrofil/lenfosit oranı uzun yoğun bakım sürecinin değerlendirilmesinde iyi bir belirteçtir.

Anahtar sözcükler: Büyük arterlerin transpozisyonu, nötrofil/lenfosit oranı, yenidoğan, yoğun bakım

January 1, 2021, and December 31, 2021. Premature cases, cases with complex congenital heart disease with additional defects such as ventricular septal defect and pulmonary stenosis, cases who had received steroids, and cases with growth in blood culture were excluded from the study. The study was approved by the Local Ethics Committee and carried out in accordance with the principles outlined in the Declaration of Helsinki.

Definitions

A data form was created for each patient. Information including age, gender, weight, diagnosis, and prostaglandin E1 use of the patient, information about the surgery performed, and the problems that developed while the patient was in the ICU were obtained from the hospital data system and recorded in the data form.

Peripheral venous blood samples were taken from all cases 24 h before and 1, 2, and 3 days after the operation and sent to the laboratory for routine blood tests. The neutrophil and lymphocyte values and the NLR value calculated using these values were recorded in the data form.

Prolonged post-operative ICU stay (PCILOS) was deemed as the primary endpoint of this study. For the purposes of this study, PCILOS was defined as a post-operative ICU stay that falls within the 25th percentile of the lengths of stay with the most extended durations.

Surgical Technique

Our anesthesia protocol was standard in all the patients. Standard monitoring started with electrocardiography (ECG) and pulse oximetry followed by Fentanyl 1 μ g/kg, rocuronium 0.6 mg/kg, and midazolam 0.1 mg/kg for anesthesia induction. Mild hypothermia was used. Del Nido was utilized approximately every 60 min during the cross-clamp period. The procedure was performed as described in the literature.^[2] Ultrafiltration on bypass and modified ultrafiltration after bypass was used.

Post-operative Care

The patients were brought to the ICU as intubated and put on mechanical ventilator support. All patients admitted to the ICU were followed up through the measurement of their saturation, central venous pressure, invasive arterial blood pressure, and end-tidal carbon dioxide (etCO₂) values and were monitored by ECG and serebral near-infrared spectroscopy (NIRS). Inotropic support was typically provided during the first several post-operative hours in the form of milrinone (0.5 microgram/kg/min) and a low dose of Noradrenaline (0.05 microgram/kg/min). Epinephrine treatment was administered in cases where deemed necessary.^[2]

Statistical Analysis

The distribution of the variables investigated within the scope of this study was analyzed in the computer environment. Descriptive values were obtained using the Statistical Package for the Social Sciences for Windows software package. The results were expressed as median (interguartile range [IQR]) and percentage-percentile values. The Shapiro-Wilk test was used to determine whether the variables conform to the normal distribution or not. Pearson's Chi-squared test and Mann–Whitney U test were used to compare the variables between groups. Receiver operating characteristic (ROC) analysis was used to determine the cutoff value of NLR that would predict prolonged hospital stays, and the area under the curve was used to verify the area under the ROC curve. The final model for the estimation of NLR parameters predicting prolonged hospital stays was expressed using odds ratio within 95% confidence interval. Probability p<0.05 was deemed to indicate statistical significance.

Results

The patient group comprised 45 patients. The median age of the patients was 3 (IQR 2–7) days, and the median operation weight was 3000 (IQR 2800–3100) grams. Of the patients included in the study, 51% were male, and 49% were female. One case had DiGeorge syndrome. Pre-operative inotropic support was provided in 15% of cases, whereas mechanical ventilation was provided in 4 (9%) cases. Balloon atrial septostomy was performed in 10 cases. Median CPB time was determined as 110 (IQR 90-140) minutes and median cross-clamp time was determined as 75 (IQR 60-100) minutes.

Median duration on a mechanical ventilator, the median length of ICU stay, and median length of hospital stay was 48 (IQR 24-96) hours, 6 (IQR 5-12) days, and 12 (IQR 10-16) days, respectively. PCILOS duration was determined as >8 days. Four (8.8%) patients died in the early period. The general characteristics of the cases are summarized in Table 1.

The PCILOS was determined as 8 days. There were 13 cases with more extended ICU stays. The pre-operative day-1,

Age/day	3	2-7
Weight/kg	3	2.8-3.1
Male	23	51
Syndrome	1	2.2
PGE1	37	82
Inotrope	7	15
Mechanical ventilation	4	9
Septostomy	10	22
Coronary Anomaly	18	45
ASD (non-restrictive)	20	44
PDA	40	88
CPB duration/minute	110	90-140
Cross-clamp ssduration/minute	75	60-100
Open sternum	18	40
Mechanical ventilation duration/hour	48	24-96
Intensive care unit length of stay/day	6	5-12
Hospital length of stay/day	12	10-16

Given as median (IQR) or n, %. PGE1: Prostaglandine E1; ASD: Atrial septal defect; PDA: Patent ductus arteriosus; CPB: Cardiopulmonary bypass; ECMO: Extracorporeal membrane oxygenator.

day-2, and day-3 hemogram parameters of these cases are summarized in Table 2.

Pre-operative day-1, day-2, and day-3 NLR values were found to be significantly higher in PCILOS (+) cases, that is, cases who stayed longer than 8 days in the ICU unit (p<0.05).

Baseline NLR value PCILOS c index=0.82 (CI:0.70-0.95 p=0.001, day-1 NLR value PCILOS c index=0.60 (CI:0.40-0.79, p=0.28), day-2 NLR value PCILOS c index=0.76 (CI: 0.60-0.90 p=0.008), day-3 NLR value PCILOS c index=0.78 (CI:0.64-0.92, p=0.004) were determined to predict PCILOS (+) cases with extended intensive ICU stays (Fig. 1).

Pre-operative NLR values of >1.5 (with 78% specificity and 92% sensitivity), post-operative day-2 NLR values of >2 (with 70% specificity and 80% sensitivity), and post-operative day-3 NLR values of >2.1 (with 74% specificity and 84% sensitivity) were determined to predict PCILOS (+) cases.

Discussion

In this study, the role of NLR, a new inflammatory marker for cardiac surgery, in predicting prolonged ICU stays in patients that were diagnosed with TGA and who underwent ASO was investigated. Consequentially, it was found that NLR values measured at different times during the pre-op-

%

8.8

8.8

n=45

n

4

4

Table 1. General characteristics of patients

Variable

ECMO

Mortality

Variable	PCILOS (+)	PCILOS (–)	р
Pre-operative Hemoglobin	13.1 (11-14)	14.3 (11.5-14.5)	NS
Pre-operative Hematocrit	43 (36-45)	41 (35-42)	NS
Pre-operative Platelet	299 (170-450)	259 (160-350)	NS
Pre-operative Neutrophil	6300 (4000-12000)	5800 (3700-9100)	NS
Pre-operative Lymphocyte	3300 (2250-5750)	3600 (3950-6400)	NS
Pre-operative NLR	2.1 (0.9-2.5)	1.6 (1.2-3)	0.030
1 st day Hemoglobin	13.5 (10-14)	13.6 (10-14)	NS
1 st day Hematocrit	40 (36-42)	40 (36-42)	NS
1 st day Platelet	163 (80-250)	210 (150-270)	NS
1 st day Neutrophil	7200 (5400-9300)	7100 (5100-10900)	NS
1 st day Lymphocyte	1800 (1500-3100)	1950 (1600-3450)	NS
1 st day NLR	4.5 (3-6)	3.9 (3.4-5.5)	NS
2 nd day Hemoglobin	12.4 (10.4-13)	12.8 (10-13.6)	NS
2 nd day Hematocrit	37 (34-40)	37 (35-41)	NS
2 nd day Platelet	150 (100-210)	170 (140-230)	NS
2 nd day Neutrophil	7200 (5000-9200)	7000 (4900-8800)	NS
2 nd day Lymphocyte	1400 (1000-2400)	1500 (1300-2100)	NS
2 nd day NLR	4.6 (4-5)	3.8 (3.5-5)	0.008
3 rd day Hemoglobin	11.9 (10-12)	11.8 (10.5-12.1)	NS
3 rd day Hematocrit	35 (33-38)	36 (34-39)	NS
3 rd day Platelet	150 (130-250)	160 (120-270)	NS
3 rd day Neutrophil	8100 (6000-10000)	7250 (5900-8500)	NS
3 rd day Lymphocyte	1900 (1550-2300)	1800 (1500-2000)	NS
3 rd day NLR	4.2 (3-5.4)	2.5 (1.8-3.2)	0.003

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erative and the early post-operative periods, the post-op-

erative day-1 in particular, were strong predictors of prolonged ICU stays. Given these findings, this study is one of the few studies in the literature on newborns with congenital heart disease.

After congenital heart surgery, systemic inflammatory response syndrome may be triggered by surgical trauma or CPB, negatively affecting mortality and morbidity. In particular, CPB equipment may come into contact with blood cells on the surface and trigger an inflammatory cascade by means of cytokine release, complement, and activation of the coagulation system. Leukocytes, platelets, and vascular endothelial cells are the cells that primarily contribute to the formation of inflammation. Oxygenation at the microcirculatory level may be impaired due to ischemia-reperfusion injury and hypothermia, which further exacerbate this complex process. Different biomarkers have been used to detect this process. However, only a few provide ease of use during routine clinical practice.[10-12]

Recently, NLR has started to be used for different purposes as a new biomarker due to its accessibility, low price, directly measurable, and repeatable nature. The hypothesis

that NLR can give an idea about the inflammatory response is based on the fact that the neutrophils are an essential part of the systemic response, increase due to tissue damage and perfusion, and that the retransformation of white blood cells results in the reduction of lymphocyte count. [10,13,14]

It has been reported in various studies conducted with adults that NLR can be used as a predictor of mortality and morbidity in cardiac surgery cases.^[15,16] Although there is a limited information on the use of NLR in predicting mortality and morbidity in children with different congenital heart disease diagnoses, it has been suggested in several studies that its use in children would prove helpful.^[10,14]

Şavluk et al.^[8] evaluated the cases who underwent Norwood Stage I operation in their series of 53 cases diagnosed with hypoplastic left heart syndrome. Consequentially, they found that pre-operative NLR values >0.74 are associated with an increased risk of mortality in these cases.

In their study, including 114 children with tetralogy of Fallot, Manuel et al.^[13] found that pre-operative NLR values greater than 0.80 were associated with increased risk of prolonged ICU and hospital stays.



Figure 1. The effect of NLR alterations by days on long hospitalization. NLR: Neutrophil lymphocyte ratio.

In the series of 424 infants, Gao et al.^[10] found that high NLR values were associated with increased risk of prolongation of time spent on mechanical ventilation and prolonged ICU and hospital stays. They also found that high NLR values are an independent risk factor for mortality.

In the series of 61 cases, Xu et al.^[14] found that high post-operative NLR values were associated with increased risk of prolongation of time spent on mechanical ventilation and prolonged ICU stays.

In another study in which the results of the Glenn shunt procedure on 141 cases with single ventricle morphology were evaluated, it was reported that pre-operative NLR values greater than 2 were significantly associated with increased risk of mortality.^[17]

In addition to predicting morbidity and mortality after congenital heart surgery operation, NLR values may also be helpful in the evaluation of different clinical conditions. For example, Iliopoulos et al.^[9] reported that significantly more cases featuring high NLR values after cardiac surgery developed low cardiac output. In another study including 116 cases, it was reported that high pre-operative NLR values predicted acute kidney injury.^[18]

In line with the relevant results in the literature, the high pre-operative and post-operative NLR values measured in this study were found to be associated with prolonged ICU stays. Particularly, pre-operative NLR values >1.5 and post-operative day-3 NLR values greater than 2.1 were found to be strong predictors of prolonged ICU stays.

Limitations of the Study

The primary limitation of the study is that it was conducted retrospectively and with a limited number of patients. The fact that prenatal diagnosis, surgical technique, and management in the ICU could not be thoroughly evaluated was another limitation of the study. Third, it had the effects of other inflammation markers been evaluated, the results could be more meaningful.

Conclusion

Measuring the NLR values in newborns who underwent ASO may help predict prolonged ICU stays and, thus, plan ideal intensive care follow-up that would reduce morbidity and mortality.

Disclosures

Ethics Committee Approval: The study was approved by The İstanbul Basaksehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Date: 14/03/2022, No: 2022.03.83).

Informed Consent: Written informed consent was obtained from all patients.

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