The Effect of Neutrophil/Lymphocyte Ratio Changes on Morbidity in the Perioperative Period of Neonates with Total Abnormal Pulmonary Venous Return Anomaly

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ABSTRACT

Introduction: Total abnormal pulmonary venous return anomaly (TAPVD) is a congenital heart disease characterized by abnormal pulmonary venous drainage to the right atrium. The Neutrophil/Lymphocyte Ratio (NLR) is used to predict mortality and morbidity after congenital heart surgery. In this study, the effect of postoperative NLR changes on prolonged intensive care unit stay in newborns with TAPVD was searched.

Patients and Methods: The newborns with TAPVD who were followed up and operated on in the pediatric cardiac intensive care unit between May 1, 2020, and May 1, 2022, were included in the study. Hematological parameters and NLR changes were recorded before and after the operation (1st-2nd-3rd days). Long ICU duration (PCILOS, being in the longest 25 percent as duration) was accepted as morbidity. The effects of NLO changes on PCILOS were examined.

Results: Twenty-four patients were included in the study. The median age was 18 days (IQR 12 days-24 days) and the median weight was 3 kg (IQR= 2.8-3.2). Fifteen patients were male (63%). Median mechanical ventilator duration, intensive care unit stay, and hospital stay were 40 hours (IQR= 30-48 hours), seven days (IQR= 5-9), and 15 days (IQR= 12-18), respectively. PCILOS duration was determined as >9 days. Three patients (12.5%) died in the postoperative first 30 days. Preoperative NLR value> 1.9 and postoperative 3rd day NLR> 2.8 predicted PCILOS strongly.

Conclusion: High NLR values in the preoperative and early postoperative periods of neonates with total abnormal pulmonary venous return anomaly may be helpful to predict prolonged ICU stay.

Key Words: Newborns; congenital heart defects; intensive care

Total Anormal Pulmoner Venöz Dönüş Anomali Yenidoğanlarda Perioperatif Dönemde Nötrofil/Lenfosit Oranı Değişikliklerinin Morbidite Üzerine Etkisi

ÖZET

Giriş: Total anormal pulmoner venöz dönüş anomalisi (TAPVD), anormal pulmoner venöz akımın sağ atriuma yönelmesi ile karekterize konjenital bir kalp hastalığıdır. Nötrofil/Lenfosit Oranı (NLO) konjenital kalp cerrahisi sonrası mortalite ve morbiditeyi tahmin etmede kullanılmaktadır. Bu çalışmada TAPVD'li yenidoğanlarda postoperatif dönemde NLO değişikliklerinin uzamış yoğun bakım kalış süresine etkisi araştırılmıştır.

Hastalar ve Yöntem: Çalışma 1 Mayıs 2020-1 Mayıs 2022 tarihleri arasında pediatrik kardiyak yoğun bakım ünitesinde izlenen ve opere edilen TAPVD'li tanılı yenidoğanlar üzerinde yapıldı. Operasyon öncesi ve sonrası (birinci, ikinci ve üçüncü gün) hematolojik parametreler ve NLO değişiklikleri kaydedildi. Morbidite olarak uzun YBÜ süresi (PCILOS, süre olarak en uzun yüzde 25'lik dilimde olması) kabul edildi. NLO değişikliklerinin PCILOS üzerine etkileri incelendi.

Bulgular: Çalışma döneminde 24 olgu olgu mevcuttu. Medyan yaş 18 gün (IQR 12 gün -24 gün) ve medyan ağırlık 3 kg (IQR= 2.8-3.2) idi. Olguların 15'i erkek (%63) idi. Medyan mekanik ventilatör kalış süresi, yoğun bakım kalış süresi ve hastanede kalış süreleri sırasıyla 40 saat (IQR= 30-48 saat), yedi gün (IQR= 5-9), 15 gün (IQR= 12-18) idi. PCILOS süresi> 9 gün olarak saptandı. Üç hasta (%12.5) ilk 30 günde kaybedildi. Preop NLO değerinin >1.9 olması ve postoperatif 3. gün NLO> 2.8 olması PCILOS'u güçlü olarak tahmin etmekteydi.

Sonuç: Total anormal pulmoner venöz dönüş anomali tanılı yenidoğanlarda kalp cerrahisi öncesi ve postoperatif erken dönemdeki yüksek NLO uzun yoğun bakım sürecini tahmin etmede yardımcı olabilir.

Anahtar Kelimeler: Yenidoğan; konjenital kalp defekti; yoğun bakım

INTRODUCTION

Total abnormal pulmonary venous return anomaly (TAPVR) is a pathology in which the pulmonary veins open into the systemic veins, right atrium, or coronary sinus instead of the left atrium, which accounts for less than 1% of all congenital heart diseases. Total abnormal pulmonary venous return anomaly may be isolated or accompany other complex cardiac defects such as right atrial isomerism and single ventricular physiology. The treatment of the disease is surgery, and mortality ranges between 2-20% in studies reported in recent years[1-2].

In most cases, complete correction is performed under cardiopulmonary bypass (CPB). However, adverse effects of CPB, such as ischemia-reperfusion injury and triggering an inflammatory response, may develop and increase mortality and morbidity, especially in newborn cases[3-4].

In the literature, different scoring systems and laboratory tests are used to evaluate the results of cardiac surgery. Neutrophil-Lymphocyte ratio (NLR), which has been used as a biomarker in diseases with intense inflammation such as chronic lung disease and sepsis in recent years, has started to be utilized as a new biomarker in congenital heart surgery. It was suggested that it may be useful in estimating low cardiac output, mortality, and morbidity even though supporting studies are limited in number[5-6].

In this study, the effect of NLR changes on the prolonged ICU stay in the perioperative period in newborns with TAPVD was investigated.

PATIENTS and METHODS

Patient Selection

This study was performed retrospectively on newborns with isolated TAPVR who were followed up in the pediatric cardiac intensive care unit of our heart center between May 1, 2020, and May 1, 2022, and underwent complete correction operation. Cases complicated with prematurity, syndromes, one of the components of complex congenital heart disease such as isomerism, previously treated with steroids before the operation, and blood culture positivity before the operation were excluded from the study.

The study was carried out in accordance with the Declaration of Helsinki and with the approval of the local ethics committee.

Descriptives

A study form was created for each case from the hospital data system, including age, gender, weight, main diagnosis, operation data of the TAPVR subgroup, and problems that developed in the intensive care follow-up.

Peripheral venous blood samples were taken from all cases 24 hours before and one, two and three days after the operation. The samples were sent to the laboratory for routine analysis. Neutrophil and lymphocyte values were recorded in the study form. The neutrophil-to-lymphocyte ratio was calculated from the results.

Long intensive care unit stay was accepted as morbidity. Long intensive care unit stay was accepted as the 25th percentile in which the duration of intensive care stay was the worst.

Operative Technique

All operations were performed under general anesthesia with median sternotomy. CPB was started with ascending aortic perfusion and bicaval cannulation. Moderate or profound hypothermia was induced. Cold blood cardioplegia infusion was used to provide myocardial protection. The conventional technique was carried out as specified in the literature. The vertical vein was closed in all cases. A 3 mm opening was left in the interatrial septum. The sternum was left open in some patients.

Postoperative Intensive Care

The patients were admitted to the intensive care unit intubated and on mechanical ventilator support. Saturation, central venous pressure (CVP), Electrocardiography (ECG), invasive arterial blood pressure, end-tidal carbon dioxide (etCO), and Near Infrared Spectroscopy (NIRS) were monitored in all patients. Inotropic support was routinely administered as milrinone (0.5 microgram/kg/min) and low-dose norepinephrine (0.05 microgram/kg/min) in the first postoperative hours. Adrenaline therapy was added if necessary.

Statistical Analysis

In the study, the distribution of variables was classified in the computer environment and descriptive values were obtained using the SPSS (Statistical Package for the Social Sciences for Windows) software. The results were expressed as median interquartile range (IQR) and percent-percentile. Shapiro-Wilk test was used to examine the normal distribution. Chi-square and Mann-Whitney U tests were used to compare variables between groups. Receiver operating characteristic (ROC) curve, and the area under the curve (AUC) were used to evaluate the cut-off values between NLR and long hospital stay. The final model for the estimation of NLR parameters affecting long hospitalization was expressed as an Odds ratio with a 95% confidence interval. $p < 0.05$ was considered statistically significant.

RESULTS

There were 24 cases included in the study. Median age and weight at the time of operation were 18 days [interquartile range (IQR)= 12-24 days] and 3 kg (IQR= 2.8-3.2 kg.) respectively. Fifteen of the cases were male (63%). When the TAPVR

subgroups of the cases were evaluated, 11 cases were supracardiac, eight cases were infracardiac, four cases were cardiac and one case was mixed type. Preoperative inotropic support was administered in 15% of cases, and five (20%) of the cases were under mechanical ventilation. The median cardiopulmonary bypass and cross-clamp times were 120 minutes (IQR= 90-140 minutes) and 85 minutes (IQR= 75-100) respectively.

Median durations of mechanical ventilation, ICU, and hospital stay were 40 hours (IQR= 30-48 hours), seven days (IQR= 5-9 days), and 15 days (IQR= 12-18), respectively. The duration of PCILOS was >9 days. Three patients (12.5%) died in the first 30 days. The general characteristics of the cases are summarized in Table 1.

Six cases exceeded the duration of PCILOS. Preoperative, 1st day, 2nd day, and 3rd day hemogram parameters of these cases are summarized in Table 2. Preoperative, 2nd day, and 3rd

day NLR values were found to be significantly higher in PCILOS (+) cases (p< 0.05).

Baseline NLR value PCILOS c index= 0.84 (CI= 0.75-0.90, p= 0.001), day one NLR value PCILOS c index= 0.62 (CI= 0.50-0.75, p= 0.28), day two NLR value PCILOS c index= 0.78 (CI= 0.66-0.88, p= 0.008), day three NLR value PCILOS c index= 0.80 (CI= 0.72-0.88, p= 0.004) can predict long intense PCILOS.

A preoperative NLR value> 1.9 (72% specificity, 85% sensitivity) and postoperative day three NLR> 2.8 (72% specificity, 80% sensitivity) strongly predicted PCILOS.

DISCUSSION

This study evaluated the effect of NLR, an inflammatory biomarker, before and after total correction operation to predict the prolonged intensive care unit stay in newborns with TAPVD. We observed that NLR on the preoperative and postoperative third day was strongly associated with prolonged intensive care unit stay. Our study is one of the limited studies conducted on newborn patients with congenital heart disease.

In newborns, systemic inflammatory response syndrome, which may negatively affect mortality and morbidity, might be triggered during cardiac surgery or in the early postoperative period due to surgical trauma or cardiopulmonary bypass. CPB equipment contact with blood cells initializes inflammatory cascade with the cytokine release and activation of complement and coagulation systems. In this complex process, ischemia-reperfusion damage and hypothermia further impair tissue oxygenation; as a result, the hemodynamics get worse. Various biomarkers are used in the diagnosis and management of this process. However, none of them is readily available, repeatable, and useful in clinical practice[7-9].

Recently, NLR has been introduced in different age groups and diseases due to its low cost, rapid access, and reproducibility. During tissue damage and reperfusion, neutrophils increase, white blood cells are reconverted, and the lymphocyte ratio reduces. Therefore, a change in the proportion of cells might provide insight into the inflammatory process[7,10-11].

The NLR has been suggested to guide the diagnosis of sepsis and acute appendicitis. Also, it has been stated as a predictor of mortality and morbidity after cardiac surgery in adults[9-10]. It has been reported that it might be useful in children with heterogeneous congenital heart diseases. Although it offers promising results, its utility is limited because many questions need to be answered before we can understand the true utility of NLR, such as the normal reference ranges for children, the cut-off level for predicting adverse outcomes, its correlation with other biomarkers, etc[12].

Table 1. General characteristics of patients

Variable	n= 24
Age (day)	
Weight (kg)	3 (2.8-3.1)
Male	15 (63)
Syndrome	1 (2.2)
Preoperative use of inotropes	6 (15)
Mechanical ventilation	5 (20)
Anatomical type	
Supracardiac	11 (46)
Cardiac	4 (17)
Infracardiac	8 (34)
Mixed	1 (4)
Pulmonary venous obstruction	14 (58)
ASD (nonrestrictive)	22 (90)
PDA	8 (33)
CPB duration (minute)	120 (90-140)
Cross-clamp duration (minute)	55 (75-100)
Open sternum (yes)	3 (12.5)
Mechanical ventilation duration (hour)	40 (30-48)
Intensive care unit length of stay (day)	7 (5-9)
Hospital length of stay (day)	15 (12-18)
ECMO (yes)	2 (8)
Mortality	3 (12.5)

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

Table 2. Changes in hemogram parameters in prolonged ICU stay

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

Median (IQR). NLR: Neutrophil lymphocyte ratio.

Gao et al. reported in a series of 424 infant patients that the high NLR was associated with prolonged mechanical ventilation, intensive care unit stay, and hospitalization[8]. They also observed that it was an independent risk factor for mortality. Manuel et al. reported a study, including 114 children with tetralogy of Fallot[11] that pre-operative NLR values greater than 0.80 were associated with an increased risk of prolonged ICU and hospital stays.

In the Xu et al. series, postoperative high NLR was associated with prolonged mechanical ventilation and intensive care unit admission[10]. In a study evaluating 141 patients with single ventricular physiology, NLR> 2 before Glenn shunt operation was associated with significantly increased mortality[13].

In the study evaluating 53 patients with hypoplastic left heart syndrome who underwent Norwood stage I operation, Şavluk et al. suggested that the preoperative NLR> 0.74 was associated with increased mortality[14]. Özcanoğlu et al. proposed that preoperative NLR> 1.5 and third-day NLR of >2.1 in newborns with transposition of great arteries could predict prolonged intensive care unit stay[15].

NLR might have different contributions other than predicting morbidity and mortality after congenital cardiac surgery. Iliopoulos et al. revealed that patients with high NLR have a higher low cardiac output incidence after cardiac surgery[16]. Also, high preoperative NLR could predict acute kidney injury[17].

In our study, similar to the other studies, high NLR in the preoperative and postoperative period was associated with prolonged intensive care unit stay. Specifically, cut-off preoperative NLR of >1.9 or postoperative third-day NLR of >2.8 were strong predictive factors of morbidity.

Limitations

The main limitation of this study is that it is a retrospective single-center study with a limited number of patients. Also, if the effects of other inflammatory markers had been evaluated, the results would have been more significant.

As a result, high NLR before cardiac surgery and early postoperative period may help predict prolonged intensive care stays in newborns with total abnormal pulmonary venous return anomaly. This new biomarker could reduce morbidity and mortality by contributing to intensive care unit follow-up.

Ethics Committee Approval: This study was approved by Başakşehir Çam ve Sakura City Hospital Ethics Committee (Decision no: 2022.03.83, Date: 14.03.2022).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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