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Do platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have a predictive value on pediatric extracorporeal membrane oxygenation (ECMO) results?

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Abstract

Background: It is difficult to predict the complications and prognosis of ECMO, which is gaining widespread use in patients with pediatric surgery. Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are emerging inflammatory markers that can be calculated from complete blood count, which is a cheap and easily accessible laboratory analysis. The ratios between cellular elements in peripheral blood have been demonstrated to provide information on inflammation, infection, and immune response. *Methods:* Sixty-seven patients who needed ECMO application after undergoing pediatric cardiovascular surgery in our clinic, between May 2005 and April 2020, were included in this study. The age of patients varied between 4 days and 17 years with a mean of 30.59 ± 147.26 months. *Results:* The relationships between PLR or NLR values and various blood parameters and blood gas results were found to be statistically nonsignificant in our group of pediatric ECMO recipients. Even if the effect of PLR and NLR values on mortality and prognosis is statistically nonsignificant in patients who need ECMO after congenital heart surgery, PLR and NLR are typically elevated in the postoperative period. An increase in these values above a certain threshold may be a statistically significant indicator for the prediction of mortality. *Conclusions:* There are few studies in the literature concerning PLR and NLR values in patients with pediatric heart surgery. We consider this study will make way for new studies in the future.

The change in ratios of the cellular components in peripheral blood can provide information about many diseases. Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) that can be calculated from complete blood counts are shown to be significant inflammation markers that are cheap, easily accessible, and indicate inflammation and infection in the body. PLR and NLR have been found to be related to mortality and morbidity in cardiac patients in addition to being valuable in the follow-up of individuals with heart failure.[1–8]

The use of ECMO in the postoperative period in patients who underwent heart surgery is becoming popular. The use of ECMO, despite carrying considerable risk, may be critical for pediatric cardiovascular surgery in cases with postoperative low output, pulmonary difficulties, and e-CPR.[1–4] ECMO is a bridge to recovery instead of a final treatment. It facilitates an opportunity for pulmonary or cardiac recovery in critically ill patients. Even though ECMO is lifesaving in many use scenarios, it brings several difficulties.[9–13]

Inflammation and the degree of the inflammation have a place in determining the prognosis in ECMO patients, since blood flows through a foreign membrane surface and the possibility for infection.[2,3]

This study was aimed to determine the relationships between cheap, easily accessible, and simple PLR and NLR values and the prognosis and mortality in patients in our clinic who received ECMO in the postoperative period of congenital heart surgery.

Material and methods

The patients were scanned retrospectively and those who had needed ECMO were selected among pediatric patients who had undergone cardiovascular surgery between May 2005 and April 2020. Complete blood count results, platelet, lymphocyte, neutrophil values and blood gas results, lactate, and other values of the patients were obtained from their files in the archive.

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The majority of patients had received central veno-arterial ECMO, while only two patients received veno-venous ECMO. As ECMO devices, the Medos, Medtronic, and Maquet devices were used in patients. Generally, the cannulation procedure was applied in the operating room but some of the patients underwent cannulation within the intensive care unit under emergency conditions. In the cannulation procedure, first, a single arterial and then a single venous cannula were placed. ECMO heater was used routinely. Blood was used routinely for priming the ECMOs and the air was cleaned. The flow of the ECMO was set at 100–150 ml/kg/min. ACT follow-up was performed on patients during ECMO, and ACT was kept between 150 and 200. Heparin perfusion was preferred to increase and keep the ACT at a certain level. Dressing changes and sternum cleaning were performed regularly in patients with prolonged stay on ECMO, and any hematomas that developed were cleared.

VIS (vasoactive-inotropic score) scores were calculated for all patients. VIS was calculated using the following formula: VIS = Dopamine dose (μg/kg/min) + Dobutamine dose (μg/kg/min) + 100 × Epinephrine dose (μg/kg/min) + 10 × Milrinone dose (μg/kg/min) + 10,000 × Vasopressin dose (μg/kg/min) + 100 × Norepinephrine dose (μg/kg/min).

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analyses. Descriptive statistical methods (Average, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum) were used in the depiction of data. The distribution of continuous variables was evaluated with the Shapiro-Wilk test. The Kruskal Wallis test was used for comparisons of three or more groups that did not show normal distribution of quantitative data, and the Mann Whitney-U test was used for comparisons of two groups. In the analyses of paired samples, the Friedman test was used for the assessment of three or more groups in which variables did not show normal distribution, and the Wilcoxon test was used to specify the differences. Spearman's Correlation coefficient was calculated to assess the relationships between quantitative data sets. Significance thresholds were defined at $p < 0.05$.

The study protocol was approved by the ethics committee. This study was conducted in accordance with the principles of the Declaration of Helsinki. (2021/4/455)

Results

A total of 67 patients were included in this study. Among these, 44.3% (n = 31) were female and 55.7% (n = 39) were male.

The age of the patients varied between 0.13 and 210 months with an average of 30.59 ± 147.26 months. The weight values varied between 2.5 and 79 kg with an average of 13.17 ± 17.38 kg. The bypass time varied between 0 and 410 min with an average of 172.72 ± 95.74 min, cross-clamp (CC) time ranged from 0 to 360 min, with an average of 98.81 ± 78.33 min. Time on ECMO was minimum 0.25 days up to a maximum of 51 days, with an average of 11.09 ± 10.27 days. VIS score varied between 5 and 102 with average of 29.81 ± 18.32. The volume of first day drainage ranged from 10 to 1500 cc with an average of 268.29 ± 250.94 cc (Table 1).

Table 1. Mean measurement results

	Mean ± SD	*Min-Max (Median)*
Age (months)	30.59 ± 147.26	0.13–210 (11)
Weight (kg)	13.17 ± 17.38	2.5–79 (5.6)
BYPASS time (minutes)	172.72 ± 95.74	0–410 (170)
CC time (minutes)	98.81 ± 78.33	0–360 (103)
ECMO time (days)	11.09 ± 10.27	0.25–51 (8)
VIS score	29.81 ± 18.32	5–102 (4.5)
Volume of 1st day drainage (cc)	268.29 ± 250.94	10–1500 (200)

There was no statistically significant difference in ECMO time, bypass time, CC time, VIS score, and first day drainage between those who died and those who were separated from ECMO ($p > 0.05$) (Table 2).

There was a positive but very weak significant relationship between bypass time and VIS score with correlation analysis ($r = 0.248$, $p < 0.05$). There was a positive but very weak significant relationship between bypass time and first day drainage volume ($r = 0.378$, $p < 0.01$). There was a negative and very weak significant relationship between bypass time and postoperative–preoperative platelet change ($r = -0.257$, $p < 0.05$). There was a positive but very weak significant relationship between bypass time and postoperative–preoperative creatinine change ($r = 0.303$, $p < 0.05$). There was a positive but very weak significant relationship between bypass time and postoperative–preoperative ALT change ($r = 0.281$, $p < 0.05$). There was a positive but very weak relationship between bypass time and postoperative–preoperative AST change ($r = 0.285$, $p < 0.05$). There was no statistically significant relationship between bypass time and ECMO time ($p > 0.05$). There was a positive but very weak significant relationship between CC time and first-day drainage volume ($r = 0.366$, $p < 0.01$). There was a negative and very weak significant relationship between CC time and postoperative–preoperative platelet change ($r = -0.246$, $p < 0.05$). There were no significant relationships between CC time and VIS score or ECMO time ($p > 0.05$).

There was a negative and very weak significant relationship between VIS score and ECMO time ($r = -0.243$, $p < 0.05$). There were no significant relationships between VIS score and first day drainage, postoperative and preoperative ALT, AST, creatinine and BUN changes ($p > 0.05$).

There was a positive but very weak significant relationship between ECMO time and the change in WBC values from the day of ECMO application to the postoperative first day ($r = 0.283$, $p < 0.05$). There was a positive but very weak relationship between ECMO time and the change in neutrophil count in the first two days ($r = 0.253$, $p < 0.05$).

There was a positive but very weak significant relationship between first-day drainage and postoperative and preoperative creatinine change ($r = 0.339$, $p < 0.01$). There was a negative and very weak significant relationship between 1st day drainage and change in lymphocyte count in the first two days ($r = -0.253$, $p < 0.05$). There was a positive and very weak significant relationship between first day drainage and change in neutrophil count in the first two days ($r = 0.301$, $p < 0.05$).

There was a positive but weak correlation between postoperative and preoperative changes in lymphocyte and platelet counts ($r = 0.397$, $p < 0.01$).

There was a moderate positive significant relationship between postoperative and preoperative PLR and NLR change ($r = 0.533$, $p < 0.01$).

There were no statistically significant relationships between PLR or NLR values and changes during the 0–6–12–24 hours of ECMO in the following values: pH, lactate, base deficit, partial oxygen/carbon dioxide ($p > 0.05$).

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Table 2. Comparison of parameters based on ECMO results

		n	Mean ± SD	Min-Max (Median)	p-value
ECMO duration (days)	*Separated*	48	9.25 ± 7.68	1–19 (5.8)	0.461
	Died	19	9 ± 7.62	2–17 (5.8)	
BYPASS duration (minutes)	*Separated*	48	77.5 ± 111.28	0–236 (37)	0.183
	Died	19	202.5 ± 95.29	145–345 (160)	
Cross-clamp duration (minutes)	*Separated*	48	51.25 ± 68.19	0–144 (5.30)	0.616
	Died	19	89.75 ± 32.79	57–134 (84)	
VIS Score	*Separated*	48	17.75 ± 5.56	11–24 (18)	0.352
	Died	19	42.25 ± 24.25	25–78 (33)	
Volume of 1st day drainage (cc)	*Separated*	48	117.5 ± 27.54	90–150 (115)	0.755
	Died	19	207.5 ± 149.08	80–400 (175)	

Kruskal Wallis Test *p < 0.05 **p < 0.01

Table 3. Comparison of NLR and PLR based on ECMO result

	n		Mean ± SD	Min-Max (Median)	p
N/L-PO1	Separated	48	2.24 ± 2.75	0.16–12.93 (1.22)	0.640
	Died	19	1.77 ± 1.64	0.34–5.35 (0.78)	
P/L-PO1	Separated	48	83.6 ± 81.76	23.02–605.71 (68.93)	0.621
	Died	19	99.65 ± 86.41	17.57–378.75 (79.89)	
N/L-PO2	Separated	48	8.28 ± 8.52	0.64–40.67 (5.18)	0.078
	Died	19	11.86 ± 13.63	2.24–65 (9.43)	
P/L-PO2	Separated	48	164.87 ± 175.38	12.78–806.25 (39.100)	0.292
	Died	19	123.08 ± 141.87	9.6–635 (3.81)	
N/L-PO3	Separated	48	9.68 ± 8.87	1.08–40 (6.92)	0.469
	Died	19	9.4 ± 5.45	1.52–18.7 (7.75)	
P/L-PO3	Separated	48	185.79 ± 158.74	7.69–800 (146)	0.066
	Died	19	106.59 ± 64.08	8.67–247.5 (23.87)	

Mann Whitney U Test *p < 0.05, **p < 0.01.
L = lymphocyte; N = neutrophil; P = platelet; PO1 = Post Operative 1st day; PO2 = Post Operative 2nd day; PO3 = Post Operative 3rd day.

Periodic measurement of NLR and PLR values was not found to demonstrate any significant changes with respect to ECMO outcome ($p > 0.05$) (Table 3).

There was a statistically significant difference between Bun, ALT, and AST values according to the periods. Preoperative values were significantly lower than the postoperative values and postoperative first-day values. There was no statistically significant difference between WBC values according to the periods ($p > 0.05$) (Table 4).

There was a statistically significant difference between PLT values according to the periods ($p = 0.001$, $p < 0.01$). Preoperative values were significantly higher than postoperative values and postoperative first-day values ($p = 0.001$; $p < 0.01$).

There was a statistically significant difference between neutrophil values according to the periods ($p = 0.003$; $p < 0.01$). Preoperative values were significantly lower than postoperative and postoperative first-day values ($p = 0.001$; $p < 0.01$).

There was a statistically significant difference between lymphocyte values according to the periods ($p = 0.001$; $p < 0.01$). Preoperative values were significantly higher than the postoperative and postoperative first-day values ($p = 0.001$; $p < 0.01$).

There was a statistically significant difference between NLR and PLR values according to the periods. Preoperative values were lower than postoperative values and postoperative first-day values (Fig 1).

According to ROC analysis, the sensitivity was 68% and the specificity was determined as 55%, with a reliable cut-off point of 0.935 for NLR. The sensitivity was 66.7% and the specificity was determined as 89%, with a reliable cut-off point of 0.35 for PLR (Table 5, Figure 2).

Discussion

Although ECMO has a special place for postoperative pediatric heart surgery, its prognosis differs from patient to patient due to additional risk factors it brings. Infection, inflammation, and heart failure are common problems encountered by these patients and there are previous studies have shown that PLR and NLR are

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Table 4. Comparisons of values according to periods

		Preop (n = 67)	Postop (n = 67)	Postop 1st day (n = 67)	p
BUN	Mean ± SD	23.78 ± 9.49	47.3 ± 23.52	58.02 ± 29.27	0.001**
	Min-Max (Median)	8–49 (24)	14–117 (41)	9.57–138 (5.54)	
Creatinine	Mean ± SD	0.42 ± 0.29	1.45 ± 4.5	1.61 ± 4.55	***0.001*****
	Min-Max (Median)	0.16–1.56 (0.29)	0.17–38 (0.74)	0.15–37 (0.9)	
ALT	Mean ± SD	23.37 ± 19.23	314.65 ± 788.71	395.85 ± 934.33	***0.001*****
	Min-Max (Median)	4.5–133 (19)	3.7–4366 (45)	6.8–6266 (5.65)	
AST	Mean ± SD	46.4ş3 ± 21.41	1019.38 ± 1793.45	1490.94 ± 2123.93	*0.001***
	Min-Max (Median)	11–124 (42)	29–7428 (317)	32–8117 (5.515)	
WBC	Mean ± SD	12 ± 5.03	10.47 ± 5.74	10.02 ± 5.81	0.055
	Min-Max (Median)	5.2–27.7 (8.10)	1.4–35.1 (9.9)	0.7–26.6 (3.9)	
Plt	Mean ± SD	281.28 ± 90.36	130.49 ± 75.9	122.17 ± 63.36	*0.001***
	Min-Max (Median)	82–560 (282)	24–454 (127)	10–311 (106)	
Neutrophil	Mean ± SD	5.75 ± 4.08	9.01 ± 8.09	8.21 ± 5.06	*0.003***
	Min-Max (Median)	1–21.6 (4.6)	1.1–61 (7.7)	0.6–21.8 (7.95)	
Lymphocyte	Mean ± SD	4.69 ± 2.99	1.62 ± 1.59	1.19 ± 0.97	*0.001***
	Min-Max (Median)	0.7–14.8 (2.4)	0.2–11.5 (1.3)	0.1–4.6 (0.85)	
NLR	Mean ± SD	2.1 ± 2.49	9.15 ± 10.26	9.59 ± 7.92	*0.001***
	Min-Max (Median)	0.16–12.93 (1.18)	0.64–65 (5.5)	1.08–40 (7.47)	
PLR	Mean ± SD	87.69 ± 83.3	143.46 ± 147.6	161.04 ± 140.74	*0.001***
	Min-Max (Median)	17.57–605.71 (68.69)	9.6–790 (89.98)	7.69–800 (79.134)	

Friedman Test **p < 0.01.

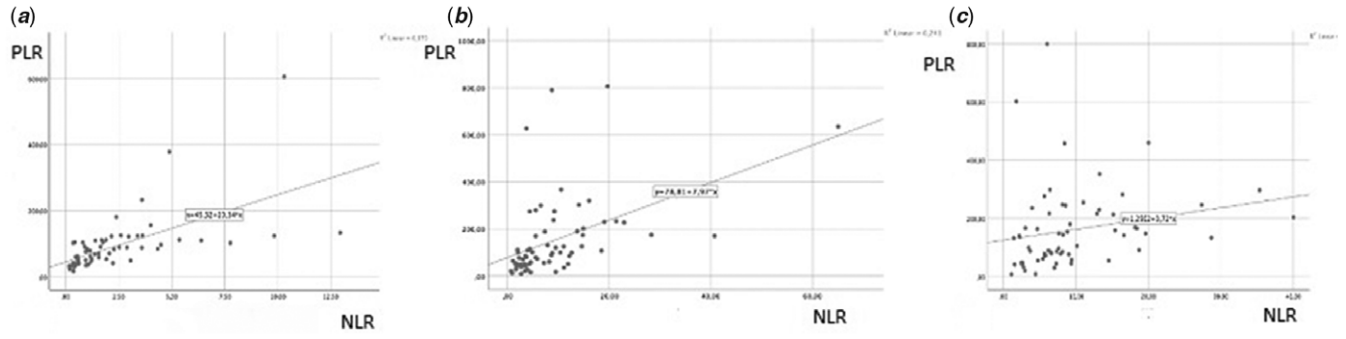

Figure 1. PLR and NLR correlations at Preop, Postop, and Postop-1st day, respectively.

valuable in the prognosis of isolated acute heart failure, isolated neonatal sepsis, and inflammation.[14,15] We reviewed the effects of PLR and NLR on ECMO prognosis in our study.

It is possible to obtain indirect information about cardiac output by examining urine output, blood pressure, lactate in blood gas, and pH levels in the postoperative period after pediatric heart surgery. Deteriorations in these parameters and increased need of inotrope medications suggest the need for ECMO in these patients. ECMO helps patients to overcome the acute phase by supporting the distal perfusion and providing peripheral organ nutrition, in postcardiotomy syndrome. ECMO is a cardiopulmonary support device with high mortality and morbidity, despite these benefits.[26] In our patient group, the need of inotrope medication increased significantly in patients with prolonged bypass time. Even if there was not a statistically significant relationship between bypass time and CC time of the group who was able to separate from ECMO and those who were not (death), the mean bypass time and CC time were found to be longer in those that died while on ECMO.

Lymphocyte count in the body shows the physiological stress, but it is inversely proportional with inflammation. Low lymphocyte count represents increased cardiovascular mortality risk. Platelets secrete thromboxane, proinflammatory cytokines, and growth factors that play a role in vascular inflammation and thrombosis. Platelet activation markers can be affected by endothelial cell damage and related changes.[27,28] Having knowledge about the influences of blood flow on a foreign surface, such as during ECMO and on other material used postoperatively, and the degree of PLR and NLR changes due to surgical stress may be important parameters that can facilitate easier follow-up of patients and could provide information concerning prognosis.

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Table 5. Cut off and AUC value as a result of ROC analysis

Parameter	Sensitivity (%)	Specificity (%)	Cut-off value	Area under curve
NLR	68.0	55.0	0.935	69.4

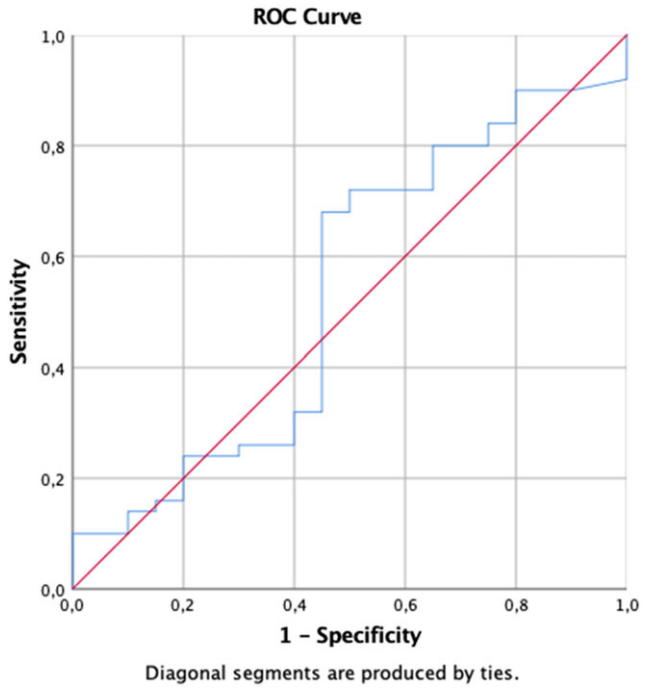

Figure 2. ROC curve of the NLR parameter.

In a study conducted on adults in the literature, typical NLR values in an adult were found to be between 0.78 and 3.53 in a healthy, nongeriatric population. It was stated that this range could be accepted as reference values for NLR.[23] However, our results do not comply with the data range demonstrated by earlier studies because our study was performed in a predominantly pediatric patient population and after the postoperative cardiac surgery.

PLR and NLR are cheap, easily accessible values that can be obtained from complete blood count analysis. Previous studies found that increased PLR was associated with poor prognosis in cardiovascular diseases. It is considered that the increase in the PLR shows increased inflammation, atherosclerosis, and platelet activation.[16–19] In our study, PLR value showed a statistically significant increase compared to the preoperative period in patients who received ECMO. We consider its reason to be increased inflammation and acute heart failure due to ECMO.

Pourafkari L. et al found in their study that high PLR values in patients with heart failure had no effect on hospital mortality but had a negative effect on long-term survival.[20] We could not detect a statistical relationship between PLR value and mortality in our ECMO patients. We also think that PLR values are insufficient for interpretation of early mortality.

In a meta-analysis on septic patients performed by Huang et al, it was shown that NLR may be a beneficial prognostic biomarker for sepsis identification, and high NLR values may indicate adverse prognosis in patients with sepsis.[21] Although there was no statistically significant relationship between the NLR values of the patients who left ECMO and those who could not be separated, mortality increased in patients with NLR values above 0.935.

In a study on pediatric intensive care patients, it was found that PLR had an effect on mortality and cut-off value was identified as 3.93.[24] Again, in a sepsis study on the pediatric population, NLR values were found to be higher in septic children and it was shown that PCT (procalcitonin) and CRP values were correlated in pediatric patients with sepsis. The importance of NLR in this patient group is that it may enable clinicians to initiate sepsis treatment early and could provide early information about patient prognosis, since changes in PCT and CRP usually develop later on, while NLR change is much swifter.[25] We did not find any statistically significant relationships between blood gas parameters, NLR and PLR, ALT, AST, urea, and creatinine in the postoperative period. We consider its reason was the effect of a secondary inflammation associated with the ECMO and the operation on PLR and NLR values.

Chao-Hui Dong et al found in their study that NLR values increase before the treatment of patients with acute coronary syndrome, and increased NLR values were associated with mortality and repetitive major cardiovascular events.[22] In our study, we could not find a statistically significant result in terms of the relationships between NLR values and ECMO prognosis. However, in the group of patients who died, NLR was higher and mortality increased statistically significantly after the NLR cut-off value of 0.935.

Limitations

There are some limitations in our study. Because of our study was performed retrospectively in a single center may limit the generalizability of the results. In addition, PLR and NLR are markers of systemic inflammation, and therefore, may be influenced by postoperative acute infections and systemic diseases. Otherwise, it is also possible that ECMO itself, or an inflammation due to previous operation, is among the factors that affect PLR and NLR values.

Conclusion

Although the effect of PLR and NLR values on mortality and prognosis in patients who required ECMO after congenital heart surgery were found to be statistically insignificant, PLR and NLR show a trend toward increase in the postoperative period. If this increase is above a certain level, it may be a statistically significant indicator of mortality.

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Conflict of interests. The authors declare that there are no conflicts of interests.

Ethical standard. The study protocol was approved by the local ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. (2021/4/455)

Patient consent statement. Consent was not obtained and waived.

Data availability statement. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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