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Original Article / Özgün Makale

Does preoperative neutrophil-lymphocyte ratio indicate postoperative morbidity after repair of tetralogy of Fallot?

Ameliyat öncesi nötrofil-lenfosit oranı Fallot tetralojisi tamiri sonrasında morbiditeyi gösterir mi?

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ABSTRACT

Background: In this study, we aimed to investigate the impact of preoperative neutrophil-lymphocyte ratio on postoperative morbidity after repair of tetralogy of Fallot.

Methods: In this retrospective study, 51 patients (30 males, 21 females; median age 2 years; 1-3. quartiles 1.19 to 3.65 years) who underwent tetralogy of Fallot repair between August 2011 and October 2013 were included. The study population was divided into two groups: group 1 including patients without morbidity and group 2 including patients with morbidity.

Results: No mortality was observed in the study population. There was no significant difference in the median of preoperative neutrophil-lymphocyte ratio between the groups [0.87 (0.68-1.29) in group 1 vs. 0.75 (0.44-1.10) in group 2; p=0.094]. Vasoactive inotrope score, duration of intubation, and mediastinal drainage index were significantly higher in group 2 (p=0.014, p=0.001 and p=0.003, respectively). While preoperative and postoperative C-reactive protein were positively correlated with the corresponding neutrophil-lymphocyte ratio (p<0.01, p<0.01, respectively), preoperative neutrophil-lymphocyte ratio was not correlated with postoperative C-reactive protein (p=0.701).

Conclusion: Our study results showed that preoperative neutrophil-lymphocyte ratio can be a good predictor of instantaneous inflammatory status, although there is no significant relationship between preoperative neutrophil-lymphocyte ratio and morbidity after complete repair of tetralogy of Fallot.

Keywords: Cardiac surgical procedure; congenital; heart defect; inflammation; outcome assessment.

ÖZ

Amaç: Bu çalışmada Fallot tetralojisi tamiri sonrasında ameliyat öncesi nötrofil-lenfosit oranının ameliyat sonrası morbiditeye etkisi araştırıldı.

Çalışma planı: Bu retrospektif çalışmaya, Ağustos 2011 - Ekim 2013 tarihleri arasında Fallot tetralojisi tamiri yapılan 51 hasta (30 erkek, 21 kadın; ortanca yaş 2 yıl; 1-3. çeyreklik 1.19-3.65 yıl) alındı. Çalışma popülasyonu iki gruba ayrıldı: morbidite gelişmeyen hastalardan oluşan grup 1 ve morbiditeli hastalardan oluşan grup 2.

Bulgular: Çalışma popülasyonunda mortalite gözlenmedi. Gruplar arasında ameliyat öncesi nötrofil-lenfosit oranı ortanca değerinde anlamlı fark saptanmadı [grup 1'de 0.87 (0.68-1.29) ve grup 2'de 0.75 (0.44-1.10); p=0.094]. Vazoaktif inotrop skoru, entübasyon süresi ve mediastinal drenaj indeksi grup 2'de anlamlı düzeyde daha yüksekti (sırasıyla p=0.014, p=0.001 ve p=0.003). Ameliyat öncesi ve sonrası C-reaktif protein, ilgili nötrofil-lenfosit oranı ile pozitif korelasyon gösterirken (sırasıyla p<0.01, p<0.01), ameliyat öncesi nötrofil-lenfosit oranı ameliyat sonrası C-reaktif protein ile korele değildi (p=0.701).

Sonuç: Çalışma bulgularımız, Fallot tetralojisinin tam düzeltme ameliyatından sonra ameliyat öncesi nötrofil-lenfosit oranı ve morbidite arasında anlamlı bir ilişki olmamasına rağmen, ameliyat öncesi nötrofil-lenfosit oranının anlık enflamatuvar durumun iyi bir göstergesi olabileceğini göstermektedir.

Anahtar sözcükler: Kardiyak cerrahi işlem; doğuştan; kalp hastalığı; enflamasyon; sonuç değerlendirmesi.

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The combination of surgical stress and the immune-modulating effect of cardiopulmonary bypass (CPB) inevitably put the patient in an acute inflammatory state.[1,2] An acute inflammatory response exceeding compensatory response may rapidly lead to endothelial damage, capillary leak, multiple organ failure (MOF), and eventually death, which are more pronounced in pediatric population.[1,2]

Recently, preoperative neutrophil-lymphocyte ratio (pNLR) which has been suggested as an indicator of inflammatory status has come into view in cardiovascular diseases as a powerful predictor of outcome.[3-8] To the best of our knowledge, although pNLR has been suggested as a valuable predictor of mortality in adults.[3-7] the literature is scarce in regard to the predictive value of pNLR on morbidity in a cyanotic pediatric cardiac surgery cohort. Therefore, in this study, we aimed to investigate the impact of preoperative pNLR on postoperative morbidity after the complete repair of tetralogy of Fallot (TOF).

PATIENTS AND METHODS

The ethical approval was obtained from the Acibadem University, Faculty of Medicine, local Ethics Committee (No. 2013-566/Date: 18th December 2013). The medical archive was retrospectively analyzed. Between August 2011 and October 2013, a total of 193 cases who were operated with the diagnosis of TOF were screened. Patients with previous palliation or reoperation,[9] pulmonary atresia,[10] emergency surgery, hypothyroidism,[11] and thymus hypo/aplasia[12] were excluded, as all might increase peri- and postoperative risk. A total of 51 cases (30 males, 21 females; median age 2 years; 1-3. quartiles 1.19 to 3.65 years) in whom complete repair was performed constituted the study population (Figure 1). Depending on the prespecified outcome variables indicative of morbidity [sepsis, septic shock, MOF, acute renal failure (ARF), seizure, need for re-intubation, intensive care unit (ICU) stay of >48 hours and hospital stay of ≥10 days], the study population was divided into two groups in which morbidity did not (group 1, n=26) and did (group 2, n=25) develop.

Data including age, sex, preoperative oxygen saturation, weight and body surface area (BSA) were recorded. As a part of routine preoperative preparation, all prespecified laboratory values were recorded. The mean of postoperative laboratory values during ICU course were calculated. The preoperative and postoperative NLRs were calculated as the corresponding ratio of absolute neutrophil count (ANC) to absolute lymphocyte count (ALC). To assess the NLR's indicator characteristic of inflammation, the correlation between preoperative and postoperative NLR with the corresponding CRP value was analyzed.

In the clinical protocol, all cases were routinely examined by a pediatrician before surgery for the presence of an active infection sign. Patients who had a sign of active infection and were prescribed antibiotherapy were excluded.

Packed red blood cells (pRBC) and platelet suspensions were irradiated for newborn and infants. Packed red blood cell and platelet transfusions were performed using leukocyte depleting filters (Haemonetics®, RC leukocyte filter for blood 1, and PL2 leukocyte filter for platelet, Massachusetts, USA).

Following anesthesia induction, 30 mg/kg intravenous methylprednisolone was administered. All surgical procedures were performed through median sternotomy and standard CPB with selective bicaval cannulation under mild hypothermia and antegrade cold blood cardioplegia. In all cases, Capiox FX05 and FX 15 (Terumo, Ann Arbor, Michigan, USA) with an integrated arterial filter along with poly-2-methoxyethylacrylate-coated circuits (X-coating, Terumo, Ann Arbor, Michigan, USA) were used. Ultrafiltration before disconnection from CPB was not done.

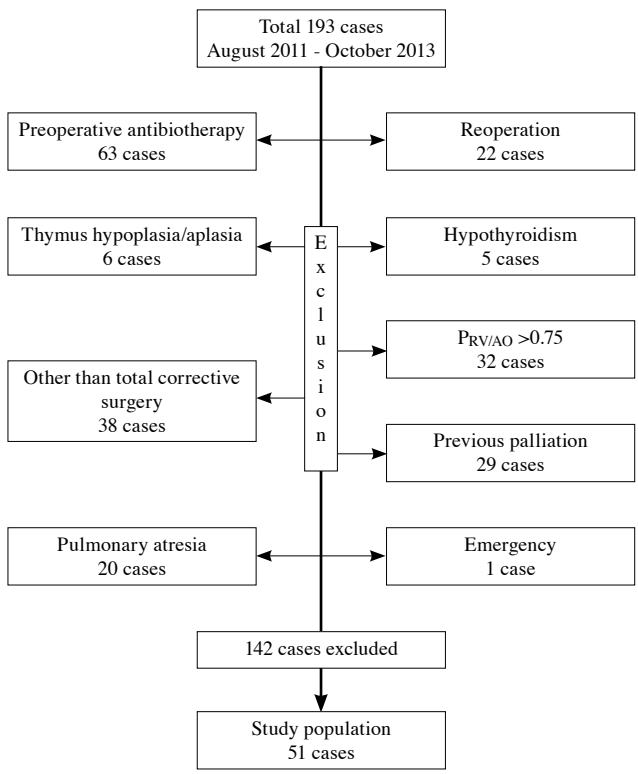

Figure 1. The exclusion process of the patients.
$P_{RV/AO}$: Right ventricle-to-aortic pressure ratio.

Table 1. Demographic and clinical characteristics of patients

Characteristics	Overall (n=51)			Group 1 (n=26)			Group 2 (n=25)			$p^{\dagger}$
	Median	Quartiles	Mean±SD	Median	Quartiles	Mean±SD	Median	Quartiles	Mean±SD	
Demographic										
Age (years)	2.00	1.19-3.65		2.79	1.33-4.33		1.57	0.99-2.84		0.095‡
Weight (kg)			11.8±4.0			13.0±3.6			10.5±4.0	0.021
BSA (m^2)			0.5±0.1			0.6±0.1			0.5±0.1	0.033
SpO_2, %			78.9±9.4			79.7±8.6			78.1±10.2	0.563
Operative										
ACC (min)			80.4±19.6			78.9±21.4			81.9±17.9	0.586
CPB (min)			105.0±22.4			101.5±22.1			108.5±22.6	0.270
Hypothermia (ºC)	30	30-32		31	30-32		30	30-32		0.685‡
$P_{RV/AO}$	0.59	0.47-0.68		0.57	0.44-0.67		0.6	0.46-0.66		0.843‡

SD: Standard deviation; BSA: Body surface area; ACC: Aortic cross-clamp; CPB: Cardiopulmonary bypass; † Student's t-test; ‡ Mann-Whitney U test; $P_{RV/AO}$: Right ventricle-to-aortic pressure ratio.

Operative variables included the degree of hypothermia, the duration of aortic cross-clamp (ACC) and CPB, the right ventricle-to-aortic pressure ratio ($P_{RV/AO}$) after weaning from CPB and the right ventricular reconstruction technique. In 32 patients with $P_{RV/AO}$ >0.75, which was probably due to hyperdynamic infundibulum, the outflow gained after right ventricular outflow tract reconstruction was considered to be anatomically proper. However, these cases were excluded due to the possible hemodynamic impact of increased $P_{RV/AO}$ on ICU recovery.

Outcome measures

Vasoactive inotrope score (VIS) was used as a measure of the amount of cardiovascular support needed. The decisions made for the necessity of inotrope support and dose adjustment of inotropic agents were based on clinical and echocardiographic evaluations. The VIS was calculated as described by Gaies et al.[13] Mediastinal drainage index (MDI) was calculated as total amount of drainage divided by BSA. During the ICU stay, the total number of orally measured (Welch Allyn, USA) body temperatures which were ≥38.5 ºC were counted, and described as "fever count". Extubation was performed depending on the clinical status of each patient. Along with the duration of intubation, the cases (n=5, 9.8%) requiring re-intubation due to cardiopulmonary insufficiency were noted. The duration of ICU and hospital stays were included; however, as they were the criteria used for definition of the groups, the difference of these variables between the groups were not analyzed.

Statistical analysis

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) v2007 and PASS (Power analysis and Sample Size) v2008 (Utah, USA) softwares. The descriptive statistical methods (mean, standard deviation, median, first and third quartile values, frequency, rate) were used. For the analysis of quantitative data between the groups, normally distributed data were analyzed using the Student t-test, while abnormally distributed data were analyzed using the Mann-Whitney U test. Intergroup comparison of normally distributed variables was done using the paired-samples t-test, whereas abnormally distributed variables were analyzed using the Wilcoxon signed-rank test. For the analysis of qualitative data, Pearson chi-square test, Fisher's exact test, and Fisher-Freeman-Hanlon exact test were used. Influencing factors on morbidity were concomitantly evaluated with the backward logistic regression analysis. The Pearson and Spearman correlation analyses were used to evaluate the intervariables relationship. A p value of <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics are shown in Table 1. There was no significant difference in the demographic and clinical characteristics of the patients between the groups except weight and BSA. Fourteen (46.7%) patients in group 1 and 16 (53.3%) patients in group 2 were male. There was no significant difference in terms of sex between the groups (p=0.461). The laboratory values of the groups are shown in Table 2.

There was no mortality in the study population. In group 2, sepsis occurred in two (3.9%), septic shock occurred in two (3.9%), MOF occurred in one (2%), ARF occurred in two (3.9%), and seizure occurred in one patient (2%). The length of ICU stay was 28.7±11.6 hours in group 1 and 80.3±65.5 hours in group 2. The length of hospital stay was 7.1±1.1 days in group 1 and 15.1±11.1 days in group 2.

Table 2. Preoperative and postoperative laboratory values

Values	Group 1 (n=26)						Group 2 (n=25)						Preoperative	Postoperative
	Preoperative			Postoperative			Preoperative			Postoperative				
	Median	Quartiles	Mean±SD	Median	Quartiles	Mean±SD	Median	Quartiles	Mean±SD	Median	Quartiles	Mean±SD	p†	p†
WBC ($10^3/\mu L$)			10.4±2.9			12.7±2.2			9.6±2.2			16.7±4.6	0.263	<0.01
ANC ($10^3/\mu L$)			4.4±1.5			7.8±1.8			3.4±1.3			10.3±2.9	0.017	0.001
ALC ($10^3/\mu L$)	3.93	3.50-5.97		3.35	2.94-3.97		5.02	3.59-6.44		3.94	3.15-5.21		0.407‡	0.06‡
NLR	0.87	0.68-1.29		2.33	1.79-3.05		0.75	0.44-1.10		2.48	2.02-3.19		0.094‡	0.429‡
PLT ($10^3/\mu L$)			297.5±85.2			214.9±57.7			298.7±85.3			186.6±39.4	0.961	0.046
CRP (mg/dL)			0.1±0.1			2.8±1.3			0.1±0.2			3.8±1.1	0.373	0.01
Creatinine (mg/dL)			0.3±0.1			0.3±0.1			0.3±0.1			0.4±0.3	0.252	0.244
AST (U/L)	34.5	29.75-41.25		117.7	96.31-136.87		34	28.5-45		148	127-196.5		0.947‡	0.001‡
TSH (μIU/mL)	2.55	2.09-3.33					2.50	1.98-3.36					0.828‡	

† Student's t-test; ‡ Mann-Whitney U test; WBC: White blood cell; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; NLR: Neutrophil-lymphocyte ratio; PLT: Platelet count; CRP: C-reactive protein; AST: Aspartate aminotransferase; TSH: Thyroid stimulating hormone.

One (1-2) pRBC, three (0-3) random platelet suspensions, and three (2-4) fresh frozen plasma were transfused per patient. There was no difference in the amount of transfused pRBC (p=0.475), platelet suspension (p=0.075), or fresh frozen plasma (p=0.508) between the groups.

The right ventricular outflow tract reconstruction as a surgical technique in terms of isolated trans-atrial myectomy, supra-annular, trans-annular, infundibular patch or conduit interposition did not show a significant difference between the groups (p=0.086, p=1, p=0.069, p=1, p=1, respectively).

Other than the ANC, which was higher in group 1, no difference in preoperative laboratory values was found between the groups. There was no significant difference in the median of pNLR between the groups [0.87 (0.68-1.29) in group 1 vs 0.75 (0.44-1.10) in group 2; p=0.094]. While postoperative ANC, CRP and AST were higher in group 2, the platelet count was lower in group 2 (Table 2).

The VIS, the duration of intubation, and MDI was higher in group 2. Although the fever count was higher in group 2, no significant difference was observed (Table 3). Age, weight, BSA, and preoperative CRP were positively correlated with pNLR (Table 4). Both preoperative and postoperative CRP was positively correlated with the corresponding NLR (r=0.37, p<0.01 and r=0.479, p<0.01, respectively). On the other hand, no correlation between pNLR and postoperative CRP was found (r=0.055, p=0.701).

In addition to the observed variables which had a significant effect on morbidity in the univariate analysis including age, BSA, VIS, and duration of intubation, the variables with a near-significant (p value between 0.05 and 0.07) effect on morbidity (fever count, transatrial resection, transannular patching) were included in the backward logistic regression analysis. The statistical model was significant (p=0.001) with a correlation coefficient of 78.4%, and the pNLR did not produce a significant effect on all-cause morbidity (Table 5).

DISCUSSION

The combination of the heart disease itself along with the surgical stress and the CPB inevitably put the patient in an acute inflammatory state through complex activation and interaction of both cellular and humeral mechanisms.[1,2] The immunological mechanisms and anatomical characteristics are relatively different in children compared to adults.[1,2] The pNLR has been investigated in cardiovascular diseases in search of

Table 3. Continuous outcome variables between the groups

Variables	Overall (n=51) Mean±SD	Group 1 (n=26) Mean±SD	Group 2 (n=25) Mean±SD	$p^{\dagger}$ (group 1 vs 2)
Vasoactive inotrope score	564.6±1190.8	169.0±243.2	976.0±1595.8	0.014
Duration of intubation (hrs)	23.7±27.8	12.0±8.2	35.9±35.1	0.001
Mediastinal drainage index (mL/m^2)	540.6±316.0	415.4±178.9	670.8±374.3	0.003
Fever count (n)	7.8±10.9	5.1±7.5	10.7±13.2	0.072

† Student's t-test.

a powerful predictor of outcome.[3-8] However, as the pNLR has not been extensively evaluated in cyanotic pediatric cardiac surgery cases, we investigated whether the pNLR could predict postoperative morbidity in TOF in whom complete repair was performed.

In the series of Gibson et al.,[5] the patients who developed AF after CABG had had a median pNLR of 3. In contrary, even though the pNLR in AF-developed group was 3.02 which was similar to the pNLR value revealed by Gibson et al.,[5] Durukan et al.[5] showed a non-significant relationship between pNLR and development of postoperative AF among CABG patients. In another study, Gibson et al.[4] followed CABG patients for 3.6 years and they showed the association of elevated pNLR with poorer survival in patients whose pNLR was >3.36. The independent predictability of pNLR for the long-term mortality among CABG patients was also discussed and pNLR was found to be directly proportional with mortality. While the five-year mortality in cases with pNLR <2.3 was 8%, 2.3-3.4 was 13% and pNLR ≥3.5 was 20%,[14] Ünal et al.[7] calculated a cut-off value of 2.81 for prediction of mortality.

Table 4. Correlation analyses of preoperative neutrophil-lymphocyte ratio and variables

Variable	pNLR Overall (n=51) r†	*p*
Age	0.508‡	0.001
Weight	0.389	0.005
Body surface area	0.393	0.004
SpO_2	0.023	0.875
Preoperative C-reactive protein	0.37	<0.01
Vasoactive inotrope score	-0.053	0.712
Duration of intubation	-0.176	0.217
Fever count	-0.11	0.442
Intensive care unit stay	-0.059	0.683
Hospital stay	0.013	0.930

pNLR: Preoperative neutrophil-lymphocyte ratio; †: Pearson's correlation coefficient, ‡: Spearman's correlation coefficient.

Gürsoy et al.[8] have recently evaluated the correlation of pNLR and CRP values with pulmonary artery pressure in 201 pediatric cardiac surgery cases. In his series, the mean pNLR and CRP were 0.82 and 0.23, respectively. In addition to the positive correlation between pNLR and CRP with pulmonary artery pressure, the pNLR was significantly higher in patients in whom postoperative pulmonary hypertensive crisis developed. The pNLR, which was 0.75 in group 2 did not reveal significant difference in our study. This can be explained by the fact that our study was lack of mortality, which was estimated to develop at higher pNLRs as in adult cohorts.[3-5] In contrary to Gürsoy et al.,[8] although the pNLR in the current series was approximate to the Gürsoy et al.'s cohort, it was probably not high enough for the development of morbidity in our cohort. This circumstance may be a reflection of the retrospective design of the study and extensive implementation of the exclusion criteria leading to a sterile patient cohort in which 142 patients with predisposing risk factors for morbidity were excluded.

Early after the end of CPB, ANC is anticipated to increase due to non-specific immune response.[16,17] Meanwhile, ALC is decreased probably due to extravasation or adhesion of activated T-lymphocytes.[13,15-17] Platelet count was also found to be decreased by 60% of the pre-bypass value mainly due to hemodilution, adhesion to foreign surfaces, use of membrane oxygenators and cardiotomy suckers.[18-20] In the current series, the change in while blood cell count, ANC, ALC, and platelet count was consistent with the given literature data.[16-20] Furthermore, although the neutrophil activity in terms of neutrophil elastase level and chemotactic activity was higher in patients with cyanotic heart disease compared to non-cyanotic ones, ANC did not differ significantly.[21,22]

As a marker of inflammation, CRP is anticipated to increase compared to preoperative values. In our study, while the preoperative and postoperative CRP values were correlated with the corresponding NLRs,

Table 5. Results of backward logistic regression analysis

Variables	*p*	OR	95% CI	
			Lower	Upper
Constant	0.240	5.068	–	–
Body surface area	0.064	0.007	0.000	1.333
Vasoactive inotrope score	0.014	1.003	1.001	1.005
Age	0.329	1.726	0.577	5.164
Fever count	0.364	1.048	0.947	1.161
Isolated transatrial resection	0.501	0.605	0.140	2.615
Duration of intubation	0.735	1.014	0.936	1.098
Transannular patching	0.849	1.184	0.210	6.683
Preoperative neutrophil-lymphocyte ratio	0.836	0.859	0.203	3.630

CI: Confidence interval; OR: Odds ratio.

no significant correlation was found between the pNLR and the postoperative CRP. In our opinion, while the NLR is a good indicator of the instantaneous inflammatory status, it is unable to accurately predict the postoperative inflammatory status. The high pNLR which is supposed to be an indicator of the inflammatory status of a patient was expected to develop with increased morbidity which was unable to be determined in our study.

In our patient cohort, none of the patients' preoperative characteristics, which were anticipated to have an impact on the postoperative course including preoperative laboratory values, transfusion requirements[23] and operative characteristics differed significantly between the groups, except the body weight. While the postoperative white blood cell count, ANC, CRP and AST were higher, the platelet count was lower in group 2. Furthermore, the continuous outcome variables including VIS, duration of intubation and MDI were all significantly higher in group 2. However, as depicted in Table 5, none of them were correlated with pNLR which was contrary to the literature. Our statistical model in logistic regression analysis was significant; however pNLR was not found to have a significant effect on morbidity (p=0.836).

In our study, to eliminate several innate factors which might lead to adverse outcomes and to achieve a homogenous study population, we implemented an extensive exclusion procedure. As the case count was partially scarce in which the categorical morbidity outcome measures (sepsis, septic shock, MOF, ARF, seizure) developed, the study can be further extended as a multicenter study with a larger sample size involving more aforementioned outcome variables.

In conclusion, neutrophil-lymphocyte ratio is a good predictor of an inflammatory status. In our study population with a preoperative neutrophil-lymphocyte ratio between 0.53 and 1.16 (median: 0.81), preoperative neutrophil-lymphocyte ratio was not found to be a predictor of morbidity in pediatric cardiac surgery cases who underwent tetralogy of Fallot repair. However, the topic merits further investigations among a large-scale sample with various congenital cardiac pathologies.

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