European Review for Medical and Pharmacological Sciences 2023; 27: 1534-1539

The role of neutrophil-lymphocyte platelet ratio in predicting in-hospital mortality after acute Type A aortic dissection operations

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Abstract. – OBJECTIVE: Acute Type A aortic dissection (ATAAD) is an emergency cardiovascular condition. In this current study, we aimed to investigate the prognostic importance of preoperative neutrophil-lymphocyte platelet ratio (NLPR) value in predicting in-hospital mortality, after surgical treatment of ATAAD.

PATIENTS AND METHODS: Consecutive patients who underwent an emergency operation as a result of ATAAD between August 2012 and August 2021 in our hospital, were retrospectively included in this study. Patients who survived the operation and were released were recorded as Group 1 and those who died in the hospital, as Group 2.

RESULTS: Mortality (in-hospital) occurred in 44 (22.5%) patients (Group 2). The median age of the 151 patients included in Group 1 and 44 patients in Group 2 were 55 (37 to 81) and 59 (33 to 72) years, respectively ($p = 0.191$). In multivariate analysis Model 1, malperfusion (OR: 3.764, 95% CI: 2.140-4.152, $p < 0.001$), total perfusion time (OR: 1.156, 95% CI: 1.040-1.469, $p = 0.012$), low platelet counts (OR: 0.894, 95% CI: 0.685-0.954, $p = 0.035$) and NLR (OR: 1.944, 95% CI: 1.230-2.390, $p < 0.001$) were determined as independent predictors for mortality. In Model 2, malperfusion (OR: 3.391, 95% CI: 2.426-3.965, $p < 0.001$) and NLPR (OR: 2.371, 95% CI: 1.892-3.519, $p < 0.001$) were determined as independent predictors for mortality.

CONCLUSIONS: According to our study, the NLPR value obtained preoperatively can be used to predict the risk of in-hospital mortality, after ATAAD surgery.

Key Words:
Aortic dissection, Inflammation, Neutrophils, Platelets, Mortality.

Introduction

Acute Type A Aortic Dissection (ATAAD) is an emergency cardiovascular condition in which the intima layer of the aorta is ruptured, the media layer is fragmented and blood moves through the adventitial space. After this situation occurs, mortality increases by 1 to 2% every hour, therefore emergency surgery should be planned[1]. When ATAAD develops, it can lead to sudden death due to causes such as acute myocardial infarction, pericardial tamponade, and hypovolemic shock. Although this disease is successfully treated with surgical methods, mortality rates are still higher than in other cardiovascular surgeries. Therefore, the factors affecting mortality are the subject of current studies[2].

Inflammation plays a role in the development of ATAAD and recovery after treatment, as in many diseases. The Neutrophil-lymphocyte ratio (NLR) obtained from white blood cell components is an important parameter as a result of its prognostic importance and easy availability[3]. Studies[4] have shown its prognostic significance after aortic dissection surgery. Platelets and the coagulation system are activated depending on the blood flow to the false lumen in dissection patients. Accordingly, low platelet counts are associated with mortality in ATAAD patients[5]. The relationship between the neutrophil-lymphocyte platelet ratio (NLPR) obtained by using platelet counts, and NLR value and cardiovascular diseases, has been demonstrated in recent studies[6,7].

In this current study, we aimed to investigate the prognostic importance of preoperative NLPR value in predicting in-hospital mortality, after surgical treatment of ATAAD.

Patients and Methods

Consecutive patients who underwent an emergency operation as a result of ATAAD between

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August 2012 and August 2021 in our hospital, were retrospectively included in this study. The study was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. The data of the patients were obtained from the hospital registry system and patient files. Demographic data (namely age, gender, presence of additional disease, malperfusion status), routine blood parameters at the time of admission (hemogram and biochemical parameters), operative (perfusion times), and postoperative data (mortality) were all recorded. Patients with inflammatory disease, renal/liver failure, hematological disease, malignancy, and shock patients, were excluded from the study. After the exclusion criteria, 195 consecutive patients were retained in the study. Patients who survived the operation and were released were recorded as Group 1 and those who died in the hospital, as Group 2.

Blood values were obtained from venous blood samples taken from the peripheral veins of the patients at the time of hospital admission. From these values, the NLPR value was calculated as follows[6]:

$$\text{NLPR} = \frac{\text{Neutrophil count } (10^3/\mu\text{L}) \times 100}{\text{Lymphocyte count } (10^3/\mu\text{L}) \times \text{Platelet count } (10^3/\mu\text{L})}$$

Statistical Analysis

In this study, statistical data were analyzed with the Statistical Package for the Social Sciences (v. 21.0, IBM Corp., Armonk, NY, USA). Continuous variables were described as median (minimum-maximum) and nominal variables were described as frequency and percentage. The Kolmogorov-Smirnov test and the Shapiro-Wilk test of normality were used to identify the distribution of data. The Mann-Whitney U test was utilized to compare two groups for continuous variables without normal distribution. The Chi-square test was used to compare two groups for nominal variables. Multivariate regression analysis was utilized to show the effects of mortality risk factors (Model 1 with NLR and platelet separately; Model 2 with NLPR). For all tests, a p-value of <0.05 was accepted as statistically significant. Receiver-operating characteristic (ROC) curve was performed for the prediction of mortality, and the area under the curve (AUC) was calculated for NLPR.

Results

Mortality (in-hospital) occurred in 44 (22.5%) patients (Group 2). The median age of the 151 patients included in Group 1 and 44 patients in Group 2 were 55 (37 to 81) and 59 (33 to 72) years, respectively ($p = 0.191$). The rates of malperfusion on admission to the hospital were higher in Group 2 ($p < 0.001$). The two groups were similar in terms of gender, hypertension and diabetes mellitus rates, smoking, history of heart surgery, left ventricular ejection fraction rates, and Marfan's syndrome. In addition, the duration of pain was similar between the two groups (Table I).

There was no significant difference between the groups in terms of white blood cell, hematocrit, neutrophil, creatinine, urea, and C-reactive protein values. In Group 2, lymphocyte and platelet values were significantly lower ($p = 0.007$ and $p < 0.001$, respectively), whereas NLR and NLPR values were significantly higher ($p < 0.001$ and $p < 0.001$, respectively). While ACT times were similar between the two groups, total perfusion times were significantly higher in Group 2 ($p < 0.001$) (Table I).

In univariate analysis, mortality was found to significantly correlate with malperfusion at the time of admission (odds ratio [OR]: 4.862, 95% confidence interval [CI]: 2.790-6.424, $p < 0.001$), total perfusion time (OR: 2.180, 95% CI: 1.850-2.896, $p < 0.001$), platelet counts (OR: 1.362, 95% CI: 1.080-1.750, $p < 0.001$), lymphocyte counts (OR: 1.070, 95% CI: 1.020-1.150, $p = 0.006$), NLR (OR: 2.285, 95% CI: 1.890-2.784, $p < 0.001$), and NLPR (OR: 3.440, 95% CI: 2.890-4.736, $p < 0.001$). In multivariate analysis Model 1, malperfusion (OR: 3.764, 95% CI: 2.140-4.152, $p < 0.001$), total perfusion time (OR: 1.156, 95% CI: 1.040-1.469, $p = 0.012$), low platelet counts (OR: 0.894, 95% CI: 0.685-0.954, $p = 0.035$) and NLR (OR: 1.944, 95% CI: 1.230-2.390, $p < 0.001$) were determined as independent predictors for mortality. In Model 2, malperfusion (OR: 3.391, 95% CI: 2.426-3.965, $p < 0.001$) and NLPR (OR: 2.371, 95% CI: 1.892-3.519, $p < 0.001$) were determined as independent predictors for mortality (Table II).

ROC curve analysis revealed that the cut-off value for NLPR was 3.8 (AUC: 0.739, 95% CI: 0.661-0.817, $p < 0.001$,70.5% sensitivity, and 56.4% specificity) (Figure 1).

Discussion

Type A acute aortic dissections are still an important condition with high morbidity and

Table I. Demographic data and perioperative features of the patients.

Variables	Group 1 (N = 151)	Group 2 (N = 44)	*p*-value
Age (years)	55 (37-81)	59 (33-72)	0.191‡
Female gender, n (%)	48 (31.8%)	16 (36.4%)	0.570*
Hypertension, n (%)	117 (77.5%)	37 (84.1%)	0.344*
Diabetes Mellitus, n (%)	33(21.9%)	12 (27.3%)	0.453*
Current smoker, n (%)	50 (33.1%)	18 (40.9%)	0.340*
Previous heart surgery, n (%)	9 (6%)	5 (11.4%)	0.222*
Marfan's syndrome, n (%)	15 (9.9%)	7 (15.9%)	0.270*
Duration of pain (hours)	2 (1-8)	3 (1-6)	0.286‡
Ejection fraction (%)	50 (30-65)	45 (30-65)	0.332‡
Malperfusion, n (%)	12 (7.9%)	19 (43.2%)	< 0.001*
De Bakey Type 1/ Type 2, n	18/133	3/41	0.337*
White blood Cell (10^3/μL)	9.8 (7.3-17.1)	10.2 (6.9-16.8)	0.297‡
Hematocrit (%)	39.6 (33.5-50.6)	40 (33.6-47.4)	0.448‡
Platelet (10^3/μL)	190 (96-330)	165 (88-408)	< 0.001‡
Neutrophil (10^3/μL)	7.1 (2.9-12.9)	7.4 (2.6-11.2)	0.176‡
Lymphocyte (10^3/μL)	1.9 (0.9-3.9)	1.5 (0.7-3.3)	0.007‡
Creatinine, mg/dL	1.4 (0.8-2.2)	1.2 (0.9-1.9)	0.217‡
Urea, mg/dL	14 (12-44)	12 (11-40)	0.128‡
C Reactive protein, (mg/dL)	12.7 (2.8-77)	13.2 (1.9-69)	0.109‡
NLR	3.9 (1.1-11.9)	7.2 (1.7-12.7)	< 0.001‡
NLPR	1.8 (0.5-6.6)	4.1 (0.9-7.7)	< 0.001‡
Total perfusion time, min	145 (114-263)	186 (130-295)	< 0.001‡
ACP time, min	28 (24-40)	30 (22-38)	0.219‡
Surgery types, n (%)			0.474*
Ascending aorta replacement	61	15	
Hemiarch replacement	78	27	
Total Arch replacement	12	2	
Concomitant AVR	9	2	0.720*
Concomitant CABG	6	3	0.429*

*Chi-square test, ‡Mann-Whitney U test [Data is expressed as median (minimum-maximum)]. Malperfusion: Coroner artery and/or visceral organ artery and/or preoperative neurological sequelae. ACP: Antegrade cerebral perfusion, NLR: Neutrophil to lymphocyte ratio, NLPR: Neutrophil to lymphocyte-platelet ratio, AVR: Aortic valve replacement, CABG: Coronary artery bypass graft surgery.

Table II. Logistic regression analysis to identify predictors of mortality after aortic dissection surgery.

	Univariate analysis			Multivariate analysis		
Variable	*p*-value	Exp(B) Odds Ratio	95% C.I. Lower – Upper	*p*-value	Exp(B) Odds Ratio	95% C.I. Lower – Upper
Age, years	0.187	1.090	0.894-1.385	--	--	--
Hypertension, n	0.339	0.894	0.697-1.190	--	--	--
Duration of pain, hours	0.275	1.116	0.879-1.465	--	--	--
Malperfusion, n	< 0.001	4.862	2.790-6.424	< 0.001[a]	3.764[a]	2.140-4.152[a]
				< 0.001[b]	3.391[b]	2.426-3.965[b]
Total perfusion time, minutes	< 0.001	2.180	1.850-2.896	0.012[a]	1.156[a]	1.040-1.469[a]
				0.079[b]	2.090[b]	0.976-3.150[b]
Platelet, 10^3/μL	< 0.001	1.362	1.080-1.750	0.035[a]	0.894[a]	0.685-0.954[a]
				--	--	--
Lymphocyte, 10^3/μL	0.006	1.070	1.020-1.150	--	--	--
NLR	< 0.001	2.285	1.890-2.784	< 0.001[a]	1.944[a]	1.230-2.390[a]
				--	--	--
NLPR	< 0.001	3.440	2.890-4.736	--	--	--
				< 0.001[b]	2.371[b]	1.892-3.519[b]

NLR: Neutrophil to lymphocyte ratio, NLPR: Neutrophil to lymphocyte-platelet ratio, PCI: Percutaneous coronary intervention, [a]: Multivariate analysis Model 1, [b]: Multivariate analysis Model 2.

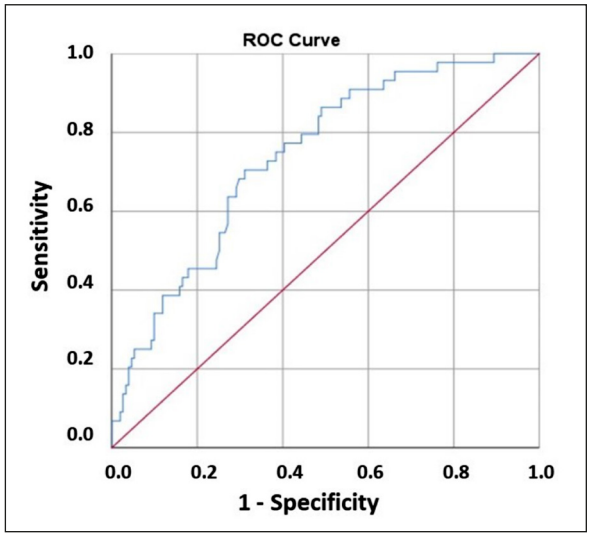

Figure 1. Receiver operating characteristic curve analysis for neutrophil lymphocyte platelet ratio to predict mortality.

mortality among acute cardiovascular diseases, despite developing technologies. Various inflammatory parameters have been investigated in the literature to predict the mortality risk of this disease and NLR comes first among these[2,4]. It has been shown that low platelet counts at the time of admission are also associated with mortal and morbid outcomes after ATAAD surgical treatment[5]. In this current study, we presented the NLPR rate calculated by NLR and platelet counts as an independent predictor of mortality after ATAAD surgical treatment, for the first time in the literature. In our study, its predictive value was higher than platelet count and NLR ratio alone.

NLR is an important clinical inflammatory marker because it is easily and inexpensively available and is not affected by daily activities. Neutrophils circulating in the blood play an important role in the development of inflammatory processes and lymphocytes are blood cells that play an important role in the modulation of these processes. Due to the prolongation of inflammatory processes, the release of immunoregulatory granulocytic myeloid-derived suppressor cells from the bone marrow increases, which causes a decrease in the number of lymphocytes, while increasing the number of white blood cells[8]. Studies[9] have shown that NLR plays an important role in the prognosis of cardiovascular diseases.

In a retrospective observational study by Kalkan et al[10], the effect of preoperative NLR value on in-hospital mortality after ATAAD surgery was investigated. In this study, the authors divided the patients into two groups, as high NLR (>6.0) and low NLR (≤ 6.0) patients and revealed that postoperative mortality and morbidity rates were higher in patients with high NLR values. In another retrospective study conducted by Öz et al[4], the relationship between NLR values at the time of admission to the clinic and early mortality was investigated. At the end of the study, the authors found high NLR to be an independent predictor of early mortality (OR: 1.913, 95% CI 1.030-1.081, $p = .04$). In a similar study published in 2020, a significant correlation was found between preoperative high NLR values and early mortality after ATAAD surgery[11]. In our study, we found a significant relationship between NLR values calculated at the time of admission and mortality.

Platelets play an important role in acute cardiovascular events. Apart from their effects on coagulation, there are also their effects on endothelial continuity[12]. When acute aortic dissection develops, platelet consumption occurs, and platelet counts decrease. In this situation, activated platelets trigger the release of proinflammatory cytokines, resulting in an inflammatory response. Afterward, platelet-neutrophil complexes are formed as a result of neutrophil rolling and adhesion and these complex structures can also cause damage to the end organs[13]. In a recent study, it has been shown that platelets play a role in the development of acute aortic dissection. Platelet factor 4 levels, which are an important indicator of platelet activation, is elevated in ATAAAD patients[14].

The relationship between admission platelet counts and in-hospital mortality was investigated by Huang et al[5]. The authors showed that platelet counts below $\leq 119 \times 10^9$/L at presentation at the end of the study, were a strong predictor of mortality[5]. In another study conducted by Yao et al[15], a significantly negative correlation was found between the development of postoperative pneumonia and platelet counts (OR 0.93; 95% CI: 0.88-0.98). In our study, there was a significant correlation between low platelet counts and mortality (Univariate analysis, OR: 1.362, $p < 0.001$).

Considering the above-mentioned prognostic effects of high NLR and low platelet counts, the NLPR value emerges as an important prognostic marker. Accordingly, the prognostic significance of NLPR value was investigated in a study by Koo et al[7], in which were included 1,099 patients who undergone cardiac surgery. In this study, patient blood parameters were evaluated in four

different periods: preoperative, post cardiotomy, and postoperative days 1 and 2, and the highest calculated NLPR value was shown as an independent predictor of early renal failure and five-year all-cause mortality[7]. In another study[6] involving 373 patients who underwent coronary bypass graft surgery, a significant correlation was found between NLPR values and early major adverse events. In our study, we showed the NLPR value, which we determined at the time of admission, as an independent predictor of early mortality after ATAAD surgery.

Advanced age is an important risk factor in the development and prognosis of many diseases. Although some studies[16] have shown mortality after AATAD surgery to be an independent risk factor, it has not been found to be associated with mortality in some others[17]. In our case, advanced age was not found to be associated with mortality. In operations where the cardiopulmonary bypass is used, blood comes into contact with foreign surfaces, and increased risks of hemolysis arise. Increases in perfusion time have been shown to increase the risk of mortality after AATAD surgery[11]. In our study, prolonged total perfusion times were significantly correlated with mortality (OR: 2.180, $p < 0.001$). Another important problem in AATAD cases is that the flap structure formed as a result of the intimal tear causes perfusion disorder in the coronary artery, carotid arteries, and visceral organ arteries. Thus, acute myocardial ischemia, neurologic sequelae, or visceral ischemia may develop in these patients, in the preoperative period. The German Registry for Acute Type A Aortic Dissection data set included 2,537 ATAAD patients in its 2020 publication, in which was presented preoperative hemiparesis (OR 1.442, 95% CI 0.996-2.065; $p = 0.049$), coronary malperfusion (OR 1.870, 95% CI 1.386-2.509); $p < 0.001$) and visceral malperfusion (OR 1.748, 95% CI 1.198-2.530; $p = 0.003$) and which have been shown as independent predictors of mortality[18]. In our current study, we showed the presence of preoperative malperfusion as an independent predictor of mortality, in both multivariate models.

Limitations

The most important limitations of our study are the retrospective single-center study and the small number of patients. In addition, evaluations showing platelet functions could not be made. The study needs to be supported by multicenter prospective studies.

Conclusions

Acute Type A aortic dissection is an important disease that can lead to very high morbid outcomes as well as high mortality risk. For this reason, it is very important to reveal new risk factors in addition to known risk factors. Thus, new risk assessment scores will be created. According to our study, the NLPR value obtained preoperatively can be used to predict the risk of in-hospital mortality, after ATAAD surgery.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The Internal Review Board approved the study protocol at the Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Protocol number: 2011-KAEK-25 2022 / 04-54).

Funding

None.

Informed Consent

Written informed consent was obtained from all patients before their surgeries.

Authors' Contribution

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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