

## Relationship of admission neutrophil-to-lymphocyte ratio with in-hospital mortality in patients with acute type I aortic dissection

Gökhan LAFÇI<sup>1\*</sup>, Ömer Faruk ÇİÇEK<sup>1</sup>, Hacı Alper UZUN<sup>2</sup>, Adnan YALÇINKAYA<sup>3</sup>, Adem İlkey DİKEN<sup>3</sup>, Osman TURAK<sup>4</sup>, Kumral ÇAĞLI<sup>4</sup>, İrfan TAŞOĞLU<sup>1</sup>, Hikmet Selçuk GEDİK<sup>5</sup>, Kemal KORKMAZ<sup>5</sup>, Orhan Eren GÜNERTEM<sup>1</sup>, Kerim ÇAĞLI<sup>1</sup>

<sup>1</sup>Department of Cardiovascular Surgery, Türkiye Yüksek İhtisas Hospital, Ankara, Turkey

<sup>2</sup>Department of Cardiovascular Surgery, Ankara Hospital, Ankara, Turkey

<sup>3</sup>Department of Cardiovascular Surgery, Faculty of Medicine, Hitit University, Çorum, Turkey

<sup>4</sup>Department of Cardiology, Türkiye Yüksek İhtisas Hospital, Ankara, Turkey

<sup>5</sup>Department of Cardiovascular Surgery, Ankara Numune Hospital, Ankara, Turkey

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**Aim:** Acute aortic dissection is a life-threatening cardiovascular emergency. Neutrophil-to-lymphocyte ratio is proposed as a prognostic marker and found to be related to worse clinical outcomes in various cardiovascular diseases. The aim of the present study was to evaluate the relationship between admission neutrophil-to-lymphocyte ratio and in-hospital mortality in acute type I aortic dissection.

**Materials and methods:** We retrospectively evaluated 123 consecutive patients who had undergone emergent surgery for acute type I aortic dissection. Patients were divided into 2 groups as patients dying in the hospital (Group 1) and those discharged alive (Group 2). All parameters, including neutrophil-to-lymphocyte ratio, were compared between the 2 groups and predictors of mortality was estimated by using multivariate analysis.

**Results:** A total of 104 patients (79 males, mean age: 55.2 ± 14 years) were included in the final analysis. In multivariate analyses, cross-clamp time, cardiopulmonary bypass time, intensive care unit duration, platelet count, and neutrophil-to-lymphocyte ratio were found to be independent predictors of mortality. Patients with higher neutrophil-to-lymphocyte ratios had a significantly higher mortality rate (hazard ratio: 1.05; 95% CI: 1.01–1.10; P = 0.033). Receiver operating characteristic analysis revealed that using a cut-off point of 8, neutrophil-to-lymphocyte ratio predicts mortality with a sensitivity of 70% and specificity of 53%.

**Conclusion:** This study suggests that admission neutrophil-to-lymphocyte ratio is a potential predictive parameter for determining the in-hospital mortality of acute type I aortic dissection.

**Key words:** Aortic dissection, neutrophil-to-lymphocyte ratio, mortality

### 1. Introduction

Acute aortic dissection (AAD) is a life-threatening cardiovascular emergency that is accompanied by several complications due to rupture of the aorta and/or malperfusion of multiple vital organs. In the absence of early diagnosis and appropriate management it has a high morbidity and mortality rate (1,2). The predictors of mortality in AAD are not fully elucidated. Two risk models including preoperative and intraoperative variables have been developed by the International Registry of Acute Aortic Dissection and are generally used, but in recent studies several biochemical markers of vascular injury, thrombosis, and inflammation have been evaluated as contributors in the diagnosis of acute aortic dissection or as risk prediction tools. These studies suggest that

AAD is associated with both tissue-level and systemic inflammatory reaction, and one of the inflammatory markers, C-reactive protein (CRP), is a useful marker to predict in-hospital and long-term adverse events (3–10).

White blood cell (WBC) subtypes, and especially the neutrophil-to-lymphocyte ratio (NLR), have been proposed as prognostic markers and seem to be related to a proinflammatory state imposing worse clinical outcomes in cardiovascular diseases (11,12). This simple and readily available ratio was used to predict the mortality of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting (CABG), chronic critical limb ischemia, and elective major vascular surgery (12–15); however, no study has investigated any possible association between NLR and mortality of AAD.

\* Correspondence: drgokhanlafci@hotmail.com

The aim of the present retrospective clinical study was to evaluate the relationship between admission NLR and in-hospital mortality in acute type I aortic dissection.

## 2. Materials and methods

### 2.1. Preoperative evaluation

We evaluated clinical, surgical, and computerized tomography (CT) data of 123 consecutive patients who had undergone emergent surgery for acute type I aortic dissection from January 2007 to January 2012 at our institution. The diagnosis of acute type I aortic dissection was established in all patients by typical clinical symptoms, chest radiography, transthoracic echocardiography, and contrast-enhanced CT. Aortic dissection was classified according to De Bakey's classification (16) and any dissections that involve the ascending aorta regardless of the entry site location were defined as type I aortic dissection. Acute aortic dissection was considered if the time from the onset of the symptoms to admission was within 14 days. A total of 14 patients (5 patients with history of open heart surgery; 4 patients presenting with hypotension, shock, or tamponade; 3 patients with pulse deficit; 1 patient with traumatic aortic dissection; and 1 patient with iatrogenic aortic dissection) were excluded from the study. Five more patients were excluded from the analysis due to acute urinary system infection ( $n = 3$ ), systemic lupus erythematosus ( $n = 1$ ), and Behçet's disease ( $n = 1$ ). The final analysis included 104 patients. This study was approved by the institutional ethics committee.

Baseline characteristics, results of CT scan and echocardiography, and peroperative details were obtained from the hospital records. For each patient, admission hemoglobin level and total WBC, neutrophil, and lymphocyte counts measured with a Siemens Advia 2120 analyzer were noted. As previously shown, this automated analyzer has an excellent correlation with manual cell counts (coefficients of variation of 2.5% for the total WBC count, 1.5% for the neutrophil count, and 2.9% for the lymphocyte count) (17). The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Admission biochemical parameters such as glucose, urea, creatinine, aspartate aminotransferase, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were also noted in all patients.

### 2.2. Surgical technique

In all patients, cardiopulmonary bypass was initiated via right axillary arterial cannulation, and after median sternotomy, a 2-stage venous cannula was inserted through the right atrium. After establishment of moderate hypothermic (28–32 °C) circulatory arrest, the heart was arrested with antegrade and retrograde cold crystalloid cardioplegia. As a standard surgical procedure, the

intimal torn aortic section was resected and the resected aorta was replaced with a presealed woven polyethylene terephthalate fiber (Dacron) graft (Boston Scientific, Inc., Natick, MA) in each patient. In 42 patients (40.4%), only supracoronary aortic replacement was performed; however, supracoronary aortic and hemiarch replacements were needed in another 42 patients (40.4%). The Bentall procedure was applied to 10 patients (9.6%) and combined supracoronary aortic replacement and CABG surgery was performed in 10 (9.6%) patients.

### 2.3. Statistical analysis

Results are presented as mean  $\pm$  SD with interquartile range unless otherwise specified. Comparisons between groups were made using chi-square tests for categorical variables, independent-samples Student t-tests for normally distributed continuous variables, and Mann-Whitney U tests when the distribution was skewed. Categorical variables were summarized as percentages. Correlations were evaluated by either Pearson or Spearman correlation tests.

The effect of NLR on outcome was studied by constructing a receiver operating characteristic (ROC) curve with mortality as the primary variable (Figure). Cox regression analysis was used to examine the association between NLR and mortality. Potential prognostic factors were entered into univariate models of mortality. Significant factors in univariate analysis were then entered into a reverse stepwise multivariate model to test for independence. Analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).  $P < 0.05$  was considered statistically significant.

## 3. Results

### 3.1. Patient population and outcome

A total of 104 patients (79 males, mean age:  $55.2 \pm 14$  years) were included in the final analysis. In-hospital mortality rate was found to be 31.7% (33 of 104 patients). There were 6 who could not be weaned from cardiopulmonary bypass and died in the operating room. The reason for intraoperative death was cardiac failure in 4 patients and bleeding in 2 patients. The causes of in-hospital mortality were reported as low cardiac output in 7 patients, major brain damage in 13 patients, respiratory failure in 3 patients, hemorrhage in 1 patient, and sepsis in 3 patients.

A comparison of patients dying in-hospital (Group 1,  $n = 33$ ) and those discharged alive (Group 2,  $n = 71$ ) regarding baseline characteristics and laboratory findings is shown in Table 1 and comparison of surgical variables is presented in Table 2. There were no significant differences between the 2 groups in terms of age, sex, presence of chronic obstructive pulmonary disease, coronary artery disease, renal dysfunction (serum creatinine level of  $\geq 2$  mg/dL), diabetes mellitus, or smoking, but hypertension

history was found to be significantly higher in Group 1 than in Group 2. Between the 2 groups, WBC and neutrophil counts were found to be similar, but lymphocyte count was significantly lower and NLR was significantly higher in Group 1 patients [ $0.99 (0.74-1.56) \times 10^9/L$  vs.  $1.3 (0.94-1.77) \times 10^9/L$ ,  $P = 0.041$ , and  $12.3 \pm 7.4$  vs.  $9.0 \pm 6.3$ ,  $P = 0.025$ , respectively; Table 1]. Among surgical variables, cross-clamp time, cardiopulmonary bypass time, intensive care unit duration, and ventilation time were found to be significantly longer in Group 1 than in Group 2 (Table 2). Bleeding amount was also significantly higher in Group 1 but reoperation for hemorrhage was similar between the 2 groups (Table 2).

**3.2. Univariable and multivariable predictors of mortality**  
Results of univariate and multivariate analysis are presented in Table 3. In multivariate regression analysis, only cross-clamp time, cardiopulmonary bypass time, intensive care unit duration, platelet count, and admission NLR were found to be independent predictors of mortality (Table 3). According to this analysis, patients with higher admission NLR have a significantly higher mortality rate (hazard ratio: 1.05; 95% CI: 1.01–1.10;  $P = 0.033$ ).

ROC analysis revealed that using a cut-off point of 8, admission NLR predicts mortality with a sensitivity of 70% and specificity of 53% in acute type I aortic dissection (Figure). The area under the curve for this relationship is 0.634 and the 95% CI is 0.516–0.753.

**Table 1.** Comparison of patients dying in-hospital and those discharged alive.

Variable	Patients dying in-hospital, Group 1 (n = 33)	Patients discharged alive, Group 2 (n = 71)	P-value*
Age (years)	55.2 ± 15.7	55.3 ± 12.3	0.956
Male	24 (72.7%)	52 (73.2%)	0.956
Hypertension	33 (100%)	65 (91%)	0.03
Chronic obstructive pulmonary disease	12 (36.4%)	22 (31%)	0.986
Coronary artery disease	12 (36.4%)	21 (29.6%)	0.489
Renal dysfunction (creatinine ≥2 mg/dL)	4 (12.1%)	3 (4.2%)	0.204
Diabetes mellitus	5 (15.2%)	8 (11.3%)	0.577
Current smoker	10 (30.3%)	21 (29.6%)	0.94
Total white blood cell count ( $\times 10^9/L$ )	14.1 ± 5.6	12.9 ± 5.9	0.372
Neutrophil count ( $\times 10^9/L$ )	11.8 ± 5.6	10.1 ± 4.7	0.118
Lymphocyte count ( $\times 10^9/L$ )	0.99 (0.74–1.56)	1.3 (0.94–1.77)	0.041
Neutrophil-to-lymphocyte ratio	12.3 ± 7.4	9.0 ± 6.3	0.025
Platelet count ( $\times 10^9/L$ )	189 (143–236)	211 (180–284)	0.011
Glucose (mg/dL)	124 (104.5–186)	119 (101–151)	0.249
Urea (mg/dL)	65.2 (40.5–83.5)	42 (35.1–58.5)	0.001
Creatinine (mg/dL)	1.34 (0.97–1.88)	1.0 (0.87–1.25)	0.003
Aspartate aminotransferase (IU/L)	53 (30–116)	25 (17–37)	<0.001
Low-density lipoprotein cholesterol (mg/dL)	76.1 ± 29.1	100.5 ± 41.9	0.003
High-density lipoprotein cholesterol (mg/dL)	35 (33.5–37.5)	38 (33–40)	0.0025
Triglycerides (mg/dL)	116 (99.5–150)	112 (85–145)	0.501

\*: A P-value of 0.05 was considered statistically significant.

**Table 2.** Comparison of surgical variables between the 2 groups.

Variable	Patients dying in-hospital, Group 1 (n = 33 )	Patients discharged alive, Group 2 (n = 71 )	P-value*
Cross-clamp time (min)	101.6 ± 11.6	77.1 ± 13.7	<0.001
Cardiopulmonary bypass time (min)	160.2 ± 32.6	102.8 ± 16.4	<0.001
Intensive care unit duration (days)	3.7 ± 1.3	1.6 ± 0.5	0.001
Ventilation time (h)	85.1 ± 29.2	12.5 ± 2.7	<0.001
Bleeding amount (mL)	1380.2 ± 331.6	1267.3 ± 269.1	<0.001
Reoperation for hemorrhage [n (%)]	8 (24)	7 (10)	0.052
Type of surgery [n (%)]			0.99
Supracoronary aortic replacement	12 (37 )	30 (42)	
Supracoronary aortic and hemiarch replacement	14 (42 )	28 (39)	
Aortic valve, root, ascending aorta replacement	1 (3)	9 (13 )	
Supracoronary aortic replacement and coronary artery bypass grafting	6 (18)	4 (6 )	

\*: A P value of 0.05 was considered statistically significant.

**Table 3.** Independent predictors of mortality in univariate and multivariate analyses.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age	1.08	(0.80–1.38)	0.844	-	-	-
Hypertension	1.02	(0.82–1.22)	0.990	-	-	-
Creatinine level	1.41	(0.94–2.12)	0.095	-	-	-
Cross-clamp time	1.12	(1.07–1.18)	<0.001	1.10	(1.04–1.15)	0.001
Cardiopulmonary bypass time	1.13	(1.07–1.19)	<0.001	1.14	(1.07–1.19)	<0.001
Intensive care unit duration	1.83	(1.31–2.53)	<0.001	1.64	(1.22–2.11)	<0.001
Ventilation time	1.09	(1.04–1.12)	<0.001	1.02	(0.78–1.24)	0.214
Hemorrhage amount	1.01	(1.00–1.03)	0.01	1.06	(0.94–1.17)	0.612
Aspartate aminotransferase level	1.01	(1.00–1.02)	0.01	0.95	(0.82–1.06)	0.346
Platelet count	0.98	(0.97–0.99)	0.014	0.96	(0.94–0.99)	0.01
Neutrophil-to-lymphocyte ratio	1.07	(1.02–1.13)	0.030	1.05	(1.01–1.10)	0.033

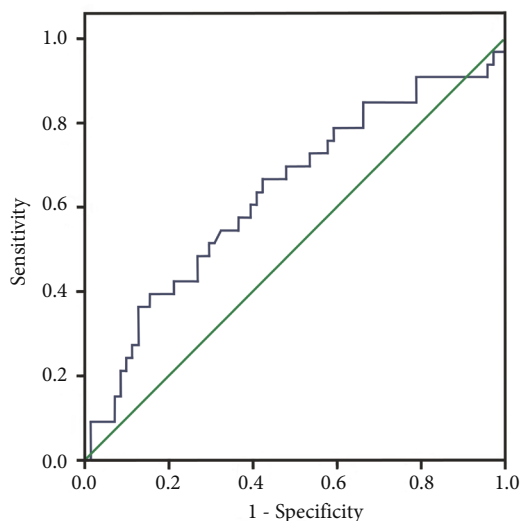
CI: Confidence interval; HR: hazard ratio.

#### 4. Discussion

This study suggests that admission NLR is a potential predictive parameter for determining the in-hospital mortality of acute type I aortic dissection. Although its sensitivity and specificity are relatively low, routine implementation of this simple and readily available parameter in clinical practice might be another step

in addressing the risk stratification of aortic dissection patients.

Aortic dissection is a multifactorial disease for which several genetic, environmental, and injury factors have been suggested to play a role in its pathogenesis (5). Several studies have shown that both local and systemic inflammation play a crucial role in initiation and



**Figure.** ROC curve for determination of the cut-off for NLR and mortality in acute type I aortic dissection. The cut-off level used in constructing this ROC was 8.0. The area under the curve for this relationship was 0.634 (95% CI: 0.516–0.753).

progression of medial degeneration and aortic dissection. Inflammatory cells such as neutrophils, lymphocytes, and macrophages are detected in the medial degeneration area (18). Moreover, in a previous study, inflammatory cell activity in the aortic wall that was determined by positron emission tomography/CT was found to be higher in patients with severe clinical symptoms than in asymptomatic and stable patients (19). On the other hand, systemic inflammatory markers, such as leukocytosis and CRP, were also reported to be independently associated with higher in-hospital and long-term mortality in aortic dissection (7–10,20,21). These inflammatory markers exhibit different time courses in their changes in acute-phase reactions and between acute and chronic aortic diseases, are associated with a poor prognosis, and remain elevated even after repair of the dissection (6). In this study we evaluated a novel inflammatory marker, NLR, in acute aortic dissection for the first time.

NLR was studied by oncological units first and proved useful as an independent predictor of survival, adverse outcomes, and recurrence risk. Recently, NLR has been shown to be predictor of morbidity and mortality in a variety of cardiovascular settings, including acute heart failure, stable coronary artery disease, and acute myocardial infarction (22–24). Several studies also suggest that NLR is a strong predictor of outcomes in percutaneous coronary intervention, CABG, and bare metal stent restenosis (11,14,25). In a previous study, Spark et al. (12) found that an NLR of  $<5.25$  correlates with survival in patients with peripheral artery disease. In another study, Bhutta et al. (15) suggested that preoperative NLR identifies patients at increased risk of death within 2 years of elective major

vascular surgery, and they proposed that this simple index may facilitate targeted preventive measures for high-risk patients. In the present study we demonstrated that this simple ratio, obtained from a universally available low-cost test, may provide potential predictive information regarding the risk of in-hospital mortality in acute aortic dissection patients.

NLR reflects the balance of the neutrophilia of inflammation and the relative lymphopenia of cortisol-induced stress response (15,26). During the inflammatory process, neutrophils increase by the way of demargination, delayed apoptosis, and stimulation of stem cells by growth factors and mediate a variety of responses including arachidonic acid metabolites, platelet activation, free oxygen radicals, and hydrolysis (15). Since AAD is also associated with both tissue-level and systemic inflammatory reaction (3–10), we suggest that neutrophilia is not a surprising finding in AAD patients. On the other hand, lymphocytes decrease in number after an acute myocardial infarction or a major surgery (22,26). The cause of decreased lymphocytes after major surgery has been attributed to neuroendocrine stress, which leads to cortisol production and in turn results in decreased lymphocyte number (26). In this study, WBC and neutrophil counts were found to be higher in patients dying in-hospital, but this difference was not statistically significant. However, lymphocyte count was found to be significantly lower in patients dying in-hospital, which leads us to propose that higher NLRs in this group are mainly driven by decreased lymphocyte count. However, to the best of our knowledge, there is no reference for the relative lymphopenia caused by stress-induced cortisol production in the AAD patient population.

On multivariate analysis, platelet count and surgical variables, including cross-clamp time, cardiopulmonary bypass time, and intensive care unit duration, were found to be other independent predictors of in-hospital mortality, but age, a well-known risk factor for mortality in AAD, was not found to be associated with mortality, probably due to the relatively young age of our patient population. Platelet count is the only negative risk factor for mortality in this study. In AAD, blood flow through the nonendothelialized false lumen can activate the coagulation system and acute massive consumption coagulopathy in the false lumen may affect both platelet number and function (27). Decreased platelet count may reflect the magnitude of consumption and may contribute to bleeding tendency. In the literature, the relationship between factors related to surgery and outcome is controversial in the AAD patient population. Longer CPB time was reported as a risk factor for short-term mortality in a study of 232 AAD patients, as in this study, but not in another study of 301 AAD patients (28,29).

Retrospective design and small patient population are the main limitations of this study. Further studies with larger patient populations are needed to evaluate the underlying mechanism of increased NLR and to determine

the clinical relevance of this marker in management of aortic dissection patients. The prognostic role of NLR in chronic aortic dissection or type III aortic dissection should be investigated in future studies.

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