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Prognostic Value of Neutrophil to Lymphocyte Ratio and Risk Factors for Mortality in Patients with Stanford Type A Aortic Dissection

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ABSTRACT

Background: Neutrophil to lymphocyte ratio (NLR) is a prognostic predictor in a wide range of cardiovascular disease. Acute aortic dissection (AD) is an uncommon but fatal cardiovascular disease. In this study, we investigated both prognostic factors in patients with AD and whether NLR can be a predictor for mortality.

Methods: We analyzed retrospectively the data of 57 patients with AD who had undergone emergent surgery in our hospital and included 128 consecutive patients with chest pain admitted to the emergency room as a control group. Also, patients who were operated on due to aortic dissection as another subgroup were compared to NLR values. Baseline clinical features, cardiovascular risk factors, and surgical and laboratory parameters were obtained from the hospital database.

Results: Patients with AD had higher NLR than the control group (1.7 ± 0.5 versus 7.6 ± 3.3, $P < .001$). In the AD group, 15 deaths occurred and non-survivors had significantly higher NLR, compared to survivors (11.6 ± 2.4 versus 6.6 ± 2.3, $P < .001$). In multivariate analysis, high NLR (odds ratio [OR] 1.913, 95% CI 1.030-1.081, $P = .04$) and cross-clamp time (OR 1.265, 95% CI 1.003-1.596, $P = .04$) were determined as independent predictors of in-hospital mortality. In receiver operating characteristics curve analyses, the NLR > 9.3 predicted the mortality in AD with a specificity of 91% and a sensitivity of 86% ($P < .001$).

Conclusion: This study shows that high NLR can be used as a marker for prognosis in short-term mortality of patient with AD. Additionally, increased lactate level in perioperative period, prolonged cardiopulmonary bypass time, and additional cardiac procedures are strong independent predictors of short-term mortality in patients with acute AD.

INTRODUCTION

Aortic dissection (AD) is one of the most serious emergent cardiovascular diseases and has a considerably high mortality rate in patients treated with surgery [Hagan 2000]. It is a life-threatening disorder in which the mortality rate in aortic dissection increases as high as 1-2% per hour within the first several hours. Early diagnosis to prevent death from aortic rupture and requiring urgent treatment is very important for survival [Nienaber 2012].

In the Stanford classification, type A AD involves the ascending aorta, and type B dissections are those that do not involve the ascending aorta [Braverman 2012]. Although type A dissections require emergent surgical repair, the medical therapy is generally performed as the initial strategy of acute type B dissections [Braverman 2010]. It has been reported that the mortality rate of patients undergoing surgery for type A dissection was 26% and for those treated medically it was 58% [Nienaber 2012]. Atherosclerosis, inflammation, and medial necrosis causing pathological weakness of the aortic wall are suspected etiologic factors for acute AD and studies have demonstrated that inflammation plays an important role in the pathophysiology of AD [Schillinger 2002; Wen 2012].

Recently, a possible relationship between CRP levels and mortality were reported in patients with acute type A AD [Wen 2011]. Therefore, high levels of inflammatory markers may be an indicator of poor prognosis and high mortality. The neutrophil to lymphocyte ratio (NLR) as a marker of inflammation in a wide range of cardiovascular diseases has been revealed by recent studies [Ayça 2015; Kaya 2014; Yalcin 2015; Ciçek 2015; Yilmaz 2015]. In addition, a correlation between long-term mortality and NLR has been demonstrated in acute myocardial infarction [Ciçek 2015; Yilmaz 2015].

In the present study, we speculated that NLR may be an early predictor of short-term mortality of patients with type A AD.

METHODS

Data from 57 patients who had undergone emergent surgery for acute type A AD in a tertiary heart center were retrospectively investigated. Demographic data, physical findings, laboratory studies, imaging procedures, surgical techniques and outcomes of the patients were evaluated. The diagnosis of acute type A AD was confirmed in all patients with the evaluation of clinical symptoms, chest radiography, transthoracic echocardiography and contrast-enhanced computed tomography. AD was classified according to the Stanford classification. Patients with AD were divided into two groups as survived or non-survived group. The hospital records were used

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Table 1. Perioperative Demographic Features and Laboratory Findings of Patients with Aortic Dissection

	Survived	Did Not Survive	*P*
Age	53 ± 11	59 ± 9	.25
Female sex, n (%)	36 (85.71)	12 (80)	<.01
Male sex, n (%)	6 (14.28)	3 (20)	.46
HT, n (%)	25 (59.52)	9 (60)	.62
DM, n (%)	6 (14.28)	3 (20)	.36
Family history, n (%)	10 (23.8)	4 (26.6)	.46
Smoking, n (%)	11 (26.19)	4 (26.6)	.85
PAD, n (%)	8 (19.04)	3 (20)	.77
CAD, n (%)	3 (7.14)	1 (6.66)	.68
Ejection fraction	52.17 ± 12.95	53.28 ± 11.02	.82
Cerebrovascular disease, n (%)	3 (7.14)	1 (6.66)	.71
COPD/Asthma, n (%)	4 (9.5)	2 (13.33)	.38
Perioperative laboratory findings in patients			
Glucose	146.29 ± 47.64	167.20 ± 68.18	.45
AST	66.12 ± 96.04	61.53 ± 34.76	.52
ALT	53.71 ± 79.21	60 ± 38.72	<.01
Leukocytes	13.41 ± 3.50	17.53 ± 5.18	<.01
Neutrophil	10.91 ± 3.43	14.21 ± 4.72	<.001
Lymphocytes	2.04 ± 1.39	1.27 ± 0.43	<.001
Platelet	200.95 ± 91.39	175.87 ± 67.62	.62
NLR	4.85 ± 2.72	11.18 ± 3.04	<.001

HT indicates hypertension; DM, diabetes mellitus; PAD, peripheral arterial disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NLR, neutrophil lymphocyte ratio. Values in bold indicate statistically significant.

for screening the results of laboratory studies. EDTA (ethylenediaminetetraacetic acid) tubes had been used for automatic blood count and the blood counts had been measured by laser procedure (Mindray BC 5800, Mainland, China). The baseline NLR was measured by dividing the neutrophil count by the lymphocyte count. Admission biochemical parameters such as cardiac biomarkers, glucose, blood urea nitrogen (BUN), creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL) cholesterol, and triglycerides were also noted in all patients. The exclusion criteria of this retrospective study were history of heart failure, acute coronary syndrome, chronic renal failure, chronic liver failure, stroke, acute infection, inflammatory disease, malignancy, any hematological disorders, history of open cardiac surgery and a history of anti-inflammatory drug use. After the initial evaluation, two patients were excluded from study because of one patient with stroke and one patient with insufficient data.

Table 2. Perioperative Status of the Aortic Valve

	Survived	Did Not Survive	*P*
Bicuspid aortic valve, n (%)	6 (14.28)	2 (13.33)	.35
Aortic regurgitation, n (%)			
Mild	29 (69.04)	10 (66.66)	.21
Moderate	3 (7.14)	1 (6.67)	.62
Severe	10 (23.80)	4 (26.66)	.54

Table 3. Operative Parameters

	Survived	Did Not Survive	*P*
CC time, min	82.64 ± 12.20	100.20 ± 11.23	<.01
CPB time, min	147.10 ± 22.15	175.40 ± 35.07	<.01
TCA time, min	22.7 ± 10.1	23.4 ± 18	.32
Peroperative high lactate, mmol/L	2.92 ± 1.55	3.69 ± 2.75	<.01
Peroperative hematocrit	29.45 ± 4.76	27.5 ± 3.85	.42
ACP, n (%)	11 (26.19)	9 (60)	<.001

CC indicates cross clamp; CPB, cardiopulmonary bypass; TCA, total circulatory arrest; ACP, additional cardiac procedure. Values in bold indicate statistically significant.

Finally, 57 patients with acute type A dissection were included in the study. The study complies with the Declaration of Helsinki and trial protocol was approved by the ethics committee of the institution.

Surgical Technique

Standard surgical management of type A dissection had been performed in all patients. Cardiopulmonary bypass (CPB) had been initiated via right axillary arterial cannulation and a two-stage venous cannula had been inserted through the right atrium after median sternotomy. After the moderate hypothermic circulatory arrest, the heart had been arrested with antegrade and rarely retrograde cold blood cardioplegia. As a standard surgical procedure, dissected aortic section had been resected and the resected aorta had been replaced with a presealed woven polyethylene terephthalate fiber (Dacron) graft (Boston Scientific, Natick, MA, USA). Supracoronary aortic replacement and hemiarch replacement procedures had been performed as needed. Ten of the patients (9.6%) had undergone Benthall procedure and in 10 patients combined supracoronary aortic graft replacement with coronary artery bypass grafting (CABG) surgery had been performed.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 17.0 for Windows (SPSS, Chicago, Illinois, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine

Table 4. Postoperative Complications or Thirty Days in Hospital Parameters in Patients

	Survived	Did Not Survive	*P*
Blood transfusion in 24 hours	1045.52 ± 213.80	1116.00 ± 1230	<.001
Reintervention due to bleeding, n (%)	6 (14.28)	6 (40)	<.001
LCOP, n (%)	8 (19.04)	4 (26.66)	<.01
Stroke, n (%)	4 (9.52)	2 (13.33)	<.01
ARDS, n (%)	2 (4.76)	1 (6.66)	.53
Septicemia, n (%)	2 (4.76)	1 (6.66)	.45
Renal failure requiring hemodialysis, n (%)	6 (14.28)	2 (13.33)	.11
Length of hospital stay, days	12.18 ± 11.25	13.17 ± 12.32	.44

LCOP indicates low cardiac output; ARDS, adult respiratory distress syndrome.

Table 5. Univariate Analysis for Prediction of Mortality in Patients

	P	OR	95% CI
Age ≥ 65 years	.04	5.53	1.25-19.67
Female	.03	8.24	1.38-32.87
CC time, min	.01	1.89	1.18-466
CPB time, min	.01	5.95	1.48-13.86
Neutrophils (%)	<.001	30.4	12.73-58.4
NLR	<.001	9.52	3.76-12.74
Perioperative high lactate (mmol/L)	<.001	17.3	5.82-24.61
Perioperative neurological deficit	.02	1.85	1.16-3.42
Perioperative hemodynamic instability	<.001	1.04	1.01-1.09
ACP	.01	3.25	2.71-4.93

CC indicates cross clamp; CPB, cardiopulmonary bypass; NLR, neutrophil lymphocyte ratio; ACP, additional cardiac procedure.

the normal distribution. Descriptive analyses are presented using means and standard deviations. The categorical variables are expressed as numbers and percentages. The Pearson chi-square test was used to compare for categorical variables and the Mann-Whitney U or Student t test for continuous variables. The capacity of NLR in predicting in-hospital mortality was analyzed using ROC curve analysis. When a significant cut-off value was observed, the sensitivity and specificity values were presented. A backward stepwise multivariate logistic regression analysis that included variables with $P < .1$ was performed to identify independent predictors of total mortality. A Hosmer-Lemeshow test and ward statistic were used for the final model selection. The odds ratio (OR) and the 95% confidence interval (CI) were also calculated. A *P* value <.05 was considered statistically significant.

RESULTS

Demographic Characteristics of Patients

57 patients who had undergone surgery for acute type A aortic dissection were analyzed as two groups of patients, 42 (73.7%) who survived and 15 (26.3%) who died on hospitalization (survived and non-survived). Survived group consisted of 42 patients, of which 36 were female and mean age was 53 ± 11 years; the non-survived group consisted of 15 patients, of which 12 were female and mean age was 59 ± 9 years. Demographic data and comorbidities of all patients were evaluated and the majority of patients in the non-survived group were female ($P < .01$). However, there was no significant difference between survived and non-survived groups in terms of mean age, hypertension, diabetes mellitus (DM), smoking, peripheral arterial disease (PAD), atherosclerosis, and family history for aortic dissection. Mean white blood cell counts (WBC), neutrophil counts, and NLR were statistically higher in the non-survived group (all of them, $P < .001$). In addition, lymphocyte counts were also significantly lower in the non-survived group than the other group ($P < .001$). Perioperative demographic features and laboratory findings of both groups are shown in Table 1.

Follow-Up and Hospital Mortality

The perioperative status of the aortic valve in patients with AD is shown in Table 2.

In cases of aortic resuspension, the valve competence was objectified through intraoperative transesophageal echocardiography which obtained full competency in 74% of patients, mild regurgitation in 23%, and moderate regurgitation in the remaining patients.

In terms of surgical parameters, the total circulation arrest time was similar in both groups. However, cross-clamp time (CC), CPB time, high level of lactate on perioperative period and additional cardiac procedure (ACP) were higher in non-survived group than survived group (Table 3). Blood transfusion rate in 24 hours, reintervention due to bleeding, low cardiac output and stroke were higher in the non-survived group than in the survived group as well (Table 4).

The univariate analysis showed old age (≥65 years), female sex, CC time, CPB time, percentage of neutrophils, NLR, perioperative lactate level, perioperative neurological deficit, perioperative hemodynamic instability, and ACP (Table 5) as predictors of mortality during follow-up. Variables that were pointing out a statistically significant difference in univariate analyses were entered into multivariate stepwise logistic regression analysis. In multivariate analysis, NLR, perioperative high lactate, CPB time, and ACP were determined to be independent predictors of mortality (Table 6) (OR 1.913, 95% CI 1.030-1.081, $P = .040$), (OR 1.265, 95% CI 1.003-1.596, $P = .04$), (OR 2.248, 95% CI 1.25-5.85, $P = .03$) and (OR 3.915, 95% CI 1.48-7.86, $P = .01$) respectively). (In addition, using ROC curve analysis, we found that the NLR > 9.3

Table 6. Multivariate Analysis with Logistic Regression for Prediction of Mortality in Patients

	Coefficient	SE	Wald	*P*	OR	95% CI
NLR	1.74	0.68	1.69	<.001	1.913	1.030-2.081
Perioperative high lactate (mmol/L)	2.37	0.75	1.22	<.001	1.265	1.003-1.596
CPB time	2.31	1.07	2.74	.03	2.248	1.25-5.85
ACP	1.52	0.65	4.35	.01	3.915	1.48-7.86

NLR indicates neutrophil lymphocyte ratio; CPB, cardiopulmonary bypass; ACP, additional cardiac procedure.

predicted mortality in patients operated on due to acute AD with a specificity of 91% and a sensitivity of 86% (area under curve: 0.919, 95% CI: 0.832-1.00; *P* < .001; Figure).

Postoperative neurologic complications (stroke or temporary neurological dysfunction [TND]) were measured in patients undergoing circulatory arrest and those who did not, and were then divided into cerebral protection method used (alone or in combination with retrograde or antegrade deep hypothermia perfusion) (Table 5). No statistically significant differences were found between any of them. The most common cause of death among patients with AD was major bleeding (n = 3); other causes were myocardial ischemia (n = 1), sepsis (n = 2), visceral ischemia (n = 1) and redissection of aortic root (n = 1), multiorgan dysfunction (n = 2), and renal failure required hemodialysis (n = 2).

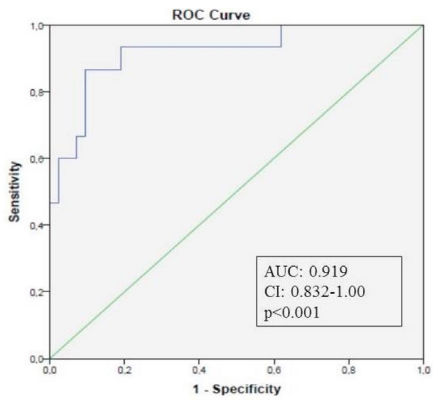
DISCUSSION

Although acute type A AD is an uncommon disorder, the outcome is frequently fatal. Multiple pathophysiological factors may play a role in the development of acute AD.

We evaluated the predictive value of NLR for mortality of patients undergoing emergency operation with acute type A AD. Several studies have shown that both local and systemic inflammation may play a crucial role in initiation and progression of medial degeneration and aortic dissection [Yilmaz 2015; He 2006]. Two types of inflammatory reactions exist in patients with acute AD and the first one is chronic vascular inflammation, which causes medial degeneration [Yilmaz 2015; He 2006]. The inflammatory cells were showed in medial degeneration by He R et al [He 2006]. Vessel wall inflammation, identified by positron emission tomography (PET-CT), was associated with poor prognosis in patients with acute type A AD as investigated by Kuehl et al [Kuehl 2008]. The second one is systemic inflammation and indicators of this process are acute phase reactants [Schillinger 2002].

Recently it has been demonstrated that elevated CRP levels were also associated with poor prognosis in patients with acute type A AD [Schillinger 2002]. Wen D et al reported the association between high WBC counts and plasma CRP levels and mortality [Wen 2012]. Furthermore, multiple studies reported that WBC count and NLR were indicators of inflammation in cardiovascular disease [Wen 2011; Ayça 2015; Kaya 2014; Yalcin 2015; Çiçek 2015; Kuehl 2008, Kalkan 2014]. The results of the present study showed NLR as a predictor marker for AD and it emerged as an independently related variable with short-term mortality in acute AD.

Pathologies causing an increase in levels of corticosteroids result in lymphopenia in consequences of increased lymphocytes apoptosis [Açar 2015]. Patients having high NLR values as in acute decompensated heart failure and ST segment elevation myocardial infarction have been associated with long-term mortality and a positive correlation has been found between hs-CRP and NLR [Kaya 2014; Yalcin 2015]. An association between postoperative prognosis and NLR was reported by Bhutta et al [Bhutta 2011]. It was concluded that perioperative high NLR values could identify patients with high risk of mortality and it was also proposed that this simple index may facilitate targeted preventive measures for high-risk patients [Núñez 2009] as in our study. Gibson et al demonstrated that the perioperative NLR was also a significant predictor of mortality among patients undergoing CABG surgery [Gibson 2007]. Moreover, the previous studies pointed out that older age, larger aortic diameter, pleural effusion, high diastolic blood pressure, high WBC, and CRP levels were the independent predictors of mortality [Wen 2012; Gibson 2007; Mehta 2002 , Hata N 2002]. Cerebral malperfusion causing perioperative cerebral deficit, prolonged reanimation or other severe complications which are in contradiction to surgery were also associated with high mortality [Hagan 2000]. Although, some studies found



In receiver operating characteristics curve analyses the NLR > 9.3 predicted the mortality in AD with a specificity of 91% and a sensitivity of 86% (Area under curve: 0.919, 95% CI: 0.832-1.00; *P* < .001).

that older age, renal failure, and hypertension were related with mortality, in the present study, we detected no relation as independent risk factor as a result of multivariate analysis with logistic regression for prediction of mortality between these factors. The study of Evangelista et al also reported no relation between mortality and such factors as age, renal failure, and hypertension [Evangelista 2012].

In the present study, patients with AD had significantly higher NLR in the mortality group than the survived group. In addition, the mortality group had the highest NLR in patients with AD and the NLR > 9.3 were found to be cut-off value for mortality in acute AD. NLR is an inexpensive and easily available marker for short-term mortality. The present study also has some limitations as it is retrospective, single-centered and has a relatively small sample size, but it also showed that NLR can be used as a predictive value independently for short-term mortality in such cases.

Study Limitations

This retrospective study was conducted in one center, thus creating a risk in patients for possible selection bias. It should be validated in an independent population. Although the number of patients included in this study was not low, it may be weak in the detection of other prognostic factors. Analyses of patient outcomes were based on the results of the initial reception.

Conclusion

In conclusion, in the present study high NLR was found as an early predictor for poor prognosis in determining mortality of patients with AD. In addition, increased lactate level on perioperative period, prolonged cardiopulmonary bypass time and additional cardiac procedures were strong independent predictors of short-term mortality in patients with acute AD.

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