

## Nötrofil/lenfosit oranının koroner ektazisi varlığı ve yaygınlığı ile ilişkisi

### Relation of neutrophil/lymphocyte ratio with the presence and extent of coronary artery ectasia

\*Dr. S. Selim Ayhan, \*Dr. Serkan Öztürk, \*Dr. Alim Erdem, \*Dr. Mehmet Fatih Özlü,  
\*Dr. Mehmet Özyaşar, \*Dr. Kemalettin Erdem, # Dr. Mehmet Yazıcı

\* Department of Cardiology, Abant İzzet Baysal University, Faculty of Medicine, Bolu  
# Department of Cardiovascular Surgery, Abant İzzet Baysal University, Faculty of Medicine, Bolu

#### ÖZET

**Amaç:** Nötrofil/lenfosit oranının (N/L oranı) kardiyovasküler olay ve mortalite ile ilişkili olduğu çalışmalarda gösterilmiştir. Bu çalışmada, koroner arter ektazisi (KAE) olan hastalarda N/L oranı araştırıldı.

**Çalışma planı:** Koroner anjiyografi sonrası KAE tanısı konulan 50 hasta (29 erkek, 21 kadın; ortalama yaş 51,1±7,1 yıl) ve normal koroner arter saptanan 28 hasta (16 erkek, 12 kadın; ortalama yaş 49,5±9,4 yıl) çalışmaya dahil edildi. Temel demografik ve klinik özellikler kaydedildi. Ektazik segment sayısı hesaplandı. Hematolojik parametreler ölçüldü ve N/L oranı hesaplandı.

**Bulgular:** Nötrofil/lenfosit oranı KAE grubunda anlamlı olarak yüksekti (sırasıyla, ortanca [%25-%75 persantil] 2,2 [1,6-3,0] ve 1,8 [1,4-2,0]; p=0,014). Spearman korelasyon analizinde N/L oranının ektazik segment sayısı ile pozitif korelasyon gösterdiği saptandı (r=0,35; p<0,002). Çok değişkenli lojistik regresyon analizi ile de KAE ve N/L oranı arasındaki bağımsız ilişki gösterildi (olasılık oranı: 2,674; %95 güven aralığı 1,184-6,039; p=0,018).

#### ABSTRACT

**Objectives:** It has been shown that the neutrophil to lymphocyte ratio (N/L ratio) is associated with cardiovascular events and mortality. In this study, we investigated the N/L ratio in patients with coronary artery ectasia (CAE).

**Study design:** Fifty patients (29 men, 21 women; mean age, 51.1±7.1 years) diagnosed as CAE using coronary angiography were included in the study. The control group consisted of 28 patients (16 men, 12 women; mean age, 49.5±9.4 years) who had normal coronary arteries as determined by coronary angiography. Baseline characteristics were recorded. The number of ectatic segments was noted. Hematologic parameters were measured and the N/L ratio was calculated.

**Results:** The N/L ratio was significantly higher in the CAE group compared with the control group (median [25-75% percentile] 2.2 [1.6-3.0] vs. 1.8 [1.4-2.0], p=0.014, respectively). The Spearman correlation analysis demonstrated that the N/L ratio positively

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Yazışma adresi: Dr. S. Selim Ayhan. Abant İzzet Baysal Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Bolu.

Tel: 0374 - 253 46 56 e-posta: ssayhan@yahoo.com

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Address of Correspondence: Dr. S. Selim Ayhan. Abant İzzet Baysal Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Bolu.

Phone: 090-374 - 253 46 56 e-mail: ssayhan@yahoo.com

**Sonuç:** Koroner ektazili hastalarda N/L oranı artmıştır. N/L oranı KAE varlığı ve ciddiyetiyle ilişkilidir.

### **Abbreviations:**

*CRP* C-reactive protein  
*Cx* Circumflex artery  
*CAE* Coronary artery ectasia  
*CAD* Coronary artery disease  
*N/L* Neutrophil/lymphocyte  
*RCA* Right coronary artery

Coronary artery ectasia (CAE) has been defined as segmental or diffuse enlargement of coronary artery  $\geq 1.5$  times greater than the diameter of the adjacent normal segment. Its reported incidence varies between 0.3, and 4.9 percent. [1] Although etiopathogenesis of CAE is not known exactly, extensive atherosclerotic changes during histopathologic examination of ectatic segment, and significant coronary artery stenosis accompanying CAE suggest atherosclerosis as the most important etiological factor.[2,3] In cases where atherosclerosis could not be revealed, risk factors in the development of CAE are not yet known exactly.[4,5] In many different publications, demonstration of relationship between CAE, and connective tissue diseases, infection, and various inflammatory conditions, and detection of

correlated with the number of ectatic segments ( $r=0.35$ ;  $p<0.002$ ). Multivariate logistic regression analysis showed an independent relationship between CAE and the N/L ratio (odds ratio 2.674, 95% confidence interval 1.184-6.039,  $p=0.018$ ).

**Conclusion:** The N/L ratio is higher in patients with CAE. This ratio is related to presence and severity of CAE.

increased levels of different inflammatory markers in patients with CAE relative to those with coronary artery disease (CAD) or healthy individuals revived the probable role of inflammation (if any) in the etiopathogenesis of CAE.[6-9]

White blood cell, neutrophil, lymphocyte counts, and neutrophil/lymphocyte (N/L) ratio are markers of systemic inflammation.[10] In previous publications, N/L ratio has been demonstrated as a predictive factor for cardiac events, and mortality in patients with stable CAD.[11] Besides in a recent study, N/L ratio has been reported as a predictor for the progression of coronary atherosclerosis in cases with CAD.[12]

As far as we know, any publication concerning the correlation between CAE, and N/L ratio is lacking in the literature. Therefore, we have investigated the potential correlation between the presence, and extent of CAE, and N/L ratio.

### **PATIENTS AND THE METHOD**

The patients who had undergone coronary angiography in our hospital

between May 2011, and June 2012 were analyzed retrospectively. Fifty patients with CAE (29 men, 21 women; mean age  $51.1 \pm 7.1$  years), and as a control group, 28 patients (16 men, 12 women; mean age,  $49.5 \pm 9.4$  years) with normal coronary arteries were included in the study. Approval for the study was obtained from the local ethics committee.

The indication for coronary angiography was made based on the detection of typical ischemia, suspect or positive results as for ischemia in non-invasive tests. Hypertension was defined as higher systolic ( $\geq 140$  mm Hg), and diastolic ( $\geq 90$  mm Hg) blood pressure or antihypertensive use. Diagnosis of diabetes mellitus was specified as fasting blood glucose levels  $\geq 126$  mg/dl, and current oral antidiabetic drug or insulin use. All regular cigarette users were accepted as current smokers.

Exclusion criteria were determined as acute coronary syndrome, previous myocardial infarction, heart failure, serious valvular disease, right or left ventricular hypertrophy, chronic obstructive pulmonary disease, atrial fibrillation, renal and hepatic failure, hematologic disease, cancer, systemic inflammatory disease, and antibiotic use.

#### **Evaluation of coronary artery ectasia**

Coronary angiography was performed by Judkins technique using 6-7 Fr right, and left cardiac catheters. Angiograms were recorded in DICOM digital directory at a rate of 25 square

/millisecond, and evaluated by two interventional cardiologists experienced in coronary angiography but blinded to the identity of the patients. Hartnell et al angiographically defined CAE as enlargement of coronary artery diameter  $\geq 1.5$  times greater than the diameter of the normal adjacent coronary artery.[13] Normal segment was described as non-stenotic, and non-ectatic coronary artery segment as detected during angiography.

In patients with coronary ectasia, the number of ectatic segments was calculated, and their diameters were measured. Measurements were performed from the proximal, middle, and distal segments of the left anterior descending (LAD), circumflex artery (Cx), and right coronary artery. The extent of CAE was determined based on the number of affected segments. Mean diameter of ectatic segments was calculated by dividing the sum of the greatest diameters of ectatic segments by the number of ectatic segments.[14]

Laboratory parameters, and collection of blood samples

After a 12-hour fasting period, blood samples were drawn from the antecubital vein while compressing forearm to create a mild degree of venous stasis. The samples were placed in potassium-EDTA containing tubes. Parameters such as hemoglobin, hematocrit, whole blood cell counts (platelets, neutrophils, lymphocytes, eosinophils, and monocytes, and their

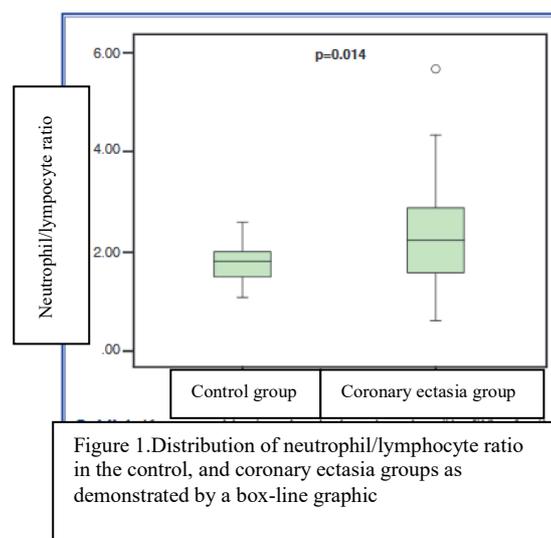
subtypes) were determined in automated blood counters (Beckman Coulter LH 750) using electrical impedance method. N/L ratio was estimated. Levels of glucose, creatinine, total cholesterol, triglyceride, HDL (high-density lipoprotein), and LDL (low-density lipoprotein) cholesterol were measured using colorimetric methods (Abbott Colorimeter, Abbott Laboratories, Illinois U.S.A.).

### Statistical analysis

For the evaluation of data “SPSS for Windows 15” statistical program was used. Variables with normal distribution were assessed using Kolmogorov-Smirnov test. Continuous variables with normal, and non-normal distribution were indicated as mean  $\pm$  standard deviation, and medians (range: 25-75 percentiles), respectively. Categorical variables were expressed as numbers, and percentages. Categorical variables with normal, and non-normal distribution were indicated using Student t-test, and Mann-Whitney U test, respectively. Categorical variables were evaluated using Pearson *chi*-square, and Fisher’s exact test. Correlation between topographical extent of CAE, and N/L ratio was assessed by Spearman correlation test. Independent factors related to the presence of CAE were investigated using multivariate logistic regression analysis.  $P < 0.05$  was accepted as statistically significant value for all analyses.

## RESULTS

Demographic, clinical, and biochemical data of the patients are summarized in Table 1. A significant difference was not found between groups as for hypertension, and diabetes mellitus. Lipid panel, glucose, creatinine levels were comparable between groups. Frequency of drug use was similar between both groups. Mean diameter, and number of ectatic segments were determined as  $5.2 \pm 1.5$  mm, and  $3.1 \pm 1.6$ , respectively. Coronary ectasia was generally observed in more than one coronary artery (single, two-, and three-vessel ectasia in 12, 20, and 18 patients, respectively). In 6 patients (12 %) only one coronary segment was ectatic. More than one segment was ectatic in the remaining 48 /82 %) patients. Coronary ectasia was seen most often in RCA, and least frequently in Cx.



Comparison of hematological data of both groups is shown in Table 2. Hemoglobin, white blood cell, and platelet counts, and mean platelet volume were similar in both groups. Neutrophil counts were significantly higher in the CAE group without any meaningful difference between groups. N/L ratio was found to be significantly higher when compared with the control group (Figure 1). In Spearman correlation analysis, a low-moderate degree of correlation was detected

between the number of ectatic segments, and N/L ratio ( $r=0.35$ ,  $p=0.002$ ). A multivariate regression analysis which assessed age, and gender of the patients, diabetes, hypertension, smoking status, mean platelet volume, and N/L has demonstrated the presence of an independent correlation between N/L ratio, and coronary ectasia (odds ratio, 2.674; 95% confidence interval, 1.184-6.039;  $p=0.018$ ) (Table 3).

**Table 1. Baseline demographic, clinical, and biochemical characteristics of the study group**

	CAE group(n=50)			Control group (n=28)			p
	n	%	Mean ± SD	n	%	Mean ± SD	
Age, years			51.1±7.1			49.5±9.4	0.401
Male	29	58		16	57		0.941
Body mass index (kg/m <sup>2</sup> )			27.2±4.2			27.9±2.9	0.399
Diabetes mellitus	6	12		5	18		0.511
Hypertension	12	24		6	21		0.857
Smoking	18	36		10	35		0.980
Heart rate (bpm)			71.8±8.7			72.2±6.8	0.800
Systolic blood pressure (mmHg)	120	118-130		120	110-130		0.575
Diastolic blood pressure (mmHg)	80	70-80		80	70-85		0.453
Beta-blocker use	5	10		3	11		0.983
ACEI/ARB use	7	14		5	18		0.830
Calcium channel blocker use	4	8		3	11		0.962
Glucose (mg/dl)	97	90-102			90-99		0.309
Creatinine (mg/dl)			0.83±0.18			0.82±0.15	0.714
LDL-cholesterol (mg/dl)			119±16			116±18	0.552
HDL-cholesterol (mg/dl)			42±4			44±4	0.288
Total cholesterol (mg/dl)			192±14			188±18	0.335
Triglyceride(mg/dl)	160	150-176		164	130-181		0.931

CAE, coronary artery ectasia; Continuous variables are expressed as mean ± SD, and medians (25-75 percentiles), and categorical variables as numbers (%). \*Student t-test, Mann-Whitney U-test, *chi* square, and Fisher's exact tests were used. CAE: Coronary artery ectasia; SD, standard deviation; ACE, angiotensin-converting enzyme inhibitor;; ARB: Angiotensin receptor blocker; LDL: low-density lipoprotein; HDL: high-density

**Table 2. Comparison of hematological parametres between groups**

	CAE group (n=50)			Control group (n=28)			<i>p</i>
	n	%	Mean ± SD	n	%	Mean ± SD	
White blood cell count (10 <sup>3</sup> /mm <sup>3</sup> )	7.1	5.8-8.1		7.0	5.5-8.1		0.599
Neutrophils (10 <sup>3</sup> /mm <sup>3</sup> )	4.2	3.6-5.1		3.6	2.9-4.4		0.029
Lymphocytes (10 <sup>3</sup> /mm <sup>3</sup> )			1.9±0.7			2.0±0.3	0.540
Neutrophil/Lymphocyte ratio	2.2	1.6-3.0		1.8	1.4-2.0		0.014
Monocytes (10 <sup>3</sup> /mm <sup>3</sup> )	0.5	0.4-0.6		0.6	0.4-0.6		0.790
Eosinophils (10 <sup>3</sup> /mm <sup>3</sup> )	0.15	0.1-0.2		0.15	0.1-0.2		0.883
Hemoglobin (g/dl)	14	13-14.6		14	12.8-14.8		0.720
Hematocrit	40.7	38.6-44.1		40.3	37.5-44.2		0.704
Red blood cell distribution width	16.6	16.3-16.9		16.4	16.2-16.8		0.237
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	229	184-259		240	220-258		0.379
Mean platelet volume (f)			8.1±0.8			7.8±0.8	0.121

Data are expressed as mean ± SD, and medians (25-75 percentiles) ; SD, standard deviation. \*Student t-testi and Mann-Whitney U-test are used.. CAE: Coronary artery ectasia

**Table 3. Results of multivariate logistic regression analysis**

	Odds ratio		<i>p</i>
	(95 % confidence interval)		
	n	%	
Age	1.042	0.973-1.115	0.261
Gender	0.665	0.225-1.968	0.461
Diabetes mellitus	0.407	0.085-1.951	0.261
Hypertension	1.683	0.451-6.280	0.438
Smoking	1.274	0.404-4.018	0.679
Mean platelet volume	0.602	0.309-1.173	0.136
N/L ratio	2.674	1.184-6.039	0.018

Dependent variable: presence of coronary artery ectasia; N/L neutrophil/lymphocyte ratio

## DISCUSSION

Our study has demonstrated that N/L ratio is significantly higher in patients with CAE relative to the control group, and correlates with atherosclerotic disease independently from the presence of coronary ectasia.

Significant role of inflammatory process in all phases of atherosclerosis is already acknowledged.[15] In previous studies, detection of inflammation as a fundamental component in the formation of vascular aneurysms has revived the possible role (if any) of inflammation in

the pathogenesis of coronary ectasias.[16] In fact, levels of some markers of inflammation as C-reactive protein (CRP), cytokines, and adhesion molecules were found to be increased in patients with CAE when compared with healthy controls.[17,18] Turhan et al [17] evaluated CRP levels in patients with isolated CAE, cases with CAD without concomitant coronary ectasia, and those with angiographically normal coronary arteries. The authors found higher CRP levels in patients with CAE when compared with the other two groups, and suggested that inflammatory process might progress more severely in patients with coronary ectasia relative to CAD patients

Many studies have demonstrated that white blood cell counts, and its subtypes are important inflammatory markers in predicting cardiovascular outcomes.[19-21] Initial studies have shown that white blood cell count is an important predictor of early phase mortality in patients with myocardial infarction.[22] In patients with ST-elevation myocardial infarction, it has been demonstrated that increase in the neutrophil counts is related to the short-term prognosis, and extent of infarction, and neutrophils act as mediators in inflammatory response developed as a result of acute myocardial damage.[23] Relative lymphopenia seen in the acute coronary syndrome has been shown to be associated with stress-related cortisol release. Besides, in previous studies, it has

been shown to be one of the early phase markers in patients suffering from myocardial infarction. [24] Nowadays, N/L ratio has been accepted as a parameter demonstrating adverse effects of both elevated neutrophil counts which reflect acute inflammation, and lymphopenia which indicates physiological stress.[25]

In patients with stable CAD, N/L ratio has been shown to be a predictor for the future cardiac events, and mortality.[11] Cho et al [26] reported N/L ratio as an important parameter in the early stage risk classification in patients with ST-elevation myocardial infarction who had previously undergone percutaneous coronary intervention. In a recent study, Kalay et al [12] revealed that higher N/L ratio in patients with stable CAD or acute coronary syndrome is an independent predictor of the progression of atherosclerosis. We have also found significantly higher N/L ratios in cases with CAE when compared with those with normal coronary arteries. Firstly in the present study, a positive correlation between only N/L ratio among other inflammatory markers, and the number of ectatic segments has been revealed. Besides, in our study N/L ratio has been detected as one of the independent predictors of coronary ectasia. As indicated by Turhan et al [17] our findings support the potential role of intense inflammatory process in the involvement, and progression of coronary ectasia.

Another outcome of our study is lack of any correlation between hematological parameters (excl neutrophil counts, and N/L ratio) , and the presence of CAE. . Various literature publications have pointed out to the correlation between increases in these parameters, especially association between in mean platelet volume, and coronary ectasia.[27,28] However in our study, mean platelet volume was higher than that in the control group without any statistically significant difference between them.. We think that this phenomenon might stem from scarce number of our patients.

The most important limitation of the present study is its retrospective design, and smaller number of its patient population. Lack of any comparison between N/L ratio, and other inflammatory markers is another limitation of the study.

To our knowledge, our study is the first in the literature which has demonstrated that N/L ratio increases in cases of CAE, and correlates with coronary ectasia, and its severity. In the evaluation of inflammatory process in patients with CAE, N/L ratio can be said to be easily available parametre relative to others.

***Conflict of interest: None declared***

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- Anahtar sözcükler: Dilatasyon, patolojik/etyoloji; koroner anevrizma/fizyopatoloji; koroner anjiyografi; koroner damarlar/patoloji; lenfosit sayısı; nötrofil; risk değerlendirmesi.
- Key words: Dilatation, pathologic/etiology; coronary aneurysm/pathophysiology; coronary angiography; coronary vessels/pathology; lymphocyte count; neutrophil; risk assessment.