Association of neutrophil to lymphocyte ratio with presence of isolated coronary artery ectasia

Nötrofilin lenfosite oranının izole koroner arter ektazisi varlığı ile ilişkisi

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ABSTRACT

Objectives: Coronary artery ectasia (CAE) has been defined as a dilated artery luminal diameter that is at least 50% greater than the diameter of the normal portion of the artery. Isolated CAE is defined as CAE without significant coronary artery stenosis and isolated CAE has more pronounced inflammatory symptoms. Neutrophil to lymphocyte ratio (NLR) is widely used as a marker of inflammation and an indicator of cardiovascular outcomes in patients with coronary artery disease. We examined a possible association between NLR and the presence of isolated CAE.

Study design: In this study, 2345 patients who underwent coronary angiography for suspected or known ischemic heart disease were evaluated retrospectively. Following the application of exclusion criteria, our study population consisted of 81 CAE patients and 85 age- and gender-matched subjects who proved to have normal coronary angiograms. Baseline neutrophil, lymphocyte and other hematologic indices were measured routinely prior to the coronary angiography.

Results: Patients with angiographic isolated CAE had significantly elevated NLR when compared to the patients with normal coronary artery pathology (3.39±1.36 *vs.* 2.25±0.58, p<0.001). A NLR level ≥2.37 measured on admission had a 77% sensitivity and 63% specificity in predicting isolated CAE at ROC curve analysis. In the multivariate analysis, hypercholesterolemia (OR=2.63, 95% CI 1.22-5.65, p=0.01), obesity (OR=3.76, 95% CI 1.43-9.87, p=0.007) and increased NLR (OR=6.03, 95% CI 2.61-13.94, p<0.001) were independent predictors for the presence of isolated CAE.

Conclusion: Neutrophil to lymphocyte ratio is a readily available clinical laboratory value that is associated with the presence of isolated CAE.

ÖZET

Amaç: Koroner arter ektazisi (KAE), koroner arterlerin normal koroner arter bölgesine göre en az %50'den daha fazla genişlemesi olarak tanımlanır. İzole KAE ciddi koroner arter darlığı olmaksızın KAE'nin bulunması olarak tanımlanır ve belirgin enflamatuvar özelliklere sahiptir. Nötrofilin lenfosite oranı (NLO) enflamasyonun yaygın kullanılan bir belirtecidir ve koroner arter hastalığı olan kişilerde hastalığın seyrinin bir göstergesidir. Bu çalışmada, NLO ile izole KAE arasındaki olası ilişki araştırıldı.

Çalışma planı: Bilinen veya şüphenilen iskemik kalp hastalığı nedeniyle koroner anjiyografi yapılan 2345 hasta geriye dönük olarak değerlendirildi. Dışlanma kriterleri sonrası, çalışma popülasyonu KAE olan 81 hasta ve bu gurupla yaş ve cinsiyet olarak eşleşmiş anjiyografileri normal 85 hastayı kapsamaktaydı. Koroner anjiyografi öncesinde tüm hastalarda nötrofil, lenfosit ve diğer hematolojik göstergelerin ölçümleri rutin olarak yapılmıştı.

Bulgular: İzole KAE'si olan hastalarda NLO düzeyinin normal koroner arterli olgulara kıyasla belirgin olarak artmış olduğu görüldü (3.39±1.36 ve 2.25±0.58, p<0.001). Receiver operating curve (ROC) eğrisi analizlerinde, başvuru anında ölçülen NLO ≥2.37 değerinin izole KAE'yi öngörmede duyarlılığının %77 ve özgüllüğünün %63 olduğu saptandı. Çok değişkenli lojistik regresyon analizinde hiperkolesterolemi (OO=2.63, %95 GA 1.22-5.65, p=0.01), obezite (OO=3.76, %95 GA 1.43-9.87, p=0.007) ve artmış NLO (OO=6.03, %95 GA 2.61-13.94, p<0.001) izole KAE varlığı için bağımsız belirleyiciler olarak saptandı.

Sonuç: Nötrofilin lenfosite oranı izole KAE varlığı ile ilişkili olan, kolaylıkla ölçülebilen bir laboratuvar bulgusudur.

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The role of inflammation in cardiovascular diseases is known.[1] White blood cell (WBC) count and related parameters are markers of inflammation in cardiovascular disease and neutrophil to lymphocyte ratio (NLR) has been shown to have the greatest predictive power for poor outcomes in patients diagnosed with or at high risk for coronary artery disease.[2,3] NLR is more predictive because the two inflammatory markers, neutrophil and lymphocyte, indicate opposing clinical outcomes.[3]

Coronary artery ectasia (CAE), an abnormality of the coronary anatomy, has been defined as a dilated artery luminal diameter that is at least 50% greater than the diameter of the normal portion of the artery.[4] Isolated CAE is defined as CAE without significant coronary artery stenosis. It has been demonstrated that isolated CAE is associated with an increased cardiovascular event rate.[5] The underlying mechanisms responsible for ectasia formation are not well understood, however previous studies have demonstrated that CAE may be a form of atherosclerosis with more active inflammatory properties than normal vessels.[6-10]

Given that the mechanism of CAE may be associated with increased inflammation and that NLR is a marker of inflammation, we hypothesized that increased NLR would be associated with the presence of isolated CAE. We evaluated this hypothesis in a population of patients who underwent coronary angiography for suspected or known ischemic heart disease.

PATIENTS AND METHODS

Study population

In this study, 2345 patients who underwent coronary angiography for suspected or known ischemic heart disease were retrospectively evaluated between April 2009 and July 2011. Out of these, 102 (4.3%) patients had isolated CAE. 21 patients were excluded due to exclusion criteria (8 patients with previous history of myocardial infarction (MI) or percutaneous coronary intervention; 4 patients with heart failure; 2 patients with valvular heart disease; 4 patients with inflammatory diseases; 1 patient with malignancy; 1 patient with hematological disorders and 1 patient with current use of corticosteroids). Finally, 81 patients with isolated CAE were included in the study. The control group consisted of 85 age- and gender-matched subjects who were selected in a consecutive manner from among catheterized patients during the same study period who had normal coronary angiograms. All patients recruited into the study underwent coronary angiography for presence of chest pain or had objective signs of ischemia (treadmill exercise or myocardial SPECT).

Abbreviations:

BMI	*Body mass index*
CAD	*Coronary artery disease*
CAE	*Coronary artery ectasia*
DM	*Diabetes mellitus*
GFR	*Glomerular filtration rate*
LVEF	*Left ventricular ejection fraction*
MI	*Myocardial infarction*
MMP	*Matrix metalloprotease*
NGAL	*Neutrophil gelatinase-associated lipocalin*
NLR	*Neutrophil to lymphocyte ratio*
ROC	*Receiver operating characteristics*
WBC	*White blood cell*

The patients' laboratory and clinical characteristics, such as age, sex, diabetes mellitus (DM), hypertension, hypercholesterolemia, smoking, family history of coronary artery disease (CAD), height and weight, were accessed through medical records. In cases of inconsistencies, the patients were contacted by telephone. The body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2).

Laboratory measurements

In our hospital, blood samples are collected from the ante-cubital vein by an atraumatic puncture prior to the coronary angiography and are sent to the laboratory for analysis within 1 hour after collection. Venous blood is collected in a tube containing K3 EDTA for measurement of hematologic indices in all patients undergoing the coronary angiography. Hematologic indices are evaluated from CBC (complete blood count) analysis performed by a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland). The glomerular filtration rate (GFR) was estimated by the simplified Modification of Diet in Renal Disease Equation.

Coronary angiography and echocardiography

Coronary angiographies were performed in our clinic using the standard Judkins technique without nitroglycerin. The right anterior oblique view was used to evaluate ectasia in the left coronary system and left anterior oblique view was used for the evaluation of the right coronary artery. Evaluations were performed visually by two experienced angiographers. The vessel diameter was calculated quantitatively in case of the presence of conflict about CAE.

Transthoracic echocardiography was performed on patients before discharge using a system V (Ving-

med, GE, Horten, Norway) with a 2.5 MHz phased-array transducer. Recordings were taken on patients positioned in the left lateral decubitus position. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson's rule.[11]

Definitions

The diagnosis of DM was based on previous history of diabetes treated with or without drug therapies. Hypercholesterolemia was defined as total cholesterol of ≥200 mg/dl. A BMI of ≥30 kg/m^2 was defined as obese. According to the results of coronary angiography, significant coronary artery stenosis was defined as ≥50% of major coronary arteries. Absence of any atherosclerotic plaques was regarded as normal coronary artery pathology.

Stable angina was defined as discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. Current smokers were defined as those who had smoked for some period during the past year. Patients were considered as having ESRD, if they were dependent on chronic dialysis. Renal insufficiency was defined as a GFR of <60 ml/min/1.732 m^2.

The local ethics committee approved this study.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as percentages. Adequacy of all parameters to normal distribution, was tested by using the Kolmogorov-Smirnov test. To compare parametric continuous variables, the Student's t test was used; to compare nonparametric continuous variables, the Mann-Whitney U-test was used; to compare categorical variables, the chi-square test was used. The Receiver Operating Characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of NLR and its respective optimal cut-off value for predicting isolated CAE. Multivariate logistic regression analysis was used to identify the independent predictors of the presence of isolated CAE. All variables showing significance values <0.25 on univariate analysis (diabetes, hypercholesterolemia, smoking, obesity, WBC, use of beta-blockers and increased NLR) were included in the model. Two-tailed p values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS, version 15.0 for Windows.

RESULTS

Among 166 patients (mean age 58.25±9.6, 69.3% male), NLR ranged from 1.30 to7.40 (median 2.50, mean 2.81±1.18). The baseline characteristics of the normal vessels or vessels where isolated CAE was present angiographically are summarized in Table 1. Patients with isolated CAE were more frequently diagnosed with diabetes, hypercholesterolemia, and obesity relative to the control group and had significantly elevated neutrophil counts and NLR and decreased lymphocyte values. There was no difference between groups for presence of hypertension, smoking, family history for CAD, renal insufficiency and medications. In addition, the baseline LVEF, WBC, hemoglobin, platelet and monocyte parameters were similar in both groups.

Moreover, we found that isolated CAE most commonly affects the right coronary artery (63.4%), left

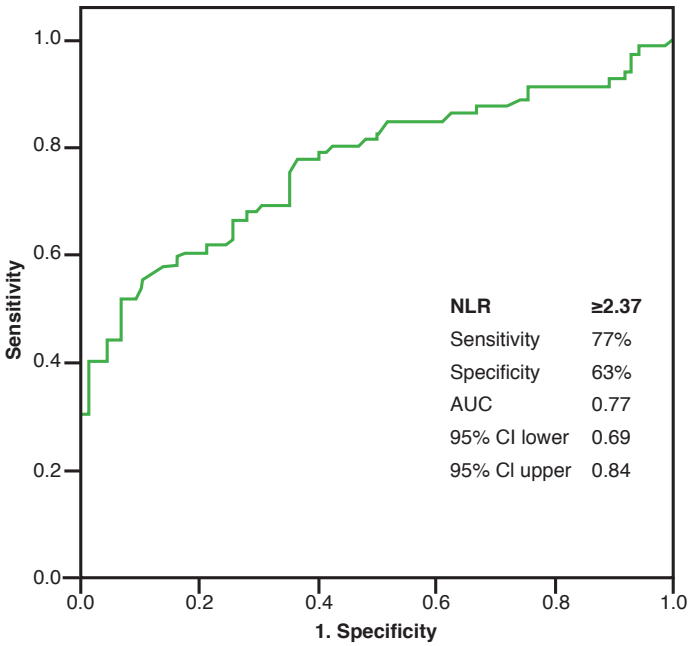

Figure 1. The receiver-operating characteristic curve of neutrophil to lymphocyte ratio for predicting isolated coronary artery ectasia. NLR: Neutrophil to lymphocyte ratio; AUC: Area under curve.

Table 1. Baseline characteristics of angiographicly normaly and ectatic coronary vessels

	Ectasia (n=81)		Normal (n=85)		*p*
	n (%)	Mean±SD	n (%)	Mean±SD	
Age (years)		59.03±11.38		57.51±7.50	0.31
Sex (male)	58 (71.6)		57 (67.1)		0.52
Diabetes mellitus	27 (33.3)		13 (15.3)		**0.007**
Hypertension	39 (48.1)		35 (41.2)		0.36
Hypercholesterolemi	36 (44.4)		22 (25.9)		**0.01**
Current smoker	38 (46.9)		29 (34.1)		**0.09**
Family history	30 (37.0)		26 (30.6)		0.38
BMI (≥30 kg/m^2)	22 (27.2)		11 (12.9)		**0.02**
GFR (<60 ml/mn/1.73 m^2)	8 (9.9)		6 (7.1)		0.51
Aspirin use	24 (29.6)		28 (32.9)		0.64
Beta-blocker use	8 (9.9)		14 (16.5)		0.21
ACE inhibitor use	24 (29.6)		25 (29.4)		0.97
Statin use	17 (21.0)		14 (16.5)		0.45
Diuretic use	11 (13.6)		10 (11.8)		0.72
Nitrates	8 (9.9)		12 (14.1)		0.40
Ejection fraction		59.17±5.36		59.84±8.68	0.42
Hemoglobin (g/dl)		14.35±1.41		14.29±1.31	0.76
White blood cell (10^3/uL)		8.50±2.53		7.81±1.67	0.15
Platelet (mm^3)		233.43±49.00		230.45±36.73	0.66
Neutrophil (mm^3)		6.12±2.13		4.44±1.14	**<0.001**
Lymphocyte (mm^3)		1.74±0.38		2.02±0.49	**<0.001**
Monocyte (mm^3)		0.54±0.17		0.54±0.13	0.60
NLR		3.39±1.36		2.25±0.58	**<0.001**
Distribution of ectasia					
LAD	47 (57.3)				
LCx	38 (46.3)				
RCA	52 (63.4)				
Number of ectasic vessels					
One vessel	35 (43.2)				
Two vessels	35 (43.2)				
Three vessels	11 (13.6)				

Results are expressed as mean±SD and percentage. To compare parametric continuous variables (age, hemoglobine and platelet), the Student's t-test was used; to compare nonparametric continuous variables (Ejection fraction, WBC, Neutrophil, Lymphocyte, Monocyte and NLR) the Mann-Whitney U-test was used. ACE: Angiotensin converting enzyme; BMI: Body mass index; GFR: Glomerular filtration rate; LAD: Left anterior descending artery; LCx: Left circumflex artery; NLR: Neutrophil to lymphocyte ratio; RCA: Right coronary artery.

anterior descending artery (57.3%), and left circumflex artery (46.3%). Isolated CAE most frequently affects one vessel (43.2%) or two vessels (43.2%) and less frequently three vessels (13.6%).

In a ROC curve analysis, a NLR value of 2.37 was identified as an effective cutpoint in the segregation of the presence or absence of isolated CAE (Area Under curve [AUC]: 0.77, CI 95%, 0.69-0.84). A NLR value ≥2.37 yielded a sensitivity of 77%, specificity of 63%, positive predictive value of 67.0% and a negative predictive value of 75.0% (Fig. 1). When we divided the study population into two groups according to the NLR

Table 2. Baseline characteristics of patients with normal and increased NLR

	NLR <2.37 (n=72)		NLR ≥2.37 (n=94)		*p*
	n (%)	Mean±SD	n (%)	Mean±SD	
Age (years)		57.47±8.11		58.86±10.60	0.35
Sex (male)	48 (66.7)		67 (71.3)		0.52
Diabetes mellitus	8 (11.1)		32 (34.0)		**<0.001**
Hypertension	25 (34.7)		49 (52.1)		**0.02**
Hypercholesterolemi	24 (33.3)		34 (36.2)		0.70
Current smoker	25 (34.7)		42 (44.7)		0.19
Family history	24 (33.3)		32 (34.0)		0.92
BMI (≥30 kg/m^2)	15 (20.8)		18 (19.1)		0.78
GFR (<60 ml/mn/1.73 m^2)	4 (5.6)		10 (10.6)		0.24
Aspirin use	22 (30.6)		30 (31.9)		0.85
Beta-blocker use	11 (15.3)		11 (11.7)		0.50
ACE inhibitor use	25 (34.7)		24 (25.5)		0.19
Statin use	12 (16.7)		19 (20.2)		0.56
Diuretic use	6 (8.3)		15 (16.0)		0.14
Nitrates	12 (16.7)		8 (8.5)		0.11
Ejection fraction		59.38±8.82		59.61±5.79	0.67
Hemoglobine (g/dl)		14.31±1.38		14.32±1.34	0.96
WBC (10^3/uL)		7.20±1.68		8.87±2.21	**<0.001**
Platelet (mm^3)		228.20±41.95		234.74±43.88	0.33
Monocyte (mm^3)		0.52±0.14		0.56±0.16	**0.09**
Isolated CAE	18 (25.0)		63 (67.0)		**<0.001**

Results are expressed as mean±SD and percentage. To compare parametric continuous variables (Age, Hemoglobine and Platelet), the Student's t test was used; to compare nonparametric continuous variables (Ejection fraction, WBC and Monocyte) the Mann-Whitney U-test was used. ACE: Angiotensin converting enzyme; BMI: Body mass index; CEA: Coronary artery ectasia; GFR: Glomerular filtration rate; NLR: Neutrophil to lymphocyte ratio, WBC: white blood cell.

level cut-off value or 2.37 used in the ROC analysis, diabetes, hypertension and the presence of isolated CAE were significantly in increased the NLR group (p<0.001, p=0.02, p<0.001, respectively, Table 2).

Variables found to be statistically significant in univariate analyses were included in multivariate logistic regression analysis. Hypercholesterolemia (OR=2.63, 95% CI 1.22-5.65, p=0.01), obesity (OR=3.76, 95% CI 1.43-9.87, p=0.007), and increased NLR (OR=6.03, 95% CI 2.61-13.94, p<0.001) were independently associated with the presence of isolated CAE (Table 3).

DISCUSSION

This is the first study that has been conducted evaluating the relationship between NLR and the presence of isolated CAE. A greater baseline NLR value was independently associated with the presence of isolated CAE.

In previous publications, CAE exists in 1.5-5% of patients included in coronary angiographic studies.[12] In this study, we reported an incidence of isolated CAE of 4.3% among patients who underwent coronary angiography for the presence of chest pain or had objective signs of ischemia. CAE can cause angina pectoris and even MI with vasospasm, dissection or thrombus in patients without CAD.[5] In several studies, patients with CAE have been shown to have increased risk of mortality equivalent to patients with CAD.[13]

Despite advances in cardiology, the pathogenesis of CAE remains unclear. The determination of factors associated with the presence of CAE may have

Table 3. Independent predictors of angiographic ectasia in multivariate logistic regression analysis

	Univariate OR (95% CI)	*p*	Mulivariate OR (95% CI)	*p*
Diabetes mellitus	2.76 (1.30-5.86)	**0.008**	1.85 (0.77-4.44)	0.16
Hypercholesterolemia	2.29 (1.19-4.40)	**0.01**	2.63 (1.22-5.65)	**0.01**
Current smoker	1.70 (0.91-3.19)	0.09	1.66 (0.80-3.45)	0.17
Body mass index (≥30 kg/m²)	2.50 (1.12-5.58)	0.02	3.76 (1.43-9.87)	**0.007**
Neutrophil to lymphocyte ratio (≥2.37)	6.09 (3.07-12.09)	**<0.001**	6.03 (2.61-13.94)	**<0.001**
Beta-blocker	0.55 (0.22-1.40)	0.21	0.43 (0.13-1.40)	0.16
White blood cell	1.16 (1.00-1.35)	**0.04**	1.03 (0.86-1.25)	0.69

a salutary influence on the management of these patients. Although CAE can be congenital, some factors associated with the presence of CAE include inflammatory markers such as C-reactive protein, IL-6, tumor necrosis factor-alpha, matrix metalloprotease (MMP),[7,8] and atherosclerotic risk factors, including advanced age, DM and smoking.[9] In addition, Li et al. demonstrated that patients with isolated CAE had increased leukocyte, neutrophil and monocyte counts when compared to patients with normal coronary arteries.[10] Similarly, in our study, neutrophil, NLR and cardiovascular risk factors, such as diabetes, hypercholesterolemia and obesity were found to be significantly increased in patients with isolated CAE. In this study, we determined a cut-off point NLR ≥2.37 for predicting isolated CAE, and a much lower cut-off point in comparison to many acute vascular conditions.[3] This may be related to chronic, mild inflammation occurring in CAE.

Antoniadis et al.[6] reported that infiltration of the media layer by inflammatory cells can be seen in ectatic segments. Neutrophils cause damage to the tissue and may play an important role in pathogenesis of CAE by secreting elastase, MMP and oxygen free radicals.[14,15] Akyel et al.[16] reported that the protein neutrophil gelatinase-associated lipocalin (NGAL) is increased in patients with isolated CAE. NGAL is secreted from activated neutrophils. NGAL prevents degradation of MMP-9 by the formation of an inhibitory complex. Therefore, MMP-9 expression increases in the presence of NGAL, and this leads to increased degradation of gelation and collagen. As a result of this destructive chronic inflammatory state, artery walls are weakened potentially resulting in ecsasia.

At the same time, in this study we observed that the lymphocyte level was decreased among the CAE group. The probable causes of lymphopenia include decreased production of lymphocyte as a result of increased steroid level due to CAE induced stressed condition,[17] and increased apoptosis of lymphocyte triggered by increased inflammation.[18] Lymphocytes may have a pivotal role in modulating the inflammatory response in this slow chronic inflammatory state, similar to atherosclerosis.[19,20] In addition, several previous studies have reported decreased lymphocytes in acute cardiovascular events, and there is a negative correlation between cardiovascular prognosis and the lymphocyte level.[3,21-23]

In this study, in addition to increased NLR in isolated CAE, there is an independent association of both obesity and hyperlipidemia with CAE. Sudhir et al.[24] demonstrated that CAE is more prevalent in patients with hypercholesterolemia. They have suggested that lipoproteins may be directly involved in this process, perhaps reducing the tensile strength of the artery wall. Waly et al.[25] reported an associated between CAE and obesity. Previous studies have indicated a positive and significant association between serum elastase activity and BMI. Increased elastase activities may contribute to CAE.[26]

This study has several limitations. First, cytokines related to inflammation were not investigated as a result of the retrospective design. Second, we did not perform an analysis of the prognostic value of NLR in CAE. The pathogenesis of CAE and CAD is similar and many studies of stable CAD have demonstrated the prognostic value of NLR.[27] Based on this point, we hypothesized that there may be a prognostic value of NLR in CAE patients. Prospective randomized controlled studies would aid in understanding this phenomena. Third, as the definition of normal coro-

nary arteries is based on angiographic views, atherosclerotic plaques could not be excluded. However in clinical practice, patients with normal coronary anatomy do not undergo intravascular ultrasound routinely and the diagnosis of normal coronary artery is usually by visual assessment at the coronary angiography procedure. Forth, although the formation of CAE is a slow, chronic condition, we only evaluated a single serum NLR in this study.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Coronary angiography; coronary vessel anomalies/complications; coronary vessels/pathology; neutrophils; lymphocytes; dilatation, pathologic.

Anahtar sözcükler: Koroner anjiyografi; koroner damar anomalisi/komplikasyon; koroner damarlar/patoloji; nötrofil; lemfosit; dilatasyon, patolojik.