Neutrophil to lymphocyte ratio is associated with more extensive, severe and complex coronary artery disease and impaired myocardial perfusion

Nötrofil lenfosit oranı daha yaygın, ciddi, kompleks koroner arter hastalığı ve miyokart perfüzyonunda bozulma ile ilişkilidir

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ABSTRACT

Objectives: We investigated the relation between neutrophil to lymphocyte ratio (N/L) and the extent, severity, and complexity of coronary artery disease (CAD) and myocardial perfusion.

Study design: One hundred and fifty-one patients who underwent coronary angiography with stable angina pectoris (SAP) (n=93) or acute coronary syndrome (ACS) (n=58) were included in the study. Blood samples were drawn before coronary angiography. Gensini and SYNTAX scores and myocardial blush grade (MBG) were assessed.

Results: Neutrophil counts were 4.4±1.4 and 5.0±1.6 in the SAP and ACS groups (p=0.018), whereas lymphocyte counts were 2.2±0.7 and 2.1±0.7, respectively (p=0.104). N/L was 2.2±1.2 in the SAP and 2.6±1.0 in the ACS (p=0.002) groups. In patients with SAP, N/L was significantly correlated with Gensini and SYNTAX scores (Gensini score r=0.32, p=0.002; SYNTAX score r=0.36, p=0.000), but there was no significant correlation between N/L and MBG. In the ACS group, N/L had a more powerful association with both Gensini and SYNTAX scores (Gensini r=0.42, p=0.001; SYNTAX r=0.51, p=0.000). N/L was negatively correlated with MBG in ACS patients (r= -0.48, p=0.000). Significant correlations persisted both in the SAP and ACS groups after correcting for age, diabetes, hyperlipidemia, and statin use; however, the associations were weaker. Cut-off N/L to predict moderate to severe CAD according to SYNTAX score was 2.26, with 72% sensitivity and 71% specificity (area under the curve [AUC]: 0.772, 95% confidence interval [CI] 0.679-0.865, p<0.001).

Conclusion: N/L is associated with severe, extensive and complex CAD and may be used to predict moderate to severe involvement in patients with CAD.

ÖZET

Amaç: Nötrofil/lenfosit oranının (N/L) koroner arter hastalığının (KAH) anjiyografik olarak belirlenen yaygınlık, ciddiyet, kompleksliği ve miyokart perfüzyonu ile ilişkisi araştırıldı.

Çalışma planı: Çalışmaya kararlı anjina pektoris (KAP) (n=93) veya akut koroner sendrom (AKS) (n=58) ile başvuran ve koroner anjiyografi yapılmasına karar verilen 151 ardışık hasta alındı. Koroner anjiyografi öncesinde tam kan sayımı için kan alındı. Gensini ve SYNTAX skorları ve miyokart perfüzyonunu değerlendirmek için miyokardın boyanma derecesi (MBG) kullanıldı.

Bulgular: Nötrofil sayıları KAP ve AKS grubunda sırasıyla 4.4±1.4 ve 5.0±1.6 olarak saptanırken (p=0.018); lenfosit sayıları sırasıyla 2.2±0.7 ve 2.1±0.7 idi (p=0.104). N/L KAP ve AKS gruplarında sırasıyla 2.2±1.2 ve 2.6±1.0 olarak saptandı (p=0.002). KAP grubunda N/L Gensini ve SYNTAX skorlarıyla anlamlı olarak ilişkili saptandı, ancak N/L ile MBG arasında anlamlı ilişki gösterilemedi (Gensini skoru r=0.32, p=0.002; SYNTAX skoru r=0.36, p=0.000). AKS grubunda N/L, Gensini skoru ve SYNTAX skoru ile daha kuvvetli korelasyon göstermekteydi (Gensini skoru r=0.42, p=0.001; SYNTAX skoru r=0.51, p=0.000). Bu grupta N/L ile MBG arasında ters yönlü bir korelasyon mevcuttu (r=-0.48 p=0.000). Yaş, diyabet, hiperlipidemi ve statin kullanımına göre düzeltme yapıldıktan sonra hem KAP hem de AKS grubunda anlamlı ilişkiler daha zayıf olmakla birlikte sebat etmekteydi. SYNTAX skoruna göre orta-ciddi KAH'ın öngörülmesinde kesim N/L %72 duyarlılık ve %71 özgüllük ile 2.26 olarak saptandı (eğri altında kalan alan 0.772, %95 GA 0.679-0.865, p<0.001).

Sonuç: Nötrofil/lenfosit oranı, ciddi ve yaygın KAH ile ilişkilidir ve orta-ciddi KAH öngörülmesinde kullanılabilir.

Received: July 28, 2013 *Accepted:* October 04, 2013

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Atherosclerosis is a complex and multifactorial disease in which inflammation plays an important role from the initial stages to the final plaque rupture stage. Leukocyte and differential leukocyte count have been addressed in several studies, and the neutrophil to lymphocyte ratio (N/L) was found to be a predictor of morbidity and mortality in patients with acute myocardial infarction and stable angina pectoris (SAP).[1,2] Increased neutrophil count was shown to be related to the presence and severity of coronary atherosclerosis.[3] Neutrophils are associated with increased blood viscosity and hypercoagulability;[4] they induce microvascular injury interacting with platelets and endothelium,[5] and take part in reperfusion injury.[6]

We aimed to investigate the association of N/L with more extensive and severe coronary artery disease, using angiographic scoring systems: Gensini score and SYNTAX score. We searched whether it might be used to identify patients with more severe coronary involvement prior to coronary angiography.

PATIENTS AND METHODS

We consecutively enrolled 151 patients meeting the inclusion and exclusion criteria who were scheduled to undergo coronary angiography with the clinical diagnosis of coronary artery disease. Patients were analyzed in two groups, as stable angina pectoris (SAP) and acute coronary syndrome (ACS). The SAP group (n=93) consisted of patients admitted to the cardiology outpatient clinic with AP and/or angina-equivalent symptoms suggestive of coronary artery disease and who had positive stress test results or other indications for coronary angiography. The ACS group (n=58) included patients who had unstable pattern of chest pain suggesting unstable AP (USAP) with or without ischemic electrocardiographic findings, and patients with acute myocardial infarction. Acute myocardial infarction patients either had non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI). Diagnosis of NSTEMI was established when characteristic chest pain lasted longer than 20 minutes (min) with/without associated ST segment depression of ≥0.1 mV and/or T wave inversion in two contiguous leads in the electrocardiogram (ECG) and presence of increased levels of troponin T. STEMI was diagnosed in the presence of chest pain lasting more than 20 min associated with ST segment elevation of ≥1 mm in at least two contiguous extremity ECG leads or ≥2 mm in at least two contiguous precordial V1, V2, V3 leads and 1 mm in the remaining precordial leads.

Abbreviations:

ACS	*Acute coronary syndrome*
AUC	*Area under the curve*
ECG	*Electrocardiogram*
MBG	*Myocardial blush grade*
N/L	*Neutrophil to lymphocyte*
NSTEMI	*Non-ST elevation myocardial infarction*
SAP	*Stable angina pectoris*
STEMI	*ST elevation myocardial infarction*
USAP	*Unstable angina pectoris*

This study was conducted according to the recommendations of the Declaration of Helsinki on biomedical research involving human subjects and was approved by the institutional ethics committee. Written informed consent was obtained from each participant.

Exclusion criteria consisted of hematologic disorders, active infectious or inflammatory diseases, rheumatological diseases, severe renal or liver disease, malignancy, and prior coronary revascularization (percutaneous or surgical) because Gensini and SYNTAX scores have been validated in native coronary artery disease.

Anthropometric parameters, medical history, presence of hypertension, diabetes and hyperlipidemia, smoking habits, family history of coronary artery disease, and medications were recorded for each patient. Blood samples were drawn from the antecubital vein at admission for complete blood count and biochemistry analysis. Total white blood cell (WBC) count and differential leukocyte count were determined using an automated blood cell counter.

Selective left and right coronary angiography was performed through the femoral artery by standard Judkins technique with 6 Fr catheters (MediCath, Barcelona, Spain) using GE Innova 4100 (GE Healthcare, Milwaukee, WI, USA). Gensini score, which considers both the extent and severity of the atherosclerotic lesions on coronary angiography, was calculated for each patient.[7] This scoring system grades the stenosis in the epicardial coronary arteries (1 for 1-25% stenosis, 2 for 26-50% stenosis, 4 for 51-75% stenosis, 8 for 76-90% stenosis, 16 for 91-99% stenosis, and 32 for total occlusion), and multiplies this number by a constant number determined according to the anatomical position of the lesion. The SYNTAX score, which is an anatomic scoring system developed to rank the

complexity of coronary artery disease, was calculated. Each lesion with >50% diameter stenosis in vessels >1.5 mm in diameter was scored using the online calculator version 2.1 at www.syntaxscore.com. A low SYNTAX score was defined as ≤22, intermediate as 23-32, and high as ≥33.[8] Patients with a SYNTAX score ≥23 were considered to have moderate to severe coronary artery disease according to this definition.

Myocardial perfusion was assessed by myocardial blush grade (MBG) using the best projection for each coronary artery. Duration of cine filming was required to exceed three cardiac cycles in the washout phase to assess the washout of myocardial blush. Grade 0 was defined as the failure of the contrast to enter the microvasculature. In Grade 1, contrast slowly enters but fails to exit the microvasculature. Grade 2 defines delayed entry and exit from the microvasculature, and Grade 3 indicates normal entry and exit from the microvasculature.[9]

Statistical Analyses

Continuous variables were given as mean±standard deviation; categorical variables were defined as percentages. Continuous variables were compared by

Table 1. Baseline characteristics of the study population

	SAP (n=93)		ACS (n=58)		*p*
	%	Mean±SD	%	Mean±SD	
Age		59.5±12.5		61.2±14.9	0.375
Sex (Female)	50		41		0.316
Body mass index (kg/m^2)		27.7±3.5		26.9±1.92	0.169
Waist circumference (cm)		90.6±9.6		88.5±8.4	0.480
Hypertension	53.8		62.1		0.398
Diabetes mellitus	29		39.7		0.214
Smoker	49.5		56.9		0.406
Familial hyperlipidemia	32.3		25.9		0.467
Hyperlipidemia	51.6		58.6		0.502
Antidiabetic medication use	28		31		0.715
Antihypertensive medication use	60.2		67.2		0.489
Statin	31.2		32.8		0.859
Hemoglobin (g/dL)		13.7±1.8		13.4±1.9	0.335
White blood cell count (10^3)		7.427±2.1		7.8±2.4	0.159
Neutrophil (10^3/μL)		4.4±1.4		5±1.6	0.021
Lymphocyte (10^3/μL)		2.2±0.7		2.1±0.7	0.257
Neutrophil to lymphocyte ratio		2.2±1.2		2.6±1.1	0.019
Platelet (10^3)		248±79		250±74	0.776
Glucose (mg/dL)		115.2±44.7		119.9±52.3	0.565
Creatinine (mg/dL)		0.8±0.3		0.9±0.5	0.016
Uric acid (mg/dL)		5.1±1.4		5.9±1.5	0.000
Low density lipoprotein (mg/dL)		123.1±32.1		127.4±39.4	0.856
High density lipoprotein (mg/dL)		47.1±16.7		40.5±11.1	0.021
Triglyceride (mg/dL)		143.9±78.2		172.1±138.4	0.195
Gensini		13.0±26.9		40.3±43.0	0.000
SYNTAX		8.5±12.1		20.6±14.8	0.000
Myocardial blush grade		2.9±0.5		2.1±1.1	0.000

SAP: Stable angina pectoris; ACS: Acute coronary syndrome; SD: Standard deviation; p<0.05 is considered significant.

Student t test, and the χ^2 test was used for the categorical variables between two groups. The Pearson's correlation coefficient was used for the analysis of the correlation between N/L and Gensini and SYNTAX scores. An optimal cut-off value to predict moderate to severe coronary artery disease by N/L was determined by receiver operating characteristics (ROC) analysis, and area under the curve (AUC) values were determined. All tests of significance were two-tailed. Statistical significance was defined as $p<0.05$. The Statistical Package for the Social Sciences software (SPSS 15.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

Table 1 demonstrates the baseline characteristics of the study population. There were 93 patients in the SAP group and 58 patients in the ACS group. The ACS group consisted of 31 USAP patients, 18 NSTEMI patients and 9 STEMI patients. Neutrophil counts were 4.4±1.4 and 5.0±1.6 in the SAP and ACS groups, respectively (p=0.018), whereas lymphocyte counts were 2.2±0.7 and 2.1±0.7, respectively (p=0.104). N/L was 2.2±1.2 in the SAP group and 2.6±1.0 in the ACS group (p=0.002). Mean Gensini and SYNTAX scores and mean MBG are also provided in Table 1.

As the inflammatory process is naturally more active in ACS, we searched whether N/L is correlated with Gensini and SYNTAX scores and MBG in the SAP and ACS groups separately. In patients with SAP, N/L was significantly correlated with Gensini and SYNTAX scores (for Gensini score r=0.32, p=0.002; for SYNTAX score r=0.36, p=0.000), but there was no significant correlation between N/L and MBG. In the ACS group, N/L had a more powerful association with both Gensini and SYNTAX scores (for Gensini score r=0.42, p=0.001; for SYNTAX score r=0.51, p=0.000). In contrast to the SAP group, N/L was significantly negatively correlated with MBG in ACS patients (r=-0.48, p=0.000).

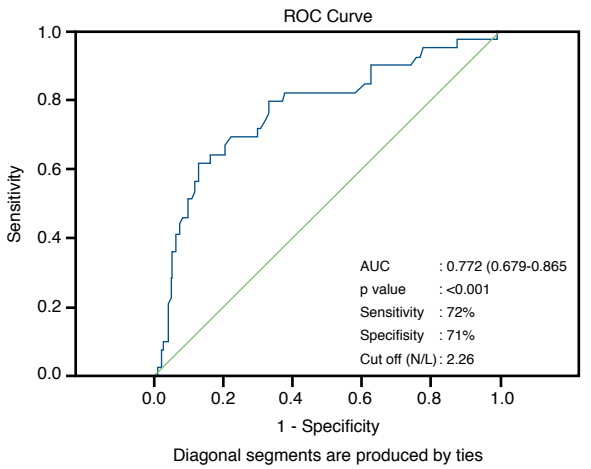

Figure 1. ROC curve demonstrating the cut-off value of N/L to predict moderate to severe coronary artery disease.

We repeated the correlation analysis correcting for age, diabetes, hyperlipidemia, and statin use in case these could have confounded the results. Significant correlations persisted in both the SAP and ACS groups; however, the associations were weaker (Table 2).

The cut-off value of N/L to predict moderate to severe coronary artery disease according to the SYNTAX score in the entire population was 2.26, with 72% sensitivity and 71% specificity (AUC: 0.772, 95% CI: 0.679-0.865, p<0.001) (Figure 1).

DISCUSSION

In the present study, we have shown that N/L is associated with severe, extensive and complex coronary ar-

Table 2. Correlation coefficients for the relation between N/L and Gensini score, SYNTAX score, and myocardial blush grade, after correction for age, diabetes, hyperlipidemia and statin use

	Gensini score	SYNTAX score	MBG
Stable angina pectoris (n=93)			
N/L	0.23 (p=0.033)	0.30 (p=0.004)	NS
Acute coronary syndrome (n=58)			
N/L	0.33 (p=0.014)	0.42 (p=0.002)	-0.45 (p=0.001)

N/L: Neutrophil to lymphocyte ratio; MBG: Myocardial blush grade. p<0.05 is considered as significant.

tery disease both in SAP and ACS. In addition, it may be used to predict the presence of moderate to severe involvement prior to coronary angiography in patients with the clinical diagnosis of coronary artery disease, with a quite satisfactory sensitivity and specificity.

The N/L has attracted attention as an easily available inflammatory marker in addition to other inflammatory markers that can be detected by a simple blood draw, like high-sensitive C-reactive protein (hs-CRP) and uric acid.[10,11] Mechanistically, neutrophils are known to induce plaque disruption by releasing proteolytic enzymes and superoxide radicals. They contribute to plugging of microvessels and cause myocardial ischemia.[12,13]

While its predictive role for morbidity and mortality has been well studied in patients with acute myocardial infarction,[14,15] we aimed to clarify its role further to identify patients with more extensive, severe and complex coronary artery disease prior to coronary angiography in both stable and unstable presentations. We found a significant association between N/L and Gensini and SYNTAX scores, even after correction for possible confounders, in patients who present with both SAP and ACS. The associations were more powerful in unstable presentations in which inflammation is definitely more active. In addition, we detected that N/L was associated with worse myocardial perfusion in ACS. Impairment of myocardial perfusion at rest is not a common finding in patients with SAP; thus, it is not surprising that no significant association was found between N/L and MBG in this subset of patients.

Kirtane et al.[16] found that, in patients with STEMI, patients with impaired MBG had a greater percentage of neutrophils. Akpek et al.[17] showed that higher N/L was associated with no reflow in patients who had undergone primary coronary intervention for STEMI.

The Gensini score is a widely accepted scoring system to evaluate the coronary atherosclerotic burden, and the SYNTAX score has gained in popularity in the last decade for assessment of native coronary artery disease taking into account the lesion characteristics. The SYNTAX score is important because it has prognostic implications in terms of death, cardiac death, myocardial infarction, and target vessel revascularization in ACS.[18]

Sahin et al.[19] showed that N/L was one of the independent predictors for SYNTAX score in patients with STEMI. In a very recent study, Kaya et al.[20] found that N/L was associated with the complexity of coronary artery disease as assessed by the SYNTAX score. They proposed a cut-off value to predict high SYNTAX score as 2.7, with a sensitivity of 72% and specificity of 61%. Their cut-off value was slightly higher compared to that determined in the present study, with a similar sensitivity. Nevertheless, the cut-off value proposed by Kaya et al.[20] had a lower specificity, and their study population consisted of only SAP patients. In another study, 172 patients who underwent coronary angiography were divided into two groups according to their Gensini scores, and it was found that extensive coronary artery disease was associated with a higher N/L.[21] They provided a cut-off value of 2.5 to predict severe atherosclerosis, with a sensitivity of 62% and specificity of 69%. This cut-off value was closer to that determined in our study, but again with a relatively lower sensitivity and specificity.

In conclusion, the present study is supportive of the very recent similar studies reporting that N/L can be used as an easily available inflammatory marker to predict severe, extensive and complex coronary artery disease. It is also associated with impaired myocardial perfusion in ACS, and may be useful for earlier risk stratification and for intensifying the atherosclerosis treatment in higher risk patients.

Acknowledgements

We thank Ms. Belgin Mekereci for her help in data collection.

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

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Key words: Coronary angiography; coronary artery disease; leukocyte count; leukocytosis/blood; myocardial infarction/therapy; neutrophils.

Anahtar sözcükler: Koroner anjiyografi; koroner arter hastalığı; lökosit sayısı; lökositoz/kan; miyokart enfarktüsü/tedavi; nötrofil.