ORIGINAL ARTICLE

Neutrophil-to-lymphocyte ratio predicts functionally significant coronary artery stenosis in patients with stable coronary artery disease

Nötrofil-lenfosit oranı kararlı koroner arter hastalığı bulunan hastalarda koroner arter darlığının fonksiyonel ciddiyetini öngörür

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ABSTRACT

Objective: The aim of this study was to determine the relationship between the neutrophil-to-lymphocyte ratio (NLR) and the functional severity of coronary stenosis assessed according to the fractional flow reserve (FFR) in stable coronary artery disease (CAD).

Methods: The clinical and laboratory data of 420 patients who underwent index coronary angiography for stable angina pectoris were analyzed retrospectively. The functional severity of an intermediate lesion was determined by FFR. An FFR value of >0.80 was considered non-significant (Group 1), whereas ≤0.80 was accepted as significant stenosis (Group 2).

Results: A total of 137 (32.6%) patients had functionally significant coronary artery stenosis. The median NLR value was significantly greater in Group 2 compared with Group 1 [3.13 (0.93–9.75) vs 2.22 (0.75–6.02); p<0.001]. In multivariable logistic regression analysis, the Gensini score [odds ratio (OR): 1.04; 95% confidence interval (CI): 1.02–1.06; p<0.001], diabetes mellitus (OR: 2.56; 95% CI: 1.38–4.75; p=0.003), smoking (OR: 2.09; 95% CI: 1.12–3.94; p=0.021), and NLR (OR: 1.62; 95% CI:1.26–2.09; p<0.001) were found to be independent predictors of the presence of functionally significant coronary stenosis using an FFR value of ≤0.80. The optimal cut-off value of NLR for predicting functionally significant coronary stenosis was 2.3. An NLR value greater than 2.3 had a sensitivity of 72% and a specificity of 61% to predict stenosis with an FFR value of ≤0.80.

Conclusion: The pre-angiographic NLR is a simple, noninvasive, and inexpensive biomarker that was significantly higher in patients with functionally significant coronary stenosis; it can be used to predict the hemodynamic severity of intermediate coronary stenosis in patients with stable CAD.

ÖZET

Amaç: Bu çalışmada, kararlı koroner arter hastalığı (KAH) bulunanlarda fraksiyonel akım rezervi (FAR) ile değerlendirilen koroner darlığının fonksiyonel ciddiyeti ile nötrofil-lenfosit oranı (NLO) arasındaki ilişkinin saptanması amaçlandı.

Yöntemler: Kararlı anjina pektoris nedeniyle ilk kez koroner anjiyografi yapılan 420 hastanın işlem öncesi klinik ve laboratuvar bilgileri ile anjiyografi verileri geriye dönük olarak incelendi. Orta dereceli lezyonların fonksiyonel ciddiyetinin değerlendirilmesi FAR ile yapıldı. FAR değerinin >0.80 olması ciddi olmayan darlık (Grup 1), ≤0.80 olması ise ciddi darlık (Grup 2) olarak tanımlandı.

Bulgular: Toplam 137 (%32.6) hastada FAR ile fonksiyonel ciddi darlık saptandı. Grup 2 hastalarında Grup 1'e göre ortanca NLO değeri anlamlı olarak daha yüksekti [3.13 (0.93–9.75) ve 2.22 (0.75–6.02), p<0.001]. Çok değişkenli lojistik regresyon analizinde, Gensini skoru [odds oranı (OO): 1.04; %95 güvenlik aralığı (GA): 1.02–1.06; p<0.001], diabetes mellitus (OO: 2.56; %95 GA: 1.38–4.75; p=0,003), sigara kullanımı (OO: 2.09; %95 GA: 1.12–3.94; p=0.021) ve NLO (OO: 1.62; %95 GA: 1.26–2.09; p<0.001) fonksiyonel olarak ciddi koroner darlığı varlığının bağımsız öngördürücüleri idi. Fonksiyonel olarak ciddi koroner darlığını öngörmede NLO optimal kestirim değeri >2.3 olarak bulundu. NLO >2.3 olması halinde FAR ≤0.80 varlığını %72 duyarlılık ve %61 özgüllükle öngörmekteydi.

Sonuç: Anjiyografi öncesi hesaplanan basit, girişimsel olmayan ve ucuz bir biyobelirteç olan NLO fonksiyonel olarak ciddi koroner darlığı olan hastalarda daha yüksektir ve kararlı KAH'lı hastalarda orta dereceli darlığın hemodinamik ciddiyetini öngörmede kullanışlı olabilir.

Received: January 14, 2017 *Accepted:* October 18, 2017

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Inflammation, the atherosclerotic process, and the occurrence of coronary artery disease (CAD) are tightly linked via various complex pathophysiological pathways. Therefore, several pro-inflammatory indicators have been determined to be significant predictors of adverse cardiovascular outcomes.[1–3] The neutrophil-to-lymphocyte ratio (NLR) has recently been shown to be a potential biomarker in the prediction of CAD anatomical severity,[4] mortality, and adverse cardiovascular events in various cardiac pathologies.[5–8]

Fractional flow reserve (FFR) is a lesion-specific index reflecting the functional severity of coronary stenosis. Currently, FFR is considered the gold standard method for the functional assessment of coronary stenosis and an indispensable tool in making a decision about coronary revascularization.[9] Although an argument exists regarding the cut-off value for FFR significance, current guidelines recommend 0.80 as a cut-off point.[10] Below this value, coronary stenosis should be accepted as a functionally significant lesion and revascularization should be performed. Due to the close association between NLR and CAD severity and the good predictive value of FFR for the hemodynamic significance of a coronary artery lesion, it was hypothesized that NLR might predict functionally significant coronary artery stenosis. The objective of this study was to assess the relationship between NLR and coronary stenosis severity assessed by FFR in patients with stable CAD.

METHODS

Study population

The clinical, laboratory, and procedural data of 473 patients who underwent initial index coronary angiography and an FFR evaluation of a specific lesion suspected for ischemia between January 2009 and January 2013 at a tertiary referral center were collected. Index coronary angiography was performed because of an abnormal (n=184) or inconclusive (n=72) treadmill exercise test, stenosis observed on coronary computerized tomographic angiography (n=105), ischemia detected with myocardial perfusion scintigraphy (n=32), and without further non-invasive tests (n=80). Patients with a second lesion in the index coronary artery or another coronary artery with a severity of ≥40% luminal narrowing seen on coronary angiography, acute coronary syndrome (ACS), history of previous coronary artery intervention (percutaneous or surgical), severe valvular heart disease, acute/chronic infectious or inflammatory disease, malignancy, hematological or autoimmune disease, renal or hepatic failure, or use of medications that have an impact on NLR, such as corticosteroids, were excluded from the present study. The remaining 420 patients (age: 62±9.5 years; 72.1% male) with stable angina pectoris and 1 intermediate coronary lesion (stenosis of 40–70%) were enrolled.[11] The research was conducted in compliance with the principles outlined in the Declaration of Helsinki and approved by the institutional ethics committee.

Abbreviations:

ACS	*Acute coronary syndrome*
CAD	*Coronary artery disease*
CI	*Confidence interval*
CX	*Circumflex artery*
FFR	*Fractional flow reserve*
LAD	*Left anterior descending artery*
LMCA	*Left main coronary artery*
NLR	*Neutrophil-to-lymphocyte ratio*
OR	*Odds ratio*
RCA	*Right coronary artery*
ROC	*Receiver operating characteristics*

Laboratory data

Blood sampling was performed from the antecubital vein with an atraumatic puncture before coronary angiography and the samples were immediately sent to the laboratory for analysis. Tubes containing ethylenediamine-tetraacetic acid were used for the hemogram assessment. A complete blood count test, including differentials, was evaluated using an automated blood cell counter (Coulter LH 780 Hematology Analyzer; Beckman Coulter, Inc., Brea, CA, USA). A biochemistry panel was measured using an autoanalyzer (Architect c16000; Abbott Diagnostics, Inc., Abbott Park, IL, USA).

Coronary angiography and fractional flow reserve

Initially, a diagnostic coronary angiogram was performed on all of the participants. The anatomical severity of coronary stenosis was assessed quantitatively offline. The Gensini score was calculated to evaluate the extent and severity of CAD.[12] The decision to measure FFR was made by a council that included cardiologists and cardiovascular surgeons.

As in any intracoronary manipulation, proper anticoagulation with unfractionated heparin (100 IU/kg) and intracoronary nitrates (200 μg) was administered prior to entering the coronary circulation. A pressure monitoring guidewire (PressureWire; St Jude Medical Inc., St. Paul, MN, USA) was calibrated and introduced into the guiding catheter. The wire was ad-

vanced up to the tip of the guiding catheter, and it was verified that the pressure measured by the guidewire was equal to the pressure measured by the guiding catheter. Then, the wire was advanced into the coronary artery until the pressure sensor was located distal to the stenosis. Adenosine (Adozin, Vem İlaç San. Tic. Ltd. Şti, Istanbul, Turkey) was administered to induce maximum hyperemia, either intravenously (140 µg/kg/minute via a femoral route), in the majority of patients, or with an intracoronary application (50 or 150 µg into the right coronary or left coronary artery, respectively). FFR was calculated as the ratio of the mean hyperemic distal coronary pressure measured with the guidewire to the mean aortic pressure measured with the guiding catheter. Lesions with an FFR value of >0.80 were accepted as non-significant stenosis (Group 1) and an FFR value of ≤0.80 was defined as significant stenosis (Group 2).

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). Patients were divided into 2 groups using the cut-off FFR value of 0.8. To test the distribution pattern, the Kolmogorov-Smirnov test was used. Continuous variables were presented as median (minimum-maximum) or mean±SD; categorical variables were defined as a percentage (%). Continuous variables were compared between the 2 groups using an independent samples t-test, and categorical variables were compared with a chi-square test, as appropriate. The Mann-Whitney U test was used to analyze the differences in biochemical markers between the patient groups. The effect of each different variable on the FFR result was calculated in univariate analysis. The variables identified as potential risk factors in logistic regression analysis were included in the full model. An exploratory evaluation of additional cut-off points was performed using receiver operating characteristics (ROC) curve analysis using MedCalc 11.4.2 (MedCalc Software, Ostend, Belgium). A p value <0.05 was considered significant and the confidence interval (CI) was set at 95%.

RESULTS

The baseline clinical characteristics and laboratory data are presented in Table 1. Functionally significant

Table 1. Baseline clinical and laboratory characteristics of the study groups (n=420)

	Fractional flow reserve >0.80 (n=283)	Fractional flow reserve ≤0.80 (n=137)	*p*
Age, years	61.56±9.7	62.33±9.4	0.442
Gender (male/female)	199/84	104/33	0.231
Diabetes, n (%)	120 (42.4)	87 (63.5)	<0.001
Hypertension, n (%)	160 (56.5)	94 (68.6)	0.018
Smoking, n (%)	138 (48.7)	85 (62)	0.011
Gensini score	12 (2–200)	32 (5–115)	<0.001
Fasting glucose (mg/dL)	104.5 (63-240)	110.5 (60–285)	0.340
Urea (mg/dL)	35.5 (19–89)	35 (13-92)	0.317
Uric acid (mg/dL)	5.6±1.5	5.8±1.6	0.600
Total cholesterol (mg/dL)	191.5 (89–288)	174 (111–335)	0.208
Low-density lipoprotein cholesterol (mg/dL)	117 (34–287)	97 (30–233)	0.048
High-density lipoprotein cholesterol (mg/dL)	42 (19–88)	40 (20–74)	0.088
Triglyceride (mg/dL)	140 (33–392)	143 (49–448)	0.300
Hemoglobin (g/dL)	14.1±2.9	13.6±1.8	0.043
Platelet count (10^3 cells/mm^3)	254.9±64.1	265.1±74.2	0.150
White blood cell (10^3 cells/mm^3)	7.8±2.0	8.5±2.3	0.002
Neutrophil-to-lymphocyte ratio	2.22 (0.75–6.02)	3.13 (0.93–9.75)	<0.001

Data are presented median (minimum-maximum), mean±standard deviation or n (%).

stenosis using an FFR value of ≤0.80 was observed in 137 (32.6%) patients. FFR measurement was performed at the left main coronary artery (LMCA) in 1.2% (n=5), the left anterior descending artery (LAD) in 96.4% (n=405), the circumflex artery (CX) in 1.2% (n=5), and the right coronary artery (RCA) in 1.2% (n=5). None of the 5 LMCA lesions, 135 of 405 LAD lesions (33.3%), 1 of 5 CX lesions (25%), and 1 of 5 RCA lesions (25%) were regarded as functionally significant stenosis after FFR measurement. The mean lesion stenosis was 55.48±8.5%. The mean FFR value after adenosine administration was 0.82±0.07.

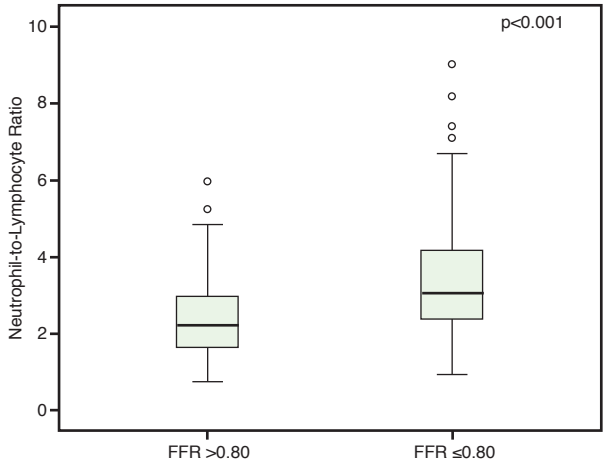

Figure 1. Comparison of neutrophil to lymphocyte ratio between patients with a fractional flow reserve value of >0.80 and ≤0.80.

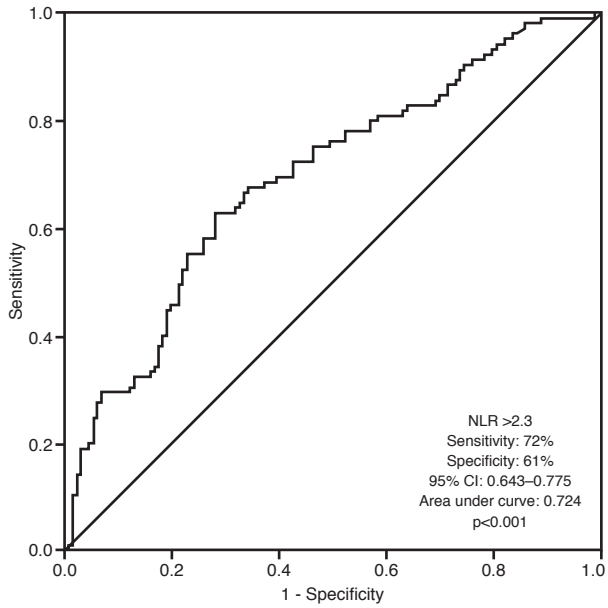

Figure 2. Receiver operating characteristic curve of the pre-angiographic neutrophil-to-lymphocyte ratio value for predicting the presence of functionally significant coronary stenosis.

There were no significant differences between the study groups (Group 1 and 2) in terms of age; gender; levels of fasting blood glucose, urea, uric acid, total cholesterol, high-density lipoprotein cholesterol, and triglyceride; or platelet count. Patients in Group 2 had a significantly higher median Gensini score than the patients in Group 1 [32 (5–115) vs 12 (2–200); p<0.001]. The median NLR was also significantly higher in Group 2 than in Group 1 [3.13 (0.93–9.75) vs 2.22 (0.75–6.02); p<0.001] (Fig. 1). Diabetes, hypertension, and smoking were significantly more prevalent in Group 2 patients, and these patients demonstrated lower hemoglobin levels and higher low-density (LDL) lipoprotein cholesterol levels.

In order to determine the predictors of significant FFR values (≤0.80), the variables found to be significantly different in univariate analysis were included in multivariate logistic regression analysis. Gensini score [odds ratio (OR): 1.04; p<0.001], diabetes mellitus (OR: 2.56; p=0.003), smoking (OR: 2.09; p=0.021), and NLR (OR: 1.62; p<0.001) were found to be independent predictors of functionally significant coronary stenosis using an FFR value of ≤0.80 (Table 2). The optimal cut-off value of NLR for predicting the presence of functionally significant coronary stenosis was 2.3 in ROC curve analysis. Any NLR value greater than 2.3 had a sensitivity of 72%, a specificity of 61%, a positive likelihood ratio of 1.85, and a negative likelihood ratio of 0.46 to predict the significance of an FFR result (Fig. 2). The area under the ROC curve of NLR was 0.724 (95% CI: 0.673–0.775; p<0.001). Patients with a pre-procedural NLR >2.3 had a 2.86-fold increased risk of functionally significant coronary stenosis (Table 2).

DISCUSSION

Our major findings in this study included: (a) The NLR was significantly higher in patients with FFR values of ≤0.80, and (b) NLR was found to be a significant predictor of the functional significance of coronary stenosis assessed by FFR in patients with stable CAD independent of other well-known risk factors like diabetes and smoking.

Table 2. Logistic regression analysis to determine the independent predictors of functionally significant coronary stenosis using fractional flow reserve value of ≤0.80

	Univariate	*p*	Multivariate	*p*
	OR (95% CI)		OR (95% CI)	
Model 1: NLR value as a continuous variable				
Diabetes	2.36 (1.55–3.59)	<0.001	2.56 (1.38–4.75)	0.003
Hypertension	1.68 (1.09–2.58)	0.018	1.18 (0.62–2.26)	0.620
Smoking	1.71 (1.13–2.60)	0.011	2.09 (1.12–3.94)	0.021
Gensini score	1.03 (1.02–1.04)	<0.001	1.04 (1.02–1.06)	<0.001
Low-density lipoprotein cholesterol	0.99 (0.98–1.00)	0.051	0.99 (0.98–1.005)	0.489
Hemoglobin	0.88 (0.78–0.99)	0.037	0.94 (0.82–1.08)	0.384
NLR	1.65 (1.39–1.96)	<0.001	1.62 (1.26–2.09)	<0.001
Model 2: NLR value as a categorical variable				
Diabetes	2.36 (1.55–3.59)	<0.001	2.34 (1.30–4.38)	0.005
Hypertension	1.68 (1.09–2.58)	0.018	1.21 (0.61–1.86)	0.732
Smoking	1.71 (1.13–2.60)	0.011	2.06 (1.12–3.81)	0.021
Gensini score	1.03 (1.02–1.04)	<0.001	1.04 (1.02–1.06)	<0.001
Low-density lipoprotein cholesterol	0.99 (0.98–1.00)	0.051	0.99 (0.98–1.004)	0.319
Hemoglobin	0.88 (0.78–0.99)	0.037	0.90 (0.78–1.05)	0.178
NLR	1.65 (1.39–1.96)	<0.001	2.86 (1.51–5.40)	<0.001

OR: Odds ratio; CI: Confidence interval; FFR: fractional flow reserve; NLR: neutrophil–to–lymphocyte ratio.

NLR has recently been recognized as a useful indicator that stratifies subjects at high risk for future adverse cardiovascular outcomes. NLR also significantly predicted the severity of CAD and cardiovascular outcomes independent of conventional risk factors. The integration of "neutrophil count" as a marker of continuing inflammation and "lymphocyte count" as a marker of regulatory pathways into a single biomarker of NLR has a more stable profile compared with each marker alone.[13,14] It has been hypothesized that endothelial damage was enhanced because of the interaction of neutrophils with endothelial cells. Additionally, such an interaction has been shown to be a contributor to platelet adhesion among patients with ACS in a study conducted by Ott et al.[15] Neutrophils have a role at each stage of the atherosclerotic process and the occurrence of ACS. Contrarily, the lymphocyte count was reduced in patients with ACS, and it was presented as associated with mechanical complications of ACS.[16] As a result of the significance of both neutrophils and lymphocytes in the atherosclerotic process, the integration of both markers into a single predictor of NLR was proposed. An increased NLR was considered a strong prognostic indicator for adverse cardiovascular outcomes in a variety of settings. Studies investigating the NLR in patients with cardiovascular diseases showed that a higher pre-procedural NLR was an independent predictor of adverse outcomes in patients undergoing coronary angiography,[17] percutaneous coronary intervention,[18] and coronary bypass graft surgery.[19]

FFR determines the functional significance of intermediate degree coronary stenosis. Several studies have clearly demonstrated that using FFR in stable CAD improves clinical outcomes and reduces major cardiovascular events.[20–22] FFR values below 0.80 point to CAD severity and significance. Patients with coronary lesions and lower FFR values have more cardiovascular risk factors and are assumed to have increased inflammatory markers. In our study, we found an increased rate of CAD risk factors, such as diabetes, smoking, and high LDL cholesterol levels, in patients with functionally significant coronary stenosis. The higher Gensini score in patients with a lower FFR in our study indicated probable increased coronary inflammation and CAD severity. This has been demonstrated with the correlation between NLR and CAD severity using the Gensini score.[23] However,

rather than the significance of single-lesion stenosis, the Gensini score yields information about the extent of CAD. NLR, which is easy to calculate, may predict the significance of single-lesion coronary stenosis before performing invasive procedures like FFR. In a small study, Akyel et al.[24] found that the pre-procedural NLR had significantly predicted the hemodynamic severity of coronary artery stenosis as measured by FFR. We also found significantly higher NLR values to be an independent inflammatory marker in patients with an FFR value of ≤0.80. In our patients, a pre-procedural NLR >2.3 proved a useful cut-off point for predicting coronary lesion functional significance assessed by FFR with a sensitivity of 72% and a specificity of 61%. These results indicate that the use of NLR with other parameters provides additional information relevant for clinical decision-making in patients with intermediate-degree coronary stenosis.

Our study should be interpreted with some limitations. First, the study is a single-center experience with a relatively small sample size. Second, because of its retrospective design, the study results lack long-term follow-up and outcome measures. Third, we did not include additional pro-inflammatory or pro-oxidant biomarkers to correlate with NLR. As mentioned in the results section, the sensitivity and specificity of the NLR in the prediction of functionally significant coronary stenosis with an FFR value of ≤0.80 were low. However, it was predictable from the pathophysiology of CAD that NLR could not be a single indicator predicting functionally significant coronary stenosis. The use of a combination of several biomarkers should be preferred, rather than a single indicator, to form a conclusion on such an outcome. Therefore, further studies are needed to assess the impact of biomarker-based scoring systems on FFR results.

In conclusion, our study results suggested that pre-angiographic NLR, a simple, noninvasive, and inexpensive biomarker to assess, was significantly higher in patients with functionally significant coronary stenosis and it can be used to predict the hemodynamic severity of intermediate coronary stenosis in patients with stable CAD.

Peer-review: Externally peer-reviewed.

Funding: None

Conflict-of-interest: None declared.

Authorship contributions: Concept – S.Y., U.C., K.B., S.A.; Design – S.Y., U.C., K.B., S.A.; Supervision – U.C., K.B., S.A.; Materials – S.Y., U.C., K.B., S.Ü., M.S.K.; Data collection &/or processing – S.Y., U.C., S.Ü., M.S.K.; Analysis and/or interpretation – S.Y., U.C., K.B., S.Ü., M.S.K., S.A.; Literature search – S.Y., U.C., K.B., S.Ü., M.S.K., S.A.; Writing – S.Y., U.C.; Critical revision – S.Y., U.C., K.B., S.Ü., M.S.K., S.A.

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Keywords: Coronary artery disease; fractional flow reserve; neutrophil-to-lymphocyte ratio.

Anahtar sözcükler: Koroner arter hastalığı; fraksiyonel akım rezervi; nötrofil-lenfosit oranı.