Neutrophil-to-lymphocyte ratio predicts hemodynamic significance of coronary artery stenosis

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Abstract

Objective: Coronary artery disease is closely linked with inflammation, and the neutrophil-to-lymphocyte ratio (NLR) has emerged as a new inflammatory marker. Fractional flow reserve (FFR) is a well-established method for determining hemodynamic significance of coronary artery stenosis. In this study, we aimed to investigate the relationship between NLR and hemodynamic significance of coronary artery lesion as assessed by FFR.

Methods: A total of 134 patients with FFR measurement between January 2012 and December 2013 were enrolled in this retrospective study. Patients with single intermediate-grade coronary artery stenosis were enrolled, and those with second intermediate or severe coronary artery stenosis were excluded from study. Patients' NLR were calculated. An FFR value of ≤0.80 was accepted for hemodynamic significance. Statistical analysis was performed by the chi-square test, Student's t-test, Mann–Whitney U test, logistic regression analysis, and ROC curve analysis.

Results: Patients with hemodynamically significant lesions had higher NLR values (3.3±1.2 vs. 2.0±0.9, p<0.001). White blood cell count, male gender, high-density lipoprotein levels, platelet-to-lymphocyte ratio, and NLR were found to be possible confounding factors predicting hemodynamically significant coronary artery stenosis. In multiple logistic regression analysis, NLR remained as the only independent predictor for hemodynamically significant coronary artery stenosis. An NLR value of 2.4 had 87.5% sensitivity and 78.4% specificity for prediction of hemodynamically significant coronary artery stenosis.

Conclusion: In present study, we showed that NLR was significantly higher in patients with hemodynamically significant coronary artery stenosis. We also found NLR to be an independent predictor of hemodynamically significant coronary artery stenosis as measured by FFR. Further studies are needed to find a causal relationship. *(Anatol J Cardiol 2015; 15: 1002-7)*

Key words: coronary artery disease, fractional flow reserve, lymphocyte, neutrophil

Introduction

Coronary artery disease (CAD) is a devastating disease with a high morbidity and mortality. The severity of CAD has been shown to be closely related to untoward cardiac events. Atherosclerosis is known to play a major role in this pathophysiological process and it was previously demonstrated that CAD and atherosclerosis are closely linked with inflammation (1). In addition, it has been shown that an increased inflammatory status is closely related to poor prognosis in patients with CAD (2, 3).

The neutrophil-to-lymphocyte ratio (NLR) has been shown to be a marker of inflammation and it has been demonstrated that NLR is closely related to increased cardiovascular mortality and morbidity (4, 5). Recently, it was shown that NLR is closely related to many cardiovascular diseases (6-9). In addition, NLR is associated with the severity and complexity of CAD (10, 11).

Fractional flow reserve (FFR) is a method that is used to measure hemodynamic significance of a coronary artery lesion when the coronary artery stenosis rate is believed to be of intermediate grade (stenosis rate: between 40% and 70%) (12). All coronary artery lesions do not cause hemodynamic disturbance at the related myocardial tissue. However, hemodynamically significant coronary artery stenosis reduces distal coronary artery pressure and thus the ratio of distal coronary artery pres-

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sure to proximal coronary artery pressure is reduced and myocardial tissue perfusion is disturbed (13). FFR is an effective procedure to decide the coronary revascularization plan and it has significant prognostic value in such patients (14). It is accepted as a gold standard in the prediction of functional relevance of coronary artery lesion severity (15).

Because NLR is closely related to the severity of CAD and FFR is a good measure of whether a coronary artery lesion is hemodynamically significant or not, we hypothesized that NLR may predict hemodynamic significance of coronary artery stenosis. Therefore, in this study, we investigated the relationship between NLR and result of FFR measurement.

Methods

The coronary angiography archives (between January 2012 and December 2013) of two tertiary centers in Ankara, Turkey were retrospectively reviewed. Patients who had undergone coronary angiography with an indication of stable angina pectoris and in whom FFR measurement was performed were planned to be involved in the present study. The inclusion criteria were as follows: FFR measurement performed for coronary artery stenosis of intermediate grade (stenosis rate: between 40% and 70%) (12). The exclusion criteria were as follows: presence of a second lesion at the index coronary artery or another coronary artery with a severity of ≥40% luminal narrowing on coronary angiography, acute coronary syndrome, history of previous coronary artery intervention (percutaneous or surgical), moderate/severe valvular heart disease, significant arrhythmia, hemodynamic instability, malignancy, chronic renal failure, anemia, and acute or chronic inflammatory/infectious disease. During the study period, 574 patients had undergone FFR measurement. After evaluation of patients according to the inclusion and exclusion criteria, 134 patients remained for final analysis. The most common reason for exclusion was presence of ≥40% stenosis of a coronary artery other than the index coronary artery. Furthermore, 88.0% of FFR measurements were performed immediately after coronary angiography and the remaining measurements were performed during a second procedure.

Demographic characteristics and blood parameters, including complete blood count (CBC), biochemistry, and lipid panel, were recorded. Blood samples were collected before coronary angiography. In our centers, blood samples are routinely collected after a 12 h of fasting. Coulter Counter LH Series (Beckman coulter Inc., Hialeah, FL) was used for CBC analysis. NLR was calculated by dividing the neutrophil count by the lymphocyte count.

All coronary angiographies were performed according to Judkins technique. For all coronary arteries, at least 2 plain images were taken. In our centers, at least two cardiologists routinely evaluate coronary angiograms. FFR measurements were performed for intermediate-grade lesions with a stenosis rate of 40%-70% according to the decision of these cardiologists. After administration of unfractioned heparin (100 U/kg), an FFR guide wire was advanced to the coronary artery. Intracoronary nitrate with a dosage of 100-200 µg to avoid vasospasm and intracoronary adenosine (if needed) to reach maximal hyperemia were administered to the study participants. FFR was calculated as the ratio of distal intracoronary pressure to aortic pressure. Because the generally accepted FFR cut-off value in guidelines is 0.80 rather than 0.75, we accepted lesions as hemodynamically significant when the FFR value was ≤0.80 (16). Two groups were established according to FFR values. Patients with an FFR value of >0.80 formed group I and patients with an FFR value of ≤0.80 formed group II.

In order to evaluate interobserver variability in the assessment of lesion severity, 2 cardiologist (1 from each center) from the authors were selected and the coronary angiograms of 15 randomly selected patients were evaluated. There was an excellent correlation between the observers in the assessment of coronary artery lesion severity (r=0.824, p<0.001).

Our study was approved by local Ethics Committee.

Statistical analysis

SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Categorical variables were presented as percentages and continuous variables were presented as mean±standard deviation or median (maximum, minimum). The Kolmogorov–Smirnov test was used to determine if the distribution was normal or not. Categorical variables were compared using the chi-square test and continuous variables were compared using the Mann–Whitney U test or Student's t-test, as appropriate. Univariate and multiple logistic regression analyses were used to determine the possible confounding factors for the functional severity of coronary artery lesions. Variables with a p value of <0.1 in univariate regression analysis were tested in the multiple regression model. The receiver-operating characteristic (ROC) curve was used to determine the optimum cut-off value of NLR in the prediction of hemodynamic significance of coronary artery stenosis. A p value of <0.05 was accepted as statistically significant.

Results

The basal characteristics were given in Table 1. The mean age of the groups were similar (61.6±11.1 vs. 60.8±10.6, p=0.724). Although the percentage of males was numerically higher in group II, the difference was not statistically significant (57.8% vs. 75.0%, p=0.081). FFR measurement was most commonly performed for intermediate-grade lesions of the left anterior descending artery (LAD) (98.0% vs. 96.9%, p=0.698). Of the 134 patients, 38 (28.3%) had an FFR value of ≤0.80.

Comparison of the laboratory parameters is given in Table 2. White blood cell (WBC) count was higher in group II (8.0±1.9 vs. 7.3±1.6×10^9/L, p=0.046). High-density lipoprotein (HDL) levels were higher numerically in group I, but the difference did not reach statistical significance (46.5±10.3 vs. 42.7±11.0, p=0.079). The neutrophil count was higher in group II (6.6±0.8 vs. 5.6±0.9, p<0.001),

Table 1. Basal characteristics of the study groups

	Group I, FFR>0.80 (n=102)	Group II, FFR≤0.80 (n=32)	*P*
Age, year	61.8±10.7	59.2±10.5	0.226
Gender, male, n, %	59 (57.8)	24 (75.0)	0.081
Hypertension, n, %	64 (62.7)	18 (56.3)	0.511
Diabetes mellitus, n, %	31 (30.4)	10 (31.3)	0.927
Drugs, n, %			
Acetylsalicylic acid	86 (84.3)	28 (87.5)	0.659
Beta-blocker	49 (48.0)	12 (37.5)	0.296
ACEI	49 (48.0)	13 (40.6)	0.463
ARB	17 (18.8)	4 (12.5)	0.558
CCB	13 (12.7)	4 (12.5)	0.971
Statin	65 (63.7)	22 (68.8)	0.603
Target vessel, n, %			
LAD	100 (98.0)	31 (96.9)	0.698
Cx	-	-	
RCA	1 (1.9)	1 (3.1)	0.698

ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; CCB - calcium channel blocker; Cx - circumflex artery; LAD - left anterior descending artery; RCA - right coronary artery

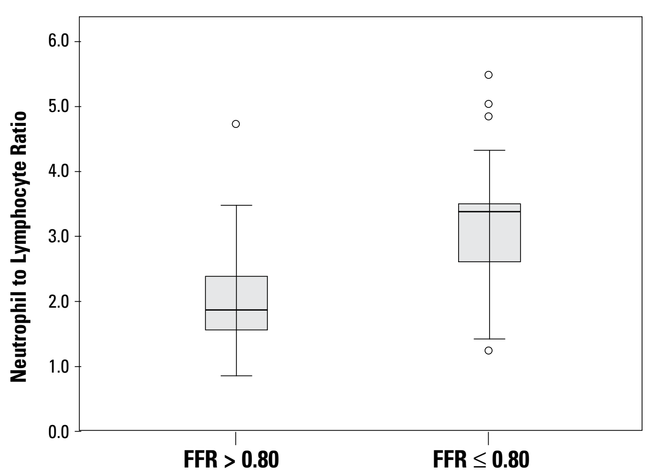

Figure 1. NLR is higher in patients with hemodynamically significant coronary artery stenosis. Assesed by Mann-Whitney U test

Table 2. Comparison of laboratory parameters between patients with hemodynamically significant coronary artery lesions and patients with hemodynamically non-significant coronary artery lesions

	Group I, FFR>0.80 (n=102)	Group II, FFR≤0.80 (n=32)	*P*
Hemoglobin, g/dL	14.3±1.3	14.7±1.5	0.164
WBC count, ×10⁹/L	7.3±1.6	8.0±1.9	0.046
Platelet count, ×10⁹/L	252.9±71.8	240.5±54.4	0.368
Creatinine, mg/dL	0.8±0.1	0.9±0.2	0.174
FBG, mg/dL*	108.0 (60.0, 364.0)	101.0 (81.0, 301.0)	0.439
Total cholesterol, mg/dL	204.3±53.4	200.9±55.4	0.763
LDL, mg/dL	129.6±45.5	126.6±42.1	0.746
HDL, mg/dL	46.5±10.3	42.7±11.0	0.079
Triglyceride, mg/dL	149.3±70.3	161.5±87.5	0.436
MPV, fL	8.7±0.7	8.9±0.6	0.357
RDW (%)*	13.7 (12.3, 17.6)	13.6 (12.1, 16.9)	0.784
Neutrophil, ×10⁹/L	5.6±0.9	6.6±0.8	<0.001
Lymphocyte, ×10⁹/L	3.0±1.0	2.1±0.5	<0.001
PLR*	79.2 (39.5, 212.0)	109.2 (45.6, 212.8)	<0.001

FBG - fasting blood glucose; FFR - fractional flow reserve; HDL - high-density lipoprotein; LDL - low-density lipoprotein; MPV - mean platelet volume; NLR - neutrophil-to-lymphocyte ratio; PLR - platelet-to-lymphocyte ratio; RDW - red cell distribution width; WBC - white blood cell.
*Non-parametric variables, values given as median (minimum, maximum).

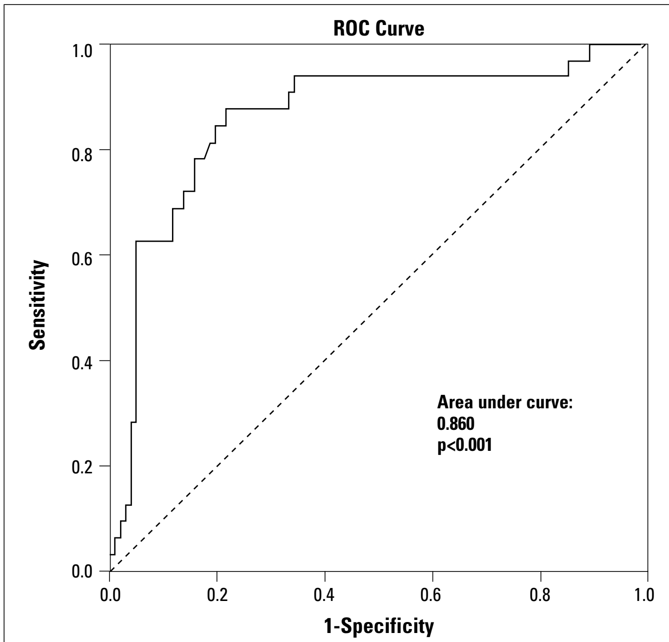

Figure 2. ROC curve analysis of NLR for hemodynamic significance of coronary artery lesions

whereas the lymphocyte count was higher in group I. NLR (3.3±1.2 vs. 2.0±0.9, $p<0.001$) (Fig. 1) and platelet-to-lymphocyte ratio (PLR) (116.8±34.2 vs. 89.5±36.1, $p<0.001$) were higher in group II.

In ROC curve analysis, an NLR value of 2.4 had 87.5% sensitivity and 78.4% specificity for the prediction of hemodynamically significant coronary artery stenosis (Fig. 2).

In univariate logistic regression analysis, WBC count [1.250 (0.997-1.566), p=0.053], HDL levels [0.965 (0.927-1.005), p=0.082], male gender [2.186 (0.897-5.332), p=0.085], NLR [3.082 (1.867-5.088), p<0.001], and PLR [1.019 (1.008-1.030), p=0.001] were identified as possible confounding factors for the prediction of hemodynamically significant coronary artery stenosis (Table 3). In the multiple logistic regression model, NLR remained the only independent predictor of hemodynamically significant coronary artery stenosis (Table 3).

Table 3. Univariate and multiple logistic regression analyses performed to find out possible confounding factors of hemodynamically significant coronary artery stenosis

	Univariate regression analysis		Multiple regression analysis	
Variables	**Odds ratio (95% confidence interval)**	***P***	**Odds ratio (95% confidence interval)**	***P***
White blood cell count	1.250 (0.997-1.566)	0.053	1.164 (0.866-1.564)	0.314
High-density lipoprotein	0.965 (0.927-1.005)	0.082	0.985 (0.941-1.032)	0.532
Male gender	2.186 (0.897-5.332)	0.085	1.632 (0.577-4.617)	0.356
Neutrophil-to-lymphocyte ratio	3.082 (1.867-5.088)	**<0.001**	2.904 (1.476-5.714)	**<0.002**
Platelet-to-lymphocyte ratio	1.019 (1.008-1.030)	**<0.001**	0.997 (0.979-1.015)	0.718

Discussion

In present study, we found that NLR was higher in patients with hemodynamically significant coronary artery stenosis. We also found NLR to be an independent predictor of hemodynamically significant coronary artery lesions with an FFR value of ≤0.80.

It is well known that anatomic stenosis does not always cause hemodynamic disturbance in the related coronary artery. In some patients, coronary angiographic appearance can underestimate or overestimate the lesion's hemodynamic severity (17). Thus, FFR is a well-established method to determine the hemodynamic significance of coronary artery stenosis. Apart from the determination of hemodynamic significance, FFR also has prognostic predictive value. Tonino et al. (16) showed that routine FFR measurement in patients with multivessel CAD who had planned to undergo PCI decreased the rate of major adverse cardiac events at 1-year follow up.

It is well known that CAD has a close relationship with the inflammatory status of a patient (1). For example, elevated C-reactive protein (CRP) levels have been shown to be an independent predictor of CAD in healthy individuals (18). Recently, it was shown that NLR is an important inflammatory marker and is closely related to various cardiovascular diseases. In a study, it was found that NLR was increased in patients with coronary artery ectasia (19). Turak et al. (7) showed that increased NLR was closely linked with bare metal stent restenosis. In addition, it has been shown that increased NLR is closely related to the extent and severity of CAD. For example, Kaya et al. (20) assessed the severity of CAD in terms of the Gensini score and they found that NLR was closely related to the severity of atherosclerosis. Sönmez et al. (11) evaluated the complexity of CAD in terms of the SYNTAX score and they found NLR as an independent predictor of both presence and complexity of CAD. Arbel et al. (10) investigated the relationship between NLR and CAD severity. They divided their patient group according to the number of diseased vessels and evaluated 3-year outcomes. They showed that NLR was significantly linked with the number of diseased vessels and the prognosis was worst in patients with higher NLR values.

It has previously been shown that hemodynamic severity is a better prognostic marker than anatomical appearance of a coronary artery lesion and FFR is a well-established method for determination of lesion severity. Therefore, we planned to investigate the relationship between NLR and FFR. In order to find out more clear results, we excluded patients with ≥40% stenosis of a coronary artery other than the index artery. Our findings showed that NLR was significantly higher in patients with an FFR value of ≤0.80, indicating that NLR was increased in patients with hemodynamically significant coronary artery lesions. In addition, we found NLR to be an independent predictor of hemodynamically significant coronary artery stenosis. In ROC curve analysis, we showed that NLR has substantial sensitivity and specificity in the prediction of hemodynamically significant CAD diagnosed using FFR. Our results can be explained by different mechanisms. First, it is known that patients with hemodynamically significant coronary lesions have poor prognosis and increased NLR has been closely linked with worse outcomes (4, 5, 15). Second, increased NLR can be a response to increased coronary artery lesion severity. In this hypothesis, we believe that ischemia can trigger some inflammatory processes and eventually change the distribution of WBC count. The study by Williams et al. (21) supports our hypothesis, because they showed a strong relationship between increased NLR and disrupted myocardial perfusion. They showed that patients with higher NLR values had an increased likelihood of advanced perfusion defect. The close relationship between inflammatory markers and poor prognosis also support our hypothesis (22, 23). Similar to inflammatory markers, NLR was shown to be significantly associated with poor prognosis. The results of the study by Sels et al. (24) can be seen as conflicting with our results, because they could not show a relationship between FFR and some inflammatory markers such as interleukin-6, interleukin-8 and tumor necrosis factor. However, these findings cannot exclude an association between NLR and FFR, because they did not study many other inflammatory markers that could be secreted from neutrophils and we still do not know all the pathogenic mechanisms and molecules that may have a role in the progression of atherosclerotic coronary artery lesion.

Recently, PLR was found to be a new predictor of some cardiovascular diseases (25, 26). Thus, we evaluated PLR in our present study. Although PLR was higher in patients with a hemodynamically significant coronary artery lesion, in multiple regression analysis, PLR was not found to be an independent predictor of hemodynamically severe coronary artery stenosis.

Study limitations

Our study has some limitations. First, it was a retrospective study with a limited number of patients. Second, we could not study many inflammatory markers such as hs-CRP, although it is impossible to evaluate all inflammatory markers. Lastly, FFR measurement was not performed for all patients with intermediate-grade coronary artery stenosis. According to the decision of the physician and patient, some patients were referred for myocardial scintigraphy, some patients underwent percutaneous coronary intervention, and others were followed-up with medical treatment. This can also be a limitation of our study.

Conclusion

In conclusion, our results suggest that NLR is increased in patients with hemodynamically significant coronary artery stenosis and NLR is an independent marker of hemodynamically significant coronary artery lesions diagnosed by FFR measurement. The causal relationship should be determined in further studies.

Conflict of interest: None declared.

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