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Original Article

Relationship Between Coronary Lesion Severity Detected in Fractional Flow Reserve with Monocyte/High-Density Lipoprotein, Neutrophil/Lymphocyte, Lymphocyte/Monocyte, and Platelet/Lymphocyte Ratios: Which Is Most Important?

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ABSTRACT

Objective: In this study, in patients with moderate coronary lesions evaluated in coronary angiography, fractional flow reserve by lesion severity, we aimed to determine the relationship between neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, and monocyte/high-density lipoprotein cholesterol ratio, which has been recently expressed as a predictor of cardiovascular disease risk.

Methods: Stenosis with a fractional flow reserve of <0.80 was considered functionally severe. According to fractional flow reserve lesion severity, a total of 131 patients were analyzed, with fractional flow reserve > 0.8 (group 1) and fractional flow reserve < 0.8 (group 2). Patients with acute coronary syndrome, severe arrhythmia, hemodynamic instability, history of previous revascularization, severe renal and hepatic failure, active infection, malignancy, hematologic disease, familial history of hyperlipidemia, rheumatologic disease, life expectancy <1 year, and age <18 and >90 years were excluded from the study.

Results: There was a statistically significant difference between monocyte/high-density lipoprotein cholesterol ratio, neutrophil /lymphocyte ratio, lymphocyte/monocyte ratio, and platelet/lymphocyte ratio, and fractional flow reserve groups ($P < .001$). Univariate and multivariate regression analyses were applied among the factors affecting the severity of the lesion detected in fractional flow reserve. Monocyte/high-density lipoprotein cholesterol ratio (odds ratio, 1.25; 95% CI, 1.05-1.47; $P = .004$), neutrophil/lymphocyte ratio (odds ratio, 3.15; 95% CI, 1.51-6.57; $P < .001$), hemoglobin A1c (odds ratio, 11.5; 95% CI, 2.76-48.4; $P = .001$), and lymphocyte/monocyte ratio (odds ratio, 0.27; 95% CI, 0.16-0.44; $P = .002$) were found to be independent predictors.

Conclusions: In this study, we would like to emphasize that simple, fast, and low-cost methods such as monocyte/high-densit y lipoprotein cholesterol ratio, neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, and platelet/lymphocyte ratio can be parameters related to lesion severity detected in fractional flow reserve. These parameters can be widely used as they are easily accessible and repeatable.

Keywords: Fractional flow reserve, high-density lipoprotein, lymphocyte, monocyte, neutrophil, platelet

INTRODUCTION

Coronary artery disease (CAD) is still the disease group most responsible for morbidity and mortality in our age. Coronary angiography (CAG) is one of the main methods used in the diagnosis of coronary artery lesions. However, the qualitative assessment of lesion severity in the coronary arteries by CAG is not always reliable. Anatomical stenosis, which is evaluated as visually severe, may not always be serious in terms of hemodynamics. Evaluation with fractional flow reserve (FFR) is an extremely important method to reveal the severity of the coronary artery lesion, especially when coronary artery stenosis is 40%-70% (i.e., moderate).[1]

The underlying cause of CAD is atherosclerosis. Inflammation is one of the leading steps in the pathogenesis of atherosclerosis. Recently, researches on the connection of inflammatory markers with cardiovascular diseases (CVD) have been the subject of study. In a study involving 105 patients with extracranial carotid artery disease, it was reported that the neutrophil/lymphocyte ratio (NLR) was positively correlated with extracranial carotid

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stenosis and was associated with lesion severity in extracranial carotid artery stenosis.[2] In a study of 963 patients with non-ST elevation myocardial infarction (NSTEMI), high monocyte/lymphocyte ratio (MLR) was stated to be riskier for major cardiac events developing in-hospital than low MLR. It has been reported that MLR is more effective than NLR in reflecting CAD in NSTEMI patients.[3] In a study of 300 patients over 70 years of age, measurements were made using the ankle-brachial index method. High platelet/lymphocyte ratio (PLR), NLR, and monocyte/high-density lipoprotein (HDL) cholesterol ratio (MHR) have been shown to be associated with peripheral arterial disease (PAD). In the study, it was stated that these 3 indices could be simple, easily accessible, and reproducible factors in the diagnosis of PAD.[4] High-density lipoprotein cholesterol protects endothelial tissue from the harmful consequences of low-density lipoprotein (LDL) cholesterol. It also prevents LDL from becoming oxidized. In addition to being an antioxidant, HDL also has antithrombotic and anti-inflammatory effects. Monocytes, on the other hand, are a parameter that plays an active role in the synthesis and distribution of cytokines with proinflammatory and prooxidant properties. In recent years, the proinflammatory effect of monocytes has been described. In addition, HDL cholesterol has been reported to have anti-inflammatory and antioxidant results. The idea has emerged that MHR is a ratio that can determine the level of oxidative stress and inflammation. It has also been associated with CVD development and long-term outcomes.[5]

In this study, with the severity of the lesion in patients who underwent FFR method after CAG, we thought to determine the relationship between NLR, PLR, MHR, and lymphocyte/monocyte ratio (LMR), which have recently been expressed as CVD risk parameters.

METHODS

We designed this study retrospectively. For this purpose, a total of 131 consecutive patients who underwent the elective FFR method were enrolled. All patients participating in our study were given detailed information and a signed consent form was requested. Biochemical, lipid, and hemogram parameters, drugs used, demographic, echocardiographic, and angiographic data of the patients were recorded. Blood tests were taken 24 hours after the patients applied to the health center. Fractional flow reserve measurement results were made at the discretion of the cardiologists. Five thousand units of heparin were given intra-arterially as a bolus. The coronary arteries were then visualized using a guide catheter without side holes. After the calibration was checked, a 0.014-inch guide wire (PrimeWire, Volcano, San Diego, Calif, USA) was placed distal to the stenosis to monitor the pressure level. Before FFR measurements, 200 µg bolus nitroglycerin was administered intracoronally. First of all, the distal intracoronary pressures of the patients were recorded. Hyperemia was triggered by administering gradually increasing doses of intracoronary adenosine until the final value in which the FFR value decreased. Fractional flow reserve value was defined as the result between the pressure measured in the intracoronary distal region and the mean aortic pressure. The highest hyperemia dimension was recorded at that time. An FFR result of <0.80 was considered functionally significant. According to FFR lesion severity, 2 groups were formed; FFR < 0.8 group (84 patients) and FFR > 0.8 group (47 patients).

Inclusion criteria for the study: patients evaluated as stable angina pectoris and undergoing the FFR procedure under elective conditions. Criteria excluded from the scope of the study: acute coronary syndrome (ACS), severe arrhythmia, hemodynamic instability, previous revascularization history, severe renal and hepatic failure, active infection, malignancy, hematologic diseases, familial history of hyperlipidemia, rheumatologic disease, life expectancy <1 year, and age <18 and >90 years.

Statistical Analysis

We obtained the statistical analysis results of the data using the Statistical Package for the Social Sciences software version 25.0 for Windows (IBM SPSS Corp., Armonk, NY, USA). Whether numerical variables were suitable for normal distribution was evaluated by analyzing with Shapiro–Wilk and Kolmogorov–Smirnov tests. The mean and standard deviation values of the numerical variables are given. Independent samples *t*-test was used if normal distribution was achieved to compare the 2 groups in terms of numerical variables. If a normal distribution could not be obtained, it was analyzed using the Mann–Whitney *U*-test. Categorical parameters were shown as number (n) and ratio (%). The correlation between categorical parameters was compared using Pearson's chi-square test and Fisher's exact test. The relationships between NLR, PLR, LMR, and MHR were compared using Spearman's rho analysis. The correlation analysis for NLR, PLR, LMR, and MHR was evaluated using univariate and multivariate regression analyses. Odds ratio and 95% CI values were recorded. In addition, receiver operating characteristic (ROC) analysis was performed for the cut-off value of NLR, PLR, LMR, and MHR ratios. The cut-off value was defined based on the Youden index. Obtaining a $P < .05$ result in all hypotheses was considered statistically significant.

Main Points

- We would like to emphasize that simple, fast, and low-cost methods such as monocyte/high-density lipoprotein cholesterol ratio, neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR) may be parameters related to lesion severity detected in fractional flow reserve (FFR).
- Monocyte/high-density lipoprotein cholesterol ratio predicted the severity of coronary lesion detected in FFR with 80% sensitivity and 75% specificity, NLR with 75% sensitivity and 70% specificity, LMR with 72% sensitivity and 70% specificity, and PLR with 71% sensitivity and 71% specificity.
- Although hemogram parameters play an important role in predicting the severity of the lesion before the FFR procedure, symptoms, other laboratory findings, and non-invasive imaging methods should be carefully examined.

RESULTS

Among the patients included in the study, 2 separate groups were formed as FFR > 0.8 (group I) and FFR < 0.8 (group II).

The mean age of the patients after the analysis was 58.5 (±9.6). Of these patients, 65.6% were male. When the mean age (58.4 (±10.3) vs. 58.5 (±9.3), $P = .941$) and male sex ratio (70.2% vs. 63.1%, $P = .411$) were examined, no statistically significant difference was found between the 2 groups. Of the patients, 94.7% were in the NYHA Class-I category. The most common symptoms detected in the patients were chest pain and shortness of breath (90.8% and 20.6%, respectively). When the 2 groups were compared, no statistically significant difference was found in terms of smoking (36.2% vs. 39.3%, $P = .725$) and alcohol use (4.3% vs. 6.0%, $P = .924$). There was no significant difference in the parameters of hypertension (44.7% vs. 40.5%, $P = .640$), history of CAD (46.8% vs. 54.8%, $P = .382$), and hyperlipidemia (51.1% vs. 52.4%, $P = .885$) (Table 1). Other demographic data and comorbidities between the groups are given in Table 1.

When the biochemical markers are examined, between group I and group II, respectively, HDL (44.30 (±10.68) vs. 38.23 (±9.80), $P = .001$), MPV (8.67 (±0.89) vs. 8.31 (±0.92)), $P = .029$), monocytes (0.73 (±0.19) vs. 0.95 (±0.20)), $P < .001$), lymphocytes (2.83 (±1.0) vs. 2.1 (±0) .51), $P < .001$), HbA1c (5.55 (±0.38 vs. 5.97 (±0.57)), $P < .001$), LMR (4.23) (±2.09) vs. 2.31 (±0.74), $P < .001$), NLR (1.81 (±0.60) vs. 2.50 (±0.95), $P < .001$), PLR (101.65 (±47.39) vs. 136.10 (±49.41), $P < .001$), and MHR (0.017 (±0.0064) vs. 0.026 (±0.0085), $P < .001$), significant difference was detected. The EF values obtained in the groups were compared and no significant difference was found (53.7% (±8.2) and 55.1% (±7.6), $P = .324$) (Table 2). Other hemogram, biochemical, and echocardiographic parameters are summarized in Table 2.

The medical treatments received by the patients are compared in Table 3.

In the applied correlation analysis method, there was a moderate positive correlation between FFR, and NLR and MHR parameters. In addition, it was concluded that there was a moderate negative correlation between FFR and LMR. A weak correlation was found between FFR and PLR (Table 4).

Table 1. Demographic and Comorbid Characteristic Results

Parameters	Group I (n = 47)	Group II (n = 84)	Total (n = 131)	*P*
Age (years)	58.4 (±10.3)	58.5 (±9.3)	58.5 (±9.6)	.941
Male sex, n (%)	33 (70.2)	53 (63.1)	86 (65.6)	.411
SBP, mmHg	128.7 (±17.8)	127.5 (±16.6)	127.9 (±17.0)	.691
DBP, mmHg	70.7 (±10.5)	70.8 (±10.2)	70.8 (±10.3)	.960
Heart rate, minute	76.4 (±12.3)	73.7 (±12.7)	74.6 (±12.5)	.230
NYHA class I, n (%)	46 (97.9)	78 (92.9)	124 (94.7)	.221
Chest pain, n (%)	41 (87.2)	78 (92.9)	119 (90.8)	.285
Dyspnea, n (%)	10 (21.3)	17 (20.2)	27 (20.6)	.888
Palpitation, n (%)	10 (21.3)	5 (6.0)	15 (11.4)	.008
Tiredness, n (%)	7 (14.9)	6 (7.1)	13 (9.9)	.155
Dizziness, n (%)	3 (6.4)	4 (4.8)	7 (5.3)	.692
Syncope, n (%)	0 (0)	1 (1.2)	1 (0.8)	.453
Smoking, n (%)	17 (36.2)	33 (39.3)	50 (38.2)	.725
Alcohol use, n (%)	2 (4.3)	5 (6.0)	7 (5.3)	.924
Hypertension, n (%)	21 (44.7)	34 (40.5)	55 (42.0)	.640
CAD, n (%)	22 (46.8)	46 (54.8)	68 (51.9)	.382
Hyperlipidemia, n (%)	24 (51.1)	44 (52.4)	68 (51.9)	.885
COPD, n (%)	8 (17.0)	12 (14.3)	20 (15.3)	.676
Thyroid disease, n (%)	4 (8.5)	6 (7.1)	10 (7.6)	.777
Stroke/TIA, n (%)	2 (4.3)	7 (8.3)	9 (6.9)	.376
CKD, n (%)	2 (4.3)	3 (3.6)	5 (3.8)	.592
Peripheral artery disease, n (%)	1 (2.1)	5 (5.9)	6 (4.6)	.315
Pacemaker/ICD/CRT, n (%)	0 (0)	2 (2.4)	2 (1.5)	.286
Malignancy, n (%)	1 (2.1)	1 (1.2)	2 (1.5)	.675
Anemia, n (%)	1 (2.1)	2 (2.4)	3 (2.3)	.926

SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; CAD, coronary artery disease; COPD, chronic obstructive pulmonary diseases; TIA, transient ischemic attack; CKD, chronic kidney disease; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; Group I, FFR > 0.8; Group II, FFR < 0.8.

Table 2. Hemogram, Biochemical, and Echocardiographic Results

Parameters Mean (±Standard Deviation)	Group I (n=47)	Group II (n=84)	Total (n=131)	*P*
Urea, mg/dL	33.79 (±12.61)	34.07 (±10.17)	33.97 (±11.06)	.893
Creatinine, mg/dL	1.06 (±0.94)	08.8 (±0.20)	0.95 (±0.59)	.111
Uric acid, mg/dL	5.48 (±1.0)	5.23 (±0.91)	5.32 (±0.95)	.150
Total cholesterol, mg/dL	187.40 (±51.27)	198.90 (±44.70)	194.78 (±47.29)	.183
Triglyceride, mg/dL	155.07 (±86.62)	179.09 (±126.06)	170.48 (±113.74)	.248
HDL, mg/dL	44.30 (±10.68)	38.23 (±9.80)	40.38 (±10.09)	**.001**
LDL, mg/dL	112.33 (±49.45)	120.34 (±37.92)	122.13 (±72.31)	.304
Hemoglobin, g/dL	13.51 (±1.24)	13.56 (±1.56)	13.54 (±1.45)	.851
Platelet, $x10^3$/μL	251.79 (±56.29)	274.30 (±71.80)	266.22 (±67.30)	.066
Leukocyte, $x10^3$/μL	8.68 (±2.32)	8.26 (±1.64)	8.41 (±1.92)	.237
MPV, fL	8.67 (±0.89)	8.31 (±0.92)	8.44 (±0.92)	**.029**
Neutrophil, $x10^3$/μL	4.91 (±1.64)	5.09 (±1.62)	5.03 (±1.63)	.541
Monocyte, $x10^3$/μL	0.73 (±0.19)	0.95 (±0.20)	0.87 (±0.19)	**<.001**
Lymphocyte, $x10^3$/μL	2.83 (±1.0)	2.10 (±0.51)	2.34 (±0.67)	**<.001**
Fasting glucose, mg/dL	98.13 (±10.55)	99.30 (±11.25)	98.88 (±10.98)	.557
TSH, μIU/Ml	2.00 (±1.33)	2.14 (±1.48)	2.09 (±1.42)	.593
T4, ng/dL	1.36 (±0.38)	1.47 (±0.50)	1.43 (±0.46)	.200
Ca, mg/dL	9.32 (±0.56)	9.36 (±0.58)	9.35 (±0.57)	.689
Sodium, mmol/L	139.51 (±2.93)	139.45 (±3.04)	139.47 (±13.63)	.915
Potasium, mmol/L	4.46 (±0.47)	4.40 (±0.48)	4.42 (±0.48)	.519
HbA1c, %	5.55 (±0.38)	5.97 (±0.57)	5.82 (±0.55)	**<.001**
LMR	4.23 (±2.09)	2.31 (±0.74)	2,95 (±1,19)	**<.001**
NLR	1.81 (±0.60)	2.50 (±0.95)	2.25 (±0.90)	**<.001**
PLR	101.65 (±47.39)	136.10 (±49.41)	123.74 (±51.27)	**<.001**
MHR	0.017 (±0.0064)	0.026 (±0.0085)	0.023 (±0.0078)	**<.001**
Sinus rhythm, n (%)	47 (100)	78 (92.9)	125 (95.4)	.061
LVEF,%	53.7 (±8.2)	55.1 (±7.6)	54.6 (±7.9)	.324
LVEDD, cm	48.25 (±5.21)	47.06 (±4.83)	47.48 (±4.98)	.189
LVESD, cm	30.47 (±6.30)	28.48 (±5.30)	29.19 (±5.73)	.056
LVDD, n (%)	29 (61.7)	59 (70.2)	88 (67.2)	.318
Moderate-severe MR, n (%)	1 (2.1)	4 (4.8)	5 (3.8)	.450
Moderate-severe MS, n (%)	0 (0)	0 (0)	0 (0)	–
Moderate-severe AR, n (%)	0 (0)	2 (2.4)	2 (1.5)	.286
Moderate-severe AS, n (%)	0 (0)	1 (1.2)	1 (0.8)	.453
Moderate-severe TR, n (%)	2 (4.3)	2 (2.4)	4 (3.1)	.535
Moderate-severe TS, n (%)	0 (0)	0 (0)	0 (0)	–

HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPV, mean platelet volume; TSH, thyroid-stimulating hormone; HbA1C, hemoglobin A1c; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MHR, monocyte/HDL ratio; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVDD, left ventricular diastolic dysfunction; MR, mitral regurgitation; MS, mitral stenosis; AR, aortic regurgitation; AS, aortic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; Group I, FFR > 0.8; Group II, FFR < 0.8.

In the univariate and multivariate regression analyses performed among the factors affecting the severity of the lesion detected in FFR, MHR (OR, 1.25; 95% CI, 1.05-1.47, $P = .004$), NLR (OR, 3.15; 95% CI, 1.51-6.57, $P < .001$), HbA1c (OR, 11.5; 95% CI, 2.76-48.4, $P = .001$), and LMR (OR, 0.27; 95% CI, 0.16-0.44, $P = .002$) were found to be independent predictors (Table 5).

Table 3. Results of Drugs Used by Patients

Parameters	Group I (n = 47)	Group II (n = 84)	Total (n = 131)	*P*
Beta-blockers, n (%)	25 (53.2)	52 (61.9)	77 (58.8)	.331
ACE-I, n (%)	10 (21.3)	26 (31.0)	36 (27.5)	.234
Statin, n (%)	28 (59.6)	47 (56.0)	75 (57.3)	.688
Antiaggregant, n (%)	31 (66.0)	58 (69.0)	89 (67.9)	.716
Anticoagulant, n (%)	2 (4.3)	6 (7.1)	8 (6.1)	.508
ARBs, n (%)	9 (19.1)	13 (15.5)	22 (16.8)	.590
Dihydropyridine CCB, n (%)	9 (19.1)	12 (14.3)	21 (16.0)	.467
Loop diuretic, n (%)	3 (6.4)	12 (14.3)	15 (11.4)	.173
Aldosterone antagonist, n (%)	3 (6.4)	8 (9.5)	11 (8.4)	.534
Thiazide diuretic, n (%)	7 (14.9)	21 (25.0)	28 (21.4)	.176
Non-dihydropyridine CCB, n (%)	0 (0)	5 (5.9)	5 (3.8)	.088

ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCB, calcium channel blockers; Group I, FFR > 0.8; Group II, FFR < 0.8.

Table 4. Correlation Analysis to Determine Predictor of FFR Lesion Severity

Parameters	Correlation Analysis	
LMR	*r*	−0.52
	P	<.001
NLR	*r*	0.50
	P	<.001
MHR	*r*	0.58
	P	<.001
PLR	*r*	0.34
	P	<.001

LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MHR, monocyte/high-density lipoprotein ratio.

ROC analysis was used to evaluate the power of the MHR, NLR, PLR, and LMR parameters to predict the severity of the lesions detected in the FFR. In the results obtained, MHR with 75% specificity and 80% sensitivity (AUC, 0.82; 95% CI, 0.74-0.90; $P < .001$), NLR with 75% sensitivity and 70% specificity (AUC, 0.79; 95% CI, 0.71-0.89; $P < .001$), LMR with 72% sensitivity and 70% specificity (AUC, 0.77; 95% CI, 0.69-0.87, $P < .001$), and PLR with 71% sensitivity and 71% specificity (AUC, 0.74; 95% CI, 0.63-0.78, $P < .001$) predicted lesion severity detected in FFR (Figure 1 and 2).

DISCUSSION

In this study, functionally severe coronary artery lesions evaluated using the FFR method were strongly associated with some inflammatory parameters. Atherosclerosis and CVD are among the most well-known causes of death worldwide.[6] It is known that atherosclerosis develops after inflammatory events and steps. Oxidative stress and inflammation are important steps that play a role in the initiation and progression of atherosclerosis.[7] An increased white blood cell count has been reported to be associated with adverse clinical outcomes in patients with CAD, ACS, percutaneous coronary intervention (PCI), and PAD.[8] Therefore, we aimed to examine these hemogram parameters in our study. The severity of stenosis and unstable plaque in atherosclerotic plaques are also life-threatening. In particular, neutrophils are an important factor in plaque destabilization, determination of reperfusion injury, and remodeling.[9] In a study conducted by Ionita et al.[10] a correlation between the severity of the atherosclerotic lesion in the carotid artery and the basal neutrophil count was found. In his works, neutrophil counts were higher if atherosclerotic plaques prone to dissociation were present with a higher macrophage content, lower collagen content, and smooth muscle cells.[9] In the first place, neutrophils and lymphocytes are involved in the onset of atherosclerosis.[2] Neutrophil; protein hydrolysis can accelerate the development of atherosclerosis through inflammatory and oxidative stress reactions, and lymphopenia has also been thought to be associated with the formation of atherosclerosis.[11] Another accepted process is that the NLR can represent the function of the autonomic nervous system. It has been determined that the distribution of leukocyte-forming subsets in the body is determined by the autonomic nervous system.[2]

Table 5. Univariable and Multivariable Regression Analysis to Determine Predictor of FFR Lesion Severity

Parameters			Model 1		Model 2	
Variables	Univariate, OR (95% CI)	*P* Value	Multivariate, OR (95% CI)	*P* Value	Multivariate, OR (95% CI)	*P* Value
MHR	1.32 (1.10–1.53)	<.001	1.25 (1.05–1.47)	.004		
NLR	3.8 (1.97–7.37)	<.001	3.15 (1.51–6.57)	<.001		
LMR	0.27 (0.16–0.44)	<.001			0.27 (0.16–0.44)	.002
HT	2.0 (0.76–5.42)	.042	1.8 (0.72–4.93)	.20	2.1 (0.78–5.85)	.13
HbA1c	11.5 (3.67–36.5)	.001	11.5 (2.76–48.4)	.001	8.8 (2.15–36.2)	.002
Age	1.00 (0.96–1.03)	.94				
LVEF	1.03 (0.97–1.10)	.29				

LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; HT, hypertension; MHR, monocyte/high-density lipoprotein ratio; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction.

Figure 1. The cut-off value of PLR, MHR, and NLR associated with FFR in the ROC curve analysis. NLR, neutrophil/ lymphocyte ratio; PLR, platelet/ lymphocyte ratio; MHR, monocyte/high-density lipoprotein ratio; FFR, fractional flow reserve; ROC, receiver operating characteristic.

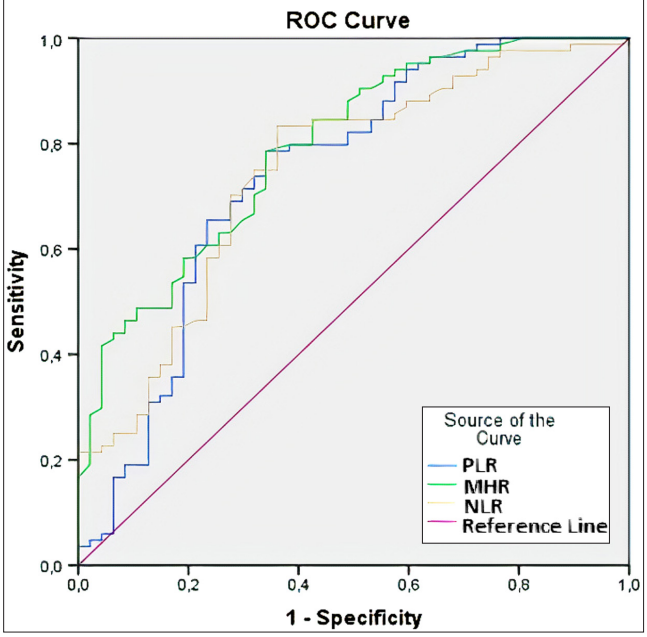
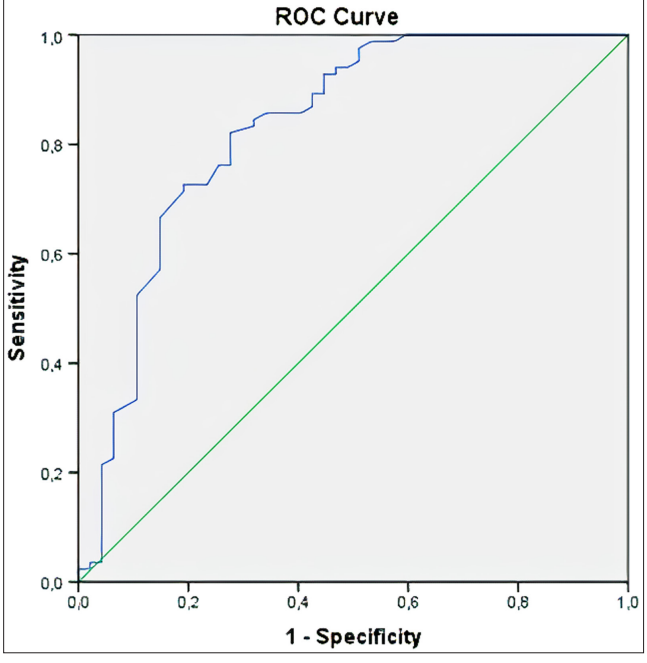


Figure 2. The cut-off value of LMR associated with FFR in the ROC curve analysis. LMR, lymphocyte/monocyte ratio; FFR, fractional flow reserve; ROC, receiver operating characteristic.



It has neutrophil adrenergic receptors. The number and function of neutrophils are determined by the sympathetic nerves. It has lymphocyte cholinergic receptor. Lymphocyte count and function are determined by parasympathetic nerves.[12] Neutr ophil/lymphocyte ratio reflected partial activity of sympatheti c/parasympathetic nerves.[13] A disruption in the autonomic nervous system may play a role in the formation of atherosclerosis.[14] In addition, NLR has been reported to be associated with early diagnosis, follow-up, treatment, and prognosis of patients hospitalized in intensive care units.[15] It has also been associated with systemic inflammatory diseases.[16] In the light of these data reported in the literature, it is consistent with the results obtained in our study. In addition, we found that NLR could be an independent predictor in patients in whom we detected severe lesions with the FFR method. In another study, a PLR ratio of >144 was found to be associated with high mortality in patients who underwent PCI after myocardial infarction (MI).[17] In addition, recent studies have reported that there is a positive correlation between the severity of PAD and NLR and PLR values, and these values may be poor prognostic markers.[18] Lymphocytes and monocytes are defense system parameters associated with the initiation and progression of the atherosclerotic process. It has been reported that low lymphocyte count and high monocyte count may have predictive and prognostic value in conditions such as stable CAD, MI, and heart failure.[19] It has been suggested that an increase in lymphocyte apoptosis and therefore a decrease in lymphocyte count has a negative effect on tissue healing and remodeling after infarction.[20] It has also been reported that deterioration in coronary microcirculation is closely associated with an increased incidence of MI and an increased risk of mortality.[21] In a few studies, it has been stated that LMR is an effective parameter that determines the systemic inflammatory response. In addition, it has been reported to be closely related to patient prognosis in many clinical conditions, including malignancies, PAH, and CAD severity.[22] In another study, LMR level before bare metal stent implantation was found to be independently associated with restenosis in patients with stable angina pectoris.[23] In our study, when we compared the PLR and LMR values, we observed that there was a statistically significant difference between the groups. Platelet/lymphocyte ratio showed poor correlation in predicting FFR lesion severity. We observed a moderate negative correlation between FFR lesion severity and LMR. In addition, we identified LMR as an independent predictor of FFR lesion severity. This result obtained in our study supports the previously reported results on this subject. Like neutrophils, monocytes play an important role in the formation of oxidative stress, inflammation, and atherosclerosis. The interaction of activated monocytes with the damaged endothelial structure leads to excessive secretion of proinflammatory cytokines.[24] Monocytes then phagocytose the oxidized LDL cholesterol molecules and differentiate into damaging macrophage cells that form foam cells. On the other hand, HDL cholesterol reduces macrophage accumulation and ensures the removal of oxidized cholesterol from the arterial wall structure. In addition to its antioxidative and anti-inflammatory properties, HDL increases the release of nitric oxide synthase in endothelial tissues and supports vasorelaxation.[25] Monocyte/high-density lipoprotein ratio is a marker that can reflect atherosclerosis severity and inflammation status. In a study by Korkmaz et al.[26] they found a correlation between atherosclerotic lesion severity and MHR after FFR. Also here,

there was no significant difference between the level of lesion severity detected in FFR and NLR, PLR, and LMR.[26] In the emergence of these findings, we think that the demographic data of the patients examined in the study, the distribution of risk factors, the inclusion criteria of the patients, and the number of patients included in the study may be effective. Cetin et al[27] reported that MHR is a predictor of stent thrombosis, severity of CAD, and CVD in long-term follow-up in patients with ACS. We can say that this finding is compatible with the results of our study. In addition, in our previous study, we found a significant correlation between the HbA1c value and the severity of the lesion detected by the FFR method.[28] In a meta-analysis examining 5 studies and a total of 1366 (606 FFR patients and 760 CAG patients) patients, MI was shown to be significantly lower in patients after FFR-guided interventional procedures compared to the CAG group. With this study, it was concluded that the FFR-based management of patients can significantly reduce the incidence of MI as it will improve the quality of life of patients, reduce the rate of rehospitalization, and reduce medical costs.[28,29] For this reason, we preferred to examine the severity of atherosclerotic lesion with the FFR method instead of CAG findings to determine more meaningful results in our study.

Study Limitations

Our study has strengths as well as some limitations. The study was retrospective. The number of patients studied was relatively small. Prospective studies with larger numbers of patients are needed to generalize the results. Many other important inflammatory parameters, such as highly sensitive C-reactive protein, were not used in the design of this study (it is unlikely to include all inflammatory parameters and perform a comprehensive analysis). The parameters we considered in the study were based on only 1 MHR, NLR, LMR, and PLR value. In other words, we did not examine THE changes in these inflammatory parameters that may develop over time.

CONCLUSION

In this study, we would like to emphasize that simple, fast, and low-cost methods such as MHR, NLR, LMR, and PLR may be parameters related to lesion severity detected in FFR. These parameters are easily accessible, reproducible, and widely used. Therefore, these parameters may be an alternative option in cases where it is difficult to apply invasive methods due to patient preference or other reasons.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İzmir Bakırçay University (Date: April 4, 2021, Decision no: 264).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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