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Original Article

Relationship between platelet-to-lymphocyte ratio and fractional flow reserve in left anterior descending artery with intermediate stenosis

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Abstract

Aim: Platelet-to-lymphocyte ratio has been used as a determinant factor for coronary artery disease. Since platelet activation is central to the initiation of atherosclerosis, our goal was to evaluate the relationship between platelet-to-lymphocyte ratio and fractional flow reserve (FFR) values in the left anterior descending artery (LAD) with intermediate coronary stenosis.

Material and Methods: The present report encompassed 173 subjects having stable angina pectoris. These subjects were categorized into 2 groups: 91 subjects with a FFR less than or equal to 0.80 and 82 patients with a FFR greater than 0.80. The platelet-to-lymphocyte ratio of each subject was determined from the complete blood count. The two groups were evaluated for differences using a Student's unpaired t-test. A p-value of <0.05 was considered statistically significant.

Results: The average platelet-to-lymphocyte ratio value of subjects with a FFR less than or equal to 0.80 were significantly higher than those with a FFR greater than 0.80 ((115.5±38.0) vs. (103.8±38.9), p=0.04). The correlation between platelet-to-lymphocyte ratio with stenosis degree was significant (r= 0.22, p= 0.003).

Conclusion: Platelet-to-lymphocyte ratio was associated with a FFR measurement of equal or less than to 0.80 in subjects with stable angina pectoris.

Keywords: Fractional flow reserve; Stable angina pectoris; Platelet-to-lymphocyte ratio; Left anterior descending artery

INTRODUCTION

Coronary angiography is routinely used to diagnose coronary artery lesions (1). Myocardial ischemia is important to determine death and myocardial infarction (MI) (2) in coronary artery disease (CAD) patients. A previous Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study highlighted the advantage of fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) over angiography in multivessel disease patients (3). Notably, FFR has been used to define the hemodynamic significance of coronary artery stenosis (4) . FFR equals 1.0 in a normal coronary artery, while an FFR value of 0.80 or lower indicates the potential for stenosis to induce myocardial ischemia (4).

Inflammation and platelet activation is central to the initiation/progression of atherosclerosis (5), while the augmented reactivity of platelets has been linked to a higher risk of MI in subjects with stable CAD (6). Moreover, lymphocyte count has been shown to be inversely proportional to inflammation, which has been associated with worse outcomes in CAD (7). Platelet-to-lymphocyte ratio (PLR) has been documented as an essential inflammatory marker (8) and has been used as a significant predictor of clinical outcomes in in cardiac disorders (9). Due to the close association between PLR and CAD severity, we hypothesized that PLR could predict physiological significant coronary artery stenosis. The aim of this report was to determine the association between PLR and significant left anterior descending (LAD) coronary stenosis by FFR.

MATERIAL and METHODS

The present study was performed from January 2014 to January 2019 and enlisted a total of 173 consecutive

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subjects having single-intermediate grade coronary stenosis (10) on their LAD artery examined using FFR measurement. The study design was retrospective and used a convenience sample of 173 patients. Subjects with stable angina pectoris (class 1 to 2 according to the Canadian Cardiovascular Society classification) were eligible for participation. Coronary angiography was performed due to an abnormal treadmill exercise test or ischemia detected using myocardial perfusion scintigraphy. Subjects were excluded if they had the following conditions: acute coronary syndrome; severe valvular regurgitation or stenosis; atrial or ventricular arrhythmia; hemodynamic instability; other lesions in the index coronary artery; circumflex or right coronary artery with a severity of ≥40% luminal narrowing; chronic total occlusion; multi vascular significant coronary diseases; a history of coronary artery by-pass grafting; inflammatory diseases (acute/chronic); acute or chronic renal failure; anemia; chronic lung disease; hepatic dysfunction or malignancy.

All coronary angiographies were performed using the percutaneous femoral approach via the Judkins method. FFR values were measured performed upon a cardiologist's recommendation. Following the intra-arterial administration of a 5,000-unit heparin bolus, the coronary artery was examined using a guide catheter without side holes. A 0.014-inch pressure monitoring guide wire was distally positioned to the stenosis after calibration. Nitroglycerin (100-200 µg) bolus was then administered intra-coronary prior to FFR evaluations. The distal intra-coronary pressure was determined at baseline, and hyperemia was triggered by applying intracoronary adenosine at gradually increasing doses until the FFR value ceased to decrease any further. FFR was reported as the ratio between the mean distal intra-coronary pressure and the mean aortic pressure at the moment during which the highest level of hyperemia was observed (11). For multiple FFR measurements, the minimum value was used. If the FFR was less than or equal to 0.80, myocardial revascularization was recommended. Medical treatment was recommended if the FFR was more than 0.80. Coronary angioplasty was performed during the same session if the lesion was suitable. Group I included subjects with an FFR value of less than 0.80, while Group II included subjects with an FFR value of greater than or equal to 0.80. The gray zone FFR was defined the values between 0.75-0.80.

Patient data and medication were determined based on the hospital record. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or requirement for antihypertensive medication. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria. Smoking included active or previous (>10 pack-years) tobacco use. Blood sampling was performed 12 hours before coronary angiography, and samples were immediately analyzed. For hemogram assessment, tubes containing ethylenediamine-tetraacetic acid was used. A complete blood count test was performed, and a biochemistry panel was measured using an auto-analyzer (Abbott Diagnostics, Inc., Abbott Park, IL, USA). The baseline PLR of patients was established by dividing their platelet count with lymphocyte level. The local ethics committee of the Adıyaman University Training and Research Hospital approved the study protocol, and informed consent was provided for each patient.

Statistical analysis

Data were analyzed using SPSS v 25.0 for Windows (Chicago, Illinois). The Kolmogorov-Smirnov test was used to ensure normally distributed continuous variables. Normally distributed variables are expressed as mean ± standard deviation (SD), while non-normally variables are given as median values with their interquartile range (IQR). The percentages are used to present the categorical variables. The two groups were evaluated for differences using a Student's unpaired t-test, or the Mann–Whitney U test for parameters with a normal or non-normal distribution. The chi-squared test was used to compare frequencies of nominal variables. In multiple comparisons, One-way analysis of variance (ANOVA) test followed by the Tukey post hoc test was used for normally distributed continuous data. For correlation analysis, the Pearson test was used. A Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cutoff level for the PLR values that best predicted hemodynamic significance of coronary artery stenosis. A p-value of <0.05 was considered statistically significant.

RESULTS

The data of study population are presented in Table 1, while angiographic data and laboratory findings are presented in Table 2. Ninety-one patients were included in Group I (mean age 61.6±9.0 and 63% male), while 82 patients were included in Group II (mean age 61.6±9.0 and 59% male). There was no difference between the groups in terms of hypertension, diabetes mellitus, history of PCI, history of MI, and smoking. The total protein and albumin values were similar between the group I and II (p >0.05). Notably, the PLR was significantly higher group I (115.57±38.08 vs. 103.89±38.91, p=0.04) (Table 2) (Figure 1). In the angiographic analysis, differences in FFR value, the degree of stenosis, minimum lumen diameters, reference vessel diameters, and lesion lengths were observed. FFR gray zone values (0.75-0.80) were compared with FFR>0.80 and FFR≤0.75 values (Table 3). PLR, the degree of stenosis, minimum lumen diameters, reference vessel diameters, and lesion lengths were similar between FFR gray zone and other FFR values. The correlation analyses between PLR and stenosis degree was significant and positive (r= 0.22, p= 0.003) (Table 4).

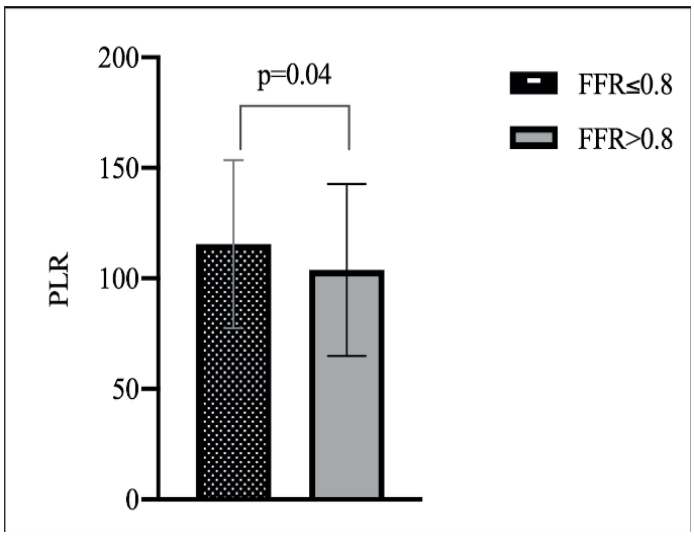

Figure 1. The PLR (Platelet-to-lymphocyte ratio) was increased in the Group I (Fractional Flow Reserve ≤0.80) compared to Group II (Fractional Flow Reserve >0.80). p value was calculated by the student's t test. p<0.05 was considered statistically significant

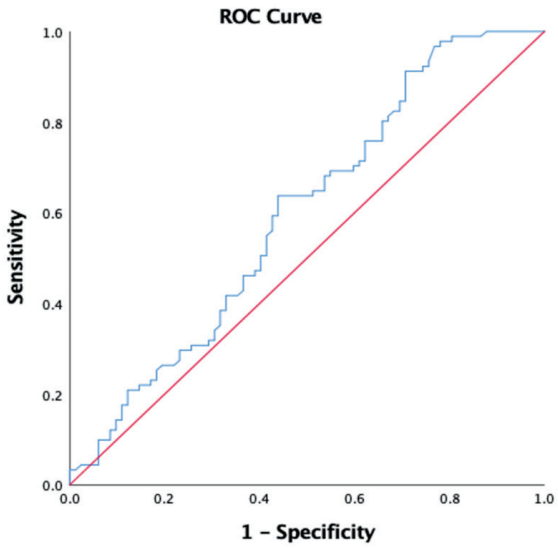

Figure 2. In ROC curve analyses, a Platelet-to-lymphocyte ratio value of 103.2 was determined as an effective cut-off point for significant fractional flow reserve with a sensitivity of 52% and a specificity of 59% (AUC=0.56 p=0.02; 95% CI (0.51-0.68)

Table 1. Baseline clinical characteristics of the study groups

	Fractional flow reserve ≤0.80 (n=91)	Fractional flow reserve >0.80 (n=82)	p
Age, years	61.6±9.0	59.4±10.7	0.15
Gender (Men), %(n)	63.7(58)	59(72)	0.24
Hypertension, %(n)	39.(36)	36(30)	0.68
Diabetes, %(n)	22(20)	18(15)	0.62
Smoking, %(n)	38(35)	50(41)	0.12
Previous MI, %(n)	15(14)	13(11)	0.71
Previous PCI, %(n)	28(26)	31(26)	0.65
Acetylsalicylic acid, %(n)	85(78)	84(69)	0.77
Beta blocker, %(n)	30(28)	40(33)	0.19
Clopidogrel, %(n)	20(19)	18(15)	0.66
ACE-inhibitors/ARB, %(n)	35(32)	35(29)	0.97
Statin, %(n)	47(43)	48(40)	0.84
Oral anti diabetic, %(n)	21(19)	15(13)	0.52
Ejection Fraction, (%)	54.6±4.9	56.0±4.2	0.05
SBP, (mm Hg)	125.1±12.7	124.8±11.2	0.88
DBP, (mm Hg)	77.6±10.8	79.7±9.5	0.18
Heart rate, (beat per minutes)	72.4±14.6	69.9±12.5	0.24

MI, myocardial infarction; ACE, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; PCI, percutaneous coronary intervention; SBP, Systolic blood pressure; DBP, diastolic blood pressure. Data are presented median mean ± standard deviation or n (%). p value was calculated by the student's t test or Chi-square test. p<0.05 was considered statistically significant

Table 2. Baseline laboratory and angiography characteristics of the study groups			
	Fractional flow reserve ≤0.80 (n=91)	Fractional flow reserve >0.80 (n=82)	p
Creatinine, (mg/dL)	0.8±0.1	0.8±0.1	0.35
Glucose, (mg/dL)	116(70-352)	109(74-252)	0.48
Total cholesterol, (mg/dL)	177.4±37.6	184.3±44.0	0.27
Triglyceride, (mg/dL)	155(91-419)	170(94-488)	0.20
LDL, (mg/dL)	110.0±30.6	108.1±28.0	0.68
HDL, (mg/dL)	37.7±8.1	37.0±7.5	0.53
Alkaline Phosphatase, (U/LI)	83.6±18.0	85.0±14.4	0.57
Total Protein, (g/dL)	6.8±0.5	6.0±0.5	0.45
Albumin, (g/dL)	3.7±0.4	3.7±0.4	0.43
White blood cell count , (103 cells/mm^3)	8.6±2.0	8.62±2.17	0.97
Hemoglobin, (g/dL)	13.2±1.6	13.9±1.8	0.53
Hematocrit (%)	41.7±4.5	43.3±4.9	0.42
Neutrophil, (103 cells/mm^3)	5.2(2.2-13.1)	4.9(2.2-11)	0.22
Platelet count, (103 cells/mm^3)	232.2±54.6	250.9±73.0	0.06
Lymphocyte, (103 cells/mm^3)	2.0±0.6	2.6±0.9	0.09
PLR	115.5±38.0	103.8±38.9	0.04
Mean platelet volume, (fL)	7.9±1.4	7.6±1.5	0.15
Platelet distribution width, (%)	18.2±3.4	18.1±3.0	0.87
Platecrit, (%)	0.15±0.11	0.15±0.06	0.90
Circumflex artery	58(53)	47(39)	0.16
Right coronary artery	38(35)	35(29)	0.67
FFR Value	0.74±0.02	0.84±0.02	**<0.01**
Stenosis Degree, (%)	75.4±10.9	64.8±12.7	**<0.01**
Minimum Lumen Diameter, (mm)	0.8±0.2	1.0±0.2	**<0.01**
Reference Diameter, (mm)	2.7±0.3	2.9±0.3	**<0.01**
Lesion length, (mm)	21.6±4.7	18.8±3.1	**<0.01**

LDL, Low-density lipoprotein cholesterol; HDL, High-density lipoprotein cholesterol; PLR, Platelet-to-lymphocyte ratio; FFR, Fractional flow reserve. Data are presented median (minimum-maximum), mean ± standard deviation or n (%). p value was calculated by the student's t test or Chi-square test. p<0.05 was considered statistically significant

Table 3. PLR and angiography characteristics according to FFR values				
	FFR ≤0.75 (n=66)	FFR 0.75-0.80 (n=25)	FFR >0.80 (n=82)	p
PLR	118.7±43.0	107.2±18.4	103.8±38.9	0.04
Stenosis Degree, (%)	76.7±10.9	72.4±10.5	64.8±12.7	<0.01
Minimum Lumen Diameter, (mm)	0.8±0.2	0.9±0.3	1.0±0.2	<0.01
Reference Diameter, (mm)	2.7±0.4	2.8±0.2	2.9±0.3	0.01
Lesion length, (mm)	21.7±4.7	21.5±5.1	18.8±3.1	<0.01

PLR, Platelet-to-lymphocyte ratio; FFR, Fractional flow reserve. Data are presented mean ± standard p value was calculated by the student's t test. In multiple comparisons, one-way analysis of variance (ANOVA) test followed by the Tukey post hoc test was used for normally distributed continuous data. p<0.05 was considered statistically significant

Table 4. Correlation between PLR and Stenosis Degree, Minimum Lumen Diameter and Lesion Length

	p	r
Stenosis Degree	0.003	0.22
Minimum Lumen Diameter	0.11	-0.11
Lesion Length	0.72	-0.02

PLR, Platelet-to-lymphocyte ratio; Pearson test was used to analyze the relationship between PLR and study variables where appropriate. correlation coefficient (r). p<0.05 was considered statistically significant

DISCUSSION

In this study, PLR was significantly elevated in subjects (FFR values of ≤0.80) with a functionally significant stenosis in the LAD. Moreover, PLR was observed to be correlated with coronary stenosis evaluated by FFR in stable CAD patients.

Notably, inflammation has been shown to serve an active role in the atherosclerosis process (12), while platelets are essential in acute coronary syndrome pathogenesis (13). Platelets can contribute to thrombocyte activation, fibrin formation, and acute MI (14). The PLR is a new prognostic factor for major cardiovascular outcomes (15) and represents the activity of hemostatic and inflammation pathways. The PLR calculation may be better for atherosclerotic coronary prediction than platelet or lymphocyte count alone. Furthermore, Yuksel et al. demonstrated that increased PLR may be related to coronary atherosclerosis severity (16). Also, Kurtul et al. noted PLR was an independent determinant for coronary artery lesion severity in acute coronary syndrome (17) . Before performing invasive procedures such as FFR, PLR may predict the severity of single-lesion coronary stenosis. These findings demonstrate that the use of PLR can complement clinical decision making for coronary stenosis patients.

MI causes symptoms and affects cardiovascular outcomes (18). However, inducible ischemia is the most important predictive element among patients with CAD (19). When objective evidence of inducible ischemia is shown and medical therapy fails, coronary revascularization is required (20). The choice of revascularization based on coronary angiogram alone is unproven (21). Angiographic stenosis severity poorly correlates with the presence of myocardial ischemia and is inferior to FFR measurements (22). According to the American Heart Association, percutaneous trans-coronary angioplasty should be performed after inducible ischemia has been documented (20). Therefore, coronary artery stenosis should align with myocardial ischemia in the revascularization process. In one FAME study, anatomic revascularization (complete functional revascularization) was superior to stenting based on using FFR values, which was effective for angina elimination (3).

Notably, FFR determines the intermediate degree of coronary stenosis, with FFR values equal to or below 0.80 pointing to significance and severity of CAD. However, FFR also has prognostic predictive value and using FFR in stable CAD improves clinical outcomes and reduces major cardiovascular events (23). Also, FFR could increase the benefit of PCI. Tonino et al. reported FFR measurement can reduce nonfatal MI, composite endpoint of death rate, and revascularization at one year in patients with multivessel CAD (3). Without ischemia, patients had a positive outcome with medical therapy. Moreover, PCI of a stenotic lesion, which does not induce ischemia (FFR >0.80), increases the probability of adverse events due to the risk of restenosis and thrombosis (24). However, the routine use of FFR may improve treatment decision making by correctly diagnosing functionally significant coronary lesions.

Many patients have been recommended for coronary angiography based on positive noninvasive tests, although existing studies have shown a poor association with the angiographic appearance of coronary stenosis (25,26). Bruyne et al. demonstrated that FFR-guided PCI improved outcomes in patients with stable CAD when compared to medical therapy alone (27). Furthermore, Muller et al. reported that medical treatment was related to excellent clinical outcomes in patients with functionally non-significant stenosis (FFR 0.80) in the proximal LAD (28). We investigated the association with FFR measurement and PLR levels and demonstrated that PLR is substantial in predicting hemodynamically significant CAD diagnosed using FFR. We assume that increased PLR might respond to augmented coronary artery lesion severity. Notably, patients with <0.80 FFR values have more cardiovascular risk factors and increased inflammatory markers, while Yılmaz et al. demonstrated that diabetes mellitus was a predictor of functionally significant coronary stenosis in stable CAD patients (29).

The present report has limitations in that it was retrospective, had a relatively small patient cohort, and was a single-center study. In addition, established inflammatory markers such as C-reactive protein were not determined, which also represents a study limitation. Also, the present study results lack long-term follow-up. Moreover, the present study was founded on a single PLR value with no temporal changes and variations in PLR. Therefore, PLR may not be a single predictor of functionally significant coronary stenosis, and the combination of some biomarkers would be favorable to form a conclusion on such an outcome. Hence, future studies are needed to determine the role of PLR values on FFR results.

CONCLUSION

In summary, this study suggests that pre-angiographic PLR is a noninvasive, inexpensive and simple biomarker which increased in patients with coronary artery stenosis. We demonstrated that PLR is associated with hemodynamic intermediate coronary stenosis severity in stable CAD patients. Moreover, PLR showed a significant association with coronary artery stenosis.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Adıyaman University Training and Research Hospital: 2018-7-9

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