ORIGINAL RESEARCH

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Correlation Between Coronary Lesion Severity Detected in Fractional Flow Reserve with Systemic Immune Inflammation Index and Atherogenic Plasma Index

Fraksiyonel Akım Rezervi Kullanılarak Saptanan Koroner Lezyon Ciddiyeti ile Sistemik İmmün Enflamasyon İndeksi ve Aterojenik Plazma İndeksi Arasındaki Korelasyon

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Abstract

Objective: Systemic immune inflammation index (SII) and atherogenic plasma index (AIP) are indices that have been defined in recent years and play an important role in the process of atherosclerosis and inflammation. In this study, we aimed to investigate the relationship between the severity of atherosclerotic lesions detected and AIP and SII in patients who underwent fractional flow reserve (FFR) in coronary angiography.

Method: In this study, 119 patients who underwent elective FFR in coronary angiography were retrospectively analyzed. According to the severity of FFR lesion, two groups were formed as FFR <0.8 group (77 patients) and FFR >0.8 group (42 patients). SII, AIP, demographic data and other parameters were compared between the two groups.

Results: In the FFR applied groups, there was a statistically significant difference between the two groups in terms of high-density lipoprotein (p=0.001), platelet (p=0.007), mean platelet volume (MPV) (p=0.016), monocytes (p<0.001), lymphocyte (p<0.001), SII (p<0.001), AIP (p=0.009) and HbA1c (p<0.001). In the univariable regression analysis, we found that HbA1c [odds ratio (OR): 10; 95% confidence interval (CI): 3.2-3.5, p<0.001], monocytes (OR: 273.8; 95% CI: 24.8-3015.3, p<0.001), MPV (OR: 0.6; 95% CI: 0.39-0.91, p=0.02), SII (OR: 1.06; 95% CI: 1.03-1.09, p<0.001) and AIP (OR: 3.7; 95% CI: 1.6-10, p=0.01) parameters were predictors. In the multivariable regression analysis, we found that HbA1c (OR: 9.41; 95% CI: 1.89-46.73, p=0.006), monocytes (OR: 108.2; 95% CI: 6.8-1726.2,

Öz

Amaç: Sistemik immün enflamasyon indeksi (SII) ve aterojenik plazma indeksi (AIP) son yıllarda tanımlanmış, ateroskleroz ve enflamasyon sürecinde önemli rol alan indekslerdir. Bu çalışmamızda koroner anjiyografide fraksiyonel akış rezervi (FFR) uygulanan hastalarda, tespit edilen aterosklerotik lezyon ciddiyeti ile AIP ve SII arasındaki ilişkiyi araştırmayı amaçladık.

Yöntem: Bu çalışma kapsamında, koroner anjiyografide elektif FFR işlemi uygulanan 119 hasta retrospektif olarak incelendi. FFR lezyon ciddiyetine göre; FFR <0,8 grup (77 hasta), FFR >0,8 grup (42 hasta) şeklinde iki grup oluşturuldu. İki grup arasında SII, AIP, demografik veriler ve diğer parametreler karşılaştırıldı.

Bulgular: FFR uygulanan gruplarda yüksek yoğunluklu lipoprotein (p=0,001), platelet (p=0,007), ortalama trombosit hacmi (MPV) (p=0,016), monosit (p<0,001), lenfosit (p<0,001), SII (p<0,001), AIP (p=0,009) ve HbA1c (p<0,001) açısından iki grup arasında istatistiksel olarak anlamlı derecede farklılık saptandı. Yapılan tek değişkenli regresyon analizinde HbA1c [olasılık oranı (OO): 10; %95 güven aralığı (GA): 3,2-3,5, p<0,001], monosit (OO: 273,8; %95 GA: 24,8-3015,3, p<0,001), MPV (OO: 0,6; %95 GA: 0,39-0,91, p=0,02), SII (OO: 1,06; %95 GA: 1,03-1,09, p<0,001) ve AIP'nin (OO: 3,7; %95 GA: 1,6-10, p=0,01) birer prediktör olduğu saptandı. Yapılan çok değişkenli regresyon analizinde ise HbA1c (OO: 9,41; %95 GA: 1,89-46,73, p=0,006), monosit (OO: 108,2; %95 GA: 6,8-1726,2, p=0,001) ve

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p=0.001) and SII (OR: 1.005; 95% CI: 1.002-1.008, p=0.004) parameters were independent predictors. With the applied ROC analysis, SII predicted FFR lesion severity with 75% sensitivity and 72% specificity [area under the curve (AUC): 0.79; 95% CI: 0.72-0.87, p<0.001], and AIP with 62% sensitivity and 60% specificity (AUC: 0.64; 95% CI: 0.54-0.75, p=0.008).

Conclusion: In this study, we would like to emphasize that simple, fast and low-cost methods such as AIP and SII may be parameters related to lesion severity detected in FFR. These parameters are easily accessible, reproducible and widely used.

Keywords: Atherogenic plasma index, coronary angiography, fractional flow reserve, systemic immune inflammation index

SII (OO: 1,005; %95 GA: 1,002-1,008, p=0,004) parametrelerinin bağımsız birer prediktör olduğu saptandı. Uygulanan ROC analizi ile SII %75 sensitivite %72 spesifite ile [eğrinin altındaki alan (AUC): 0,79; %95 GA: 0,72-0,87, p<0,001], AIP %62 sensitivite %60 spesifite ile (AUC: 0,64; %95 GA: 0,54-0,75, p=0,008) FFR lezyon ciddiyetini öngörmekteydi.

Sonuç: Bu çalışmamızda özellikle AIP ve SII gibi basit, hızlı ve düşük maliyetli yöntemlerin, FFR'de saptanan lezyon ciddiyeti ile ilişkili parametreler olabileceğine vurgu yapmak istiyoruz. Bu parametreler kolay ulaşılabilir, tekrarlanabilir ve yaygın olarak kullanılabilmektedirler.

Anahtar kelimeler: Aterojenik plazma indeks, fraksiyonel akış rezervi, koroner anjiyografi, sistemik immün enflamasyon indeks

Introduction

Cardiovascular diseases associated with atherosclerosis are still the leading cause of death worldwide (1). Coronary angiography (CAG) is the most important diagnostic method in the evaluation of coronary artery lesions. However, the visual assessment of the severity of the lesion in the coronary arteries by CAG is not always reliable. It is important to measure fractional flow reserve (FFR) in the coronary arteries, especially when the level of stenosis is 40-70% (i.e., moderate). FFR is a reliable method especially for the functional assessment of lesion severity (2). Coronary atherosclerosis formation is multifactorial and atheromatous plaque is affected by many parameters (3). In some studies, the importance of triglycerides in atherosclerosis has been emphasized (4). A high triglyceride concentration stimulates the activity of the cholesteryl ester transfer protein. This enables the lipoprotein particles to be enriched with triglycerides, making them better substrates for lipolysis. This leads to more high-density lipoprotein (HDL) catabolism and more low-density lipoprotein (LDL) particles to form (5). In addition to the atherogenic plasma index (AIP) serum cholesterol levels, cholesterol esterification rates are based on the relationship of lipoprotein particle size and residual lipoproteinemia. And this index has been shown to be a marker of plasma atherogenicity (6,7). However, data on changes in coronary atherosclerosis depending on AIP levels are limited. It is known to be effective in the formation of atherosclerosis and inflammation as well as lipid parameters. Therefore, parameters associated with inflammation have often been the subject of research. These parameters are mostly hematological inflammatory markers such as platelets, neutrophils and/or lymphocyte cells. Among them, platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) are some inflammation markers that can be easily obtained by looking at the complete blood count. The association of these markers with mortality and adverse clinical outcomes in cardiovascular diseases has been reported (8). Previous studies have revealed that PLR and NLR correlate with the anatomical severity of atherosclerotic lesions in the coronary arteries (9). In addition, it has been reported to be associated with hemodynamically severe coronary artery stenosis (10). The systemic immune inflammation index (SII) is a new definition that combines these three hemogram parameters and is an indicator of inflammation. SII is an important marker of adverse clinical outcomes in many cancer types (11). In addition, in a recent study, SII was reported to be a marker for functionally severe coronary stenosis in patients with a diagnosis of chronic coronary syndrome (12).

In this study, we aimed to examine the relationship between the severity of atherosclerotic stenosis and AIP and SII in patients evaluated with FFR in CAG.

Materials and Methods

Study Population

This study was planned as a retrospective, single-center study. Within the scope of the study, patients who underwent CAG at Dicle University Faculty of Medicine between January 2013 and November 2019 were examined. Patients with angina unresponsive to medical treatment and stable angina pectoris, who showed high-risk markers in non-invasive imaging methods, were analyzed consecutively. Among these patients, 119 consecutive patients who underwent elective FFR were included in the study. Inclusion criteria for the study were determined as patients who were evaluated as stable angina pectoris and underwent FFR procedure under elective conditions. Exclusion criteria included patients with acute coronary syndrome, severe arrhythmia, hemodynamic instability, previous history of revascularization (percutaneous coronary intervention

or coronary artery bypass graft), moderate/severe heart valve pathology, acute decompensated and/or severe heart failure patients with severe kidney and liver failure, active infection, malignancy, hematological diseases, patients receiving steroid therapy, familial history of hyperlipidemia, rheumatological disease, life expectancy <1 year, age <18 and >90 years. A signed informed consent form was obtained from each patient participating in the study. The study was designed in accordance with the principles of the Declaration of Helsinki. Our clinical study was approved by the ethics committee of İzmir Bakırçay University with the date of 29.04.2021 and number 264.

Demographic and Laboratory Data

Venous blood samples were obtained from all patients included in the study after they were admitted to our cardiology clinic, and after an overnight fasting period. Blood was drawn from the anterior surface of the forearm in the supine position. For complete blood count, blood was drawn into tubes containing standard EDTA and measurements were made immediately after blood collection. Measurements of lipid levels were made in serum separated by centrifugation at 3000 rpm at room temperature. Total cholesterol, triglyceride, and HDL were evaluated in Konnelab kits, Konnelab 60i and Thermo Clinical Labsystems (Thermo Clinical Labsystems Oy Ratostic 2, Vantae, Finland) devices. LDL cholesterol levels in patients were calculated with the Friedewald formula. Drugs used by the patients, demographic and echocardiographic data were obtained from hospital records.

Definitions

Hypertension (HT) was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure ≥90 mmHg or using antihypertensive medication. Hyperlipidemia was defined as a total cholesterol level >200 mg/dL or an LDL level >130 mg/dL. Smoking was defined as currently smoking in the past 6 months. AIP was obtained by applying logarithmic transformation to the triglyceride/HDL ratio (13). SII was determined as the ratio of absolute platelet count x absolute neutrophil count/absolute lymphocyte count (14).

CAG and FFR

Selective CAG was performed on the patients with a right-left femoral or radial approach, using 6F or 7F catheters with the Judkins technique. CAG images were evaluated by two experienced cardiologists, who were unaware of the laboratory values and clinical features of the patients. The degree of stenosis in the coronary arteries was decided on the basis of the projection showing the greatest stenosis. Evaluation by applying the FFR was left to the discretion and discretion of the cardiologists. After an intra-arterial bolus of 5000 units of heparin, the coronary arteries were visualized using a guide catheter without side holes. A 0.014 inch pressure monitoring guidewire (PrimeWire, Volcano, San Diego, CA, USA) was placed distal to the stenosis after calibration. Before FFR measurements, 200 µg bolus nitroglycerin was administered intracoronally. Initially, distal intracoronary pressures of the patients were recorded. Hyperemia was triggered by administering gradually increasing doses of intracoronary adenosine until the last value where the FFR value decreased. FFR value was determined as the ratio between the mean distal intracoronary pressure and the mean aortic pressure, at which time the highest level of hyperemia was observed. An FFR value of <0.80 was defined as functionally significant. According to FFR lesion severity, two groups were formed, as FFR <0.8 group (77 patients) and FFR >0.8 group (42 patients).

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) software version 25.0 for Windows (IBM Co., Armonk, NY, USA). The conformity of numerical variables to the normal distribution was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Numerical variables are given as mean and standard deviation. In order to compare the two groups in terms of numerical variables, the independent samples t-test was used if normal distribution was achieved, and the Mann-Whitney U test was used if not. Categorical variables were shown as numbers (n) and ratios (%). The relationship between categorical variables was examined with the Pearson chi-square and Fisher's Exact tests. Relationships between SII and AIP were evaluated using the Spearman's RHO analysis. The power of SII and AIP values in predicting FFR lesion severity was evaluated with univariable and multivariable analyses. Odds ratio (OR) and 95% confidence interval (CI) values were recorded. In addition, ROC analysis was performed for SII and AIP cut-off values. Cut-off value was determined according to Youden index. Descriptive data were expressed as mean ± standard deviation values for normally distributed continuous variables, and median (minimum-maximum) values for non-normally distributed variables. The significance level for all hypotheses was accepted as <0.05.

G Power 3.1.9.7 programme was used for the sample size calculation. Estimated sample size was calculated using the Student's t-test with 0.95 (1-β err probe) power, α=0.05 error level and Cohen (d) effect size =0.8. Accordingly, it was found appropriate to complete the study with at least 70 (group 1 =35 patients, group 2 =35 patients) patients. G Power 3.1.9.7 programme was used for post-hoc power. Difference between two independent means tests was applied. The power (1-β err probe) was determined as 0.993 with alpha 0.05 error level, Cohen (d) effect size =0.8.

Results

Patients included in the study were divided into groups as group-I: FFR>0.8; group-II, with FFR<0.8. The mean age of the patients included in the study was 58.3 (±9.8) years, and 66.4% of them were male. When the means of age and gender were compared between the groups, there was no statistically significant difference [57.9 (±10.2) vs. 58.4 (±9.6), p=0.764; 71.4% vs. 63.6%, p=0.390, respectively]. 94.1% of the patients were in the NYHA class-I category. The most common symptoms among the patients included in the study were chest pain and shortness of breath (90.8% and 21%, respectively). Between the two groups, no significant difference was found in terms of smoking (33.4% versus 42.9%, p=0.310), HT (47.6% versus 39%, p=0.36), coronary artery disease (CAD) (50% versus 54.5%, p=0.635), and hyperlipidemia (57.1% vs 50.6%, p=0.498) (Table 1). Other demographic data and comorbid diseases between the groups are given in Table 1.

When the biochemical and hemogram parameters were examined, there was a statistically significant difference between the two groups in terms of HDL (p=0.001), platelet (p=0.007), MPV (p=0.016), monocytes (p<0.001), lymphocyte (p<0.001), SII (p<0.001), AIP (p=0.009) and HbA1c (p<0.001). When the left ventricular ejection fraction values [53.3 (±8.4) vs. 54.7 (±7.9), p=0.356] were compared, there was no statistically significant difference between the two groups (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. The results of the CAG data are shown in Table 4.

In the univariable regression analysis performed among the factors affecting the severity of the lesion detected in FFR, we found that HbA1c (OR: 10; 95% CI: 3.2-3.5, p<0.001), monocytes (OR: 273.8; 95% CI: 24.8-3015.3, p<0.001), MPV (OR: 0.6; 95% CI: 0.39-0.91, p=0.02), SII (OR: 1.06; 95% CI: 1.03-1.09, p<0.001) and AIP (OR: 3.7; 95% CI: 1.6-10, p=0.01) parameters were each a predictor. In the multivariable regression analysis, we found that HbA1c (OR: 9.41; 95% CI: 1.89-46.73, p=0.006), monocytes (OR: 108.2; 95% CI: 6.8-1726.2, p=0.001) and SII (OR: 1.005; 95% CI: 1.002-1.008, p=0.004) parameters were each an independent predictor (Table 5).

ROC analysis was used to reveal the power of SII and AIP parameters to predict lesion severity detected in FFR. According to the results obtained, SII predicted FFR lesion severity with 75 % sensitivity and 72% specificity (AUC: 0.79; 95% CI: 0.72-0.87, p<0.001), and AIP with 62% sensitivity and 60% specificity (AUC: 0.64; 95% CI: 0.54-0.75, p=0.008) (Figure 1).

Discussion

In this study, SII, a new marker that includes neutrophil, platelet, and lymphocyte counts, as well as AIP, a marker that includes triglycerides and HDL, were independently associated with coronary artery lesions, which were evaluated by FFR measurement and considered functionally significant. In addition, SII was superior to AIP in predicting hemodynamically significant coronary obstruction. FFR is a technique that guides the operator in the decision of percutaneous intervention in moderate to severe lesions during CAG (15). Functionally severe coronary stenosis is associated with ischemia in addition to adverse clinical outcomes (16). Therefore, in this study, FFR measurements were used to identify hemodynamically severe lesions, instead of visually evaluating them in angiography.

It is known that atherosclerosis and inflammation are in a cause-effect relationship. Many inflammatory parameters have a role from the onset of CAD to its progression (17). Neutrophils, lymphocytes and platelet cells play an important role in this process (17,18). Neutrophil infiltration into endothelial tissue initiates the atherosclerotic process, and this is the event that initiates increased damage to the endothelium. In addition, neutrophil cells secrete parameters and markers related to acute inflammation after tissue damage (18). It has been described that low lymphocyte cell counts in the blood cause CAD and adverse clinical outcomes (19). When chronic inflammation develops in the body, a decrease in the number of lymphocyte cells occurs in response to the stress process (19). Lymphocytes are often the regulators of the immune system and have positive contributions to the immune system. On the contrary, neutrophils are associated with negative events in the inflammatory response (20). Platelets are cells that play

Table 1. Demographic and comorbid characteristic results

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
Age, (years)	57.9 (±10.2)	58.4 (±9.6)	58.3 (±9.8)	0.764
Male sex, n (%)	30 (71.4)	49 (63.6)	79 (66.4)	0.390
SBP, mmHg	129.3 (±16.8)	127.7 (±16.5)	128.3 (±16.5)	0.614
DBP, mmHg	70.7 (±10.6)	70.6 (±10.2)	70.7 (±10.3)	0.964
Heart rate, minute	75.7 (±12.1)	73.7 (±12.5)	74.4 (±12.3)	0.403
NYHA class I, n (%)	41 (97.6)	71 (92.2)	112 (94.1)	0.231
Chest pain, n (%)	36 (85.7)	72 (93.5)	108 (90.8)	0.161
Dyspnea, n (%)	10 (23.8)	15 (19.5)	25 (21.0)	0.580
Palpitation, n (%)	10 (23.8)	5 (6.5)	15 (12.6)	**0.007**
Tiredness, n (%)	7 (16.7)	4 (5.2)	11 (9.2)	**0.039**
Dizziness, n (%)	3 (7.1)	4 (5.2)	7 (5.9)	0.666
Syncope, n (%)	0 (0)	1 (1.3)	1 (0.8)	0.458
Smoking, n (%)	14 (33.4)	33 (42.9)	47 (39.5)	0.310
Alcohol use, n (%)	1 (2.4)	4 (5.2)	5 (4.2)	0.465
Hypertension, n (%)	20 (47.6)	30 (39.0)	50 (42.0)	0.360
CAD, n (%)	21 (50.0)	42 (54.5)	63 (52.9)	0.635
Hyperlipidemia, n (%)	24 (57.1)	39 (50.6)	63 (52.9)	0.498
COPD, n (%)	8 (19.0)	11 (14.3)	19 (16.0)	0.498
Thyroid disease, n (%)	4 (9.5)	6 (7.8)	10 (8.4)	0.745
Stroke/TIA, n (%)	1 (2.4)	6 (7.8)	7 (5.9)	0.231
CKD, n (%)	1 (2.4)	2 (2.6)	3 (2.5)	0.943
Peripheral artery disease, n (%)	1 (2.4)	4 (5.2)	5 (4.2)	0.465
Pacemaker/ICD/CRT, n (%)	0 (0)	2 (2.6)	2 (1.7)	0.292
Malignancy, n (%)	1 (2.4)	1 (1.3)	2 (1.7)	0.661
Anemia, n (%)	1 (2.4)	2 (2.6)	3 (2.5)	0.943

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

a serious role in inflammation and atherogenesis as well as thrombosis. Therefore, it is associated with these three pathological events and acts as a bridge. It also mediates the recruitment of leukocytes and progenitor cells to damaged sites in vascular tissue. In addition, these parameters reveal chemokines together with cytokines that mediate vascular inflammation (21). Biomarkers obtained using these three parameters have been the subject of extensive research in recent years, as they are inexpensive, easy to calculate and easy to obtain. In a study conducted, it has been reported that high mean platelet volume/lymphocyte ratio and mean platelet volume/platelet ratio are associated with mortality in patients with GFR <60 mL/min and admitted with the diagnosis of acute myocardial infarction (22). SII, which is formulated by considering neutrophil, thrombocyte and lymphocyte parameters, has been defined and researched recently. It reveals the relationship between the inflammatory process and the immune system status (11). SII has also been used as a prognostic marker in many cardiovascular diseases and malignancies (9,14,23). Recently, Yang et al. (24) reported that higher SII values were associated with CAD, myocardial infarction, and stroke. They also found that SII was a better predictor than traditional markers (24). Consistent with these studies and available data, we demonstrated a strong association with the severity of coronary artery stenosis, and assessed it using the SII FFR method.

In addition to inflammatory parameters, abnormal lipid metabolism also plays a serious role in the progression of coronary atherosclerosis, formation of calcified plaque and unstable plaque formation (25). Lipid deposition in the vascular intima layer is a very important event in the emergence and progression of the atherosclerotic process. In a study conducted, high monocyte/HDL ratio

Table 2. Hemogram, biochemical and echocardiographic results

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
Urea, mg/dL	33.80 (±13.32)	34.02 (±10.52)	33.94 (±11.53)	0.921
Creatinine, mg/dL	1.07 (±0.99)	0.89 (±0.20)	0.95 (±0.61)	0.123
Uric acid, mg/dL	5.54 (±1.02)	5.28 (±0.89)	5.37 (±0.94)	0.162
Total cholesterol, mg/dL	190.55 (±52.37)	198.73 (±44.18)	195.84 (±46.57)	0.362
Triglyceride, mg/dL	156.72 (±84.62)	184.18 (±129.09)	174.49 (±115.74)	0.218
HDL, mg/dL	44.10 (±10.86)	37.51 (±9.39)	39.83 (±10.38)	**0.001**
LDL, mg/dL	112.67 (±53.60)	128.66 (±83.30)	123.10 (±74.48)	0.269
Hemoglobin, g/dL	13.56 (±1.29)	13.56 (±1.54)	13.56 (±1.45)	0.981
Platelet, $x10^3$/µL	243.19 (±46.54)	277.65 (±72.91)	265.49 (±66.71)	**0.007**
Leukocyte, $x10^3$/µL	8.63 (±2.42)	8.44 (±1.55)	8.50 (±1.89)	0.593
MPV, fL	8.72 (±0.89)	8.29 (±0.92)	8.44 (±0.93)	0.016
Neutrophil, $x10^3$/µL	4.80 (±1.68)	5.27 (±1.53)	5.10 (±1.59)	0.123
Monocyte, $x10^3$/µL	0.72 (±0.20)	0.95 (±0.21)	0.87 (±0.23)	**<0.001**
Lymphocyte, $x10^3$/µL	2.88 (±1.04)	2.11 (±0.53)	2.38 (±0.83)	**<0.001**
Fasting glucose, mg/dL	97.93 (±10.83)	99.56 (±10.95)	98.98 (±10.89)	0.438
TSH, µIU/Ml	2.03 (±1.37)	2.18 (±1.49)	2.12 (±1.45)	0.588
T4, ng/dL	1.37 (±0.40)	1.45 (±0.50)	1.42 (±0.47)	0.319
Calcium, mg/dL	9.31 (±0.55)	9.38 (±0.58)	9.36 (±0.57)	0.578
Sodium, mmol/L	137.21 (±15.64)	140.81 (±13.43)	139.54 (±14.29)	0.191
Potassium, mmol/L	4.47 (±0.48)	4.39 (±0.49)	4.42 (±0.49)	0.429
AST, U/L	26.07 (±19.32)	24.69 (±15.03)	25.18 (±16.60)	0.666
ALT, U/L	23.02 (±10.17)	20.19 (±8.28)	21.19 (±9.04)	0.103
SII	426.61 (±152.41)	753.29 (±428.16)	637.99 (±388.23)	**<0.001**
AIP	0.52 (±0.25)	0.65 (±0.25)	0.60 (±0.26)	**0.009**
HbA1c, %	5.56 (±0.39)	5.98 (±0.59)	5.83 (±0.56)	**<0.001**
Sinus rhythm, n (%)	42 (100)	71 (92.2)	113 (95.0)	0.063
LVEF, %	53.3 (±8.4)	54.7 (±7.9)	54.2 (±8.0)	0.356
LVEDD, cm	48.45 (±5.31)	47.08 (±4.91)	47.56 (±5.07)	0.159
LVESD, cm	30.93 (±6.42)	28.56 (±5.45)	29.39 (±5.90)	**0.036**
LVDD, n (%)	26 (61.9)	55 (71.4)	81 (68.1)	0.287

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MPV: Mean platelet volume, TSH: Thyroid stimulating hormone, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SII: Systemic immune inflammation index, AIP: Atherogenic plasma index, HbA1C: Hemoglobin A1c, LVEF: Left Ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter; LVDD: Left ventricular diastolic dysfunction, Group I: FFR>0.8, Group II: FFR<0.8

Table 3. Results of drugs used by patients

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
Beta-blockers, n (%)	24 (57.1)	48 (62.3)	72 (60.5)	0.580
ACE-I, n (%)	9 (21.4)	25 (32.5)	34 (28.6)	0.203
Statine, n (%)	26 (61.9)	41 (53.2)	67 (56.3)	0.363
Antiaggregant, n (%)	28 (66.7)	52 (67.5)	80 (67.2)	0.923
Anticoagulant, n (%)	2 (4.8)	6 (7.8)	8 (6.7)	0.528
ARBs, n (%)	8 (19.0)	12 (15.6)	20 (16.8)	0.629
Dihydropyridine CCB, n (%)	7 (16.7)	11 (14.3)	18 (15.1)	0.729
Loop diuretic, n (%)	3 (7.1)	12 (15.6)	15 (12.6)	0.185
Aldosterone antagonist, n (%)	3 (7.1)	8 (10.4)	11 (9.2)	0.559
Thiazide diuretic, n (%)	5 (11.9)	20 (26.0)	25 (21.0)	0.072
Non-dihydropyridine CCB, n (%)	0 (0)	4 (5.2)	4 (3.4)	0.133

ACE-I: Angiotensin converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCB: Calcium channel blockers, Group I: FFR>0.8, Group II: FFR<0.8

was found to be significant in predicting mixed plaques in asymptomatic intermediary carotid artery stenosis (26). In addition, AIP predicts CAD; triglyceride is more valuable than LDL, HDL and total cholesterol (27). An increase in the AIP value leads to a decrease in LDL particle, an increase in the emergence of foam cells. It has also been reported that there is an increase in the ratio of small dense low-density lipoprotein-cholesterol (sdLDL), which is a marker supporting the development of atherosclerotic plaque (28). Studies show that the AIP value is the determining factor and parameter in the atherosclerotic process and cardiovascular diseases (29). Onat et al. (30) have reported that high AIP is a risk factor for CAD in both men and women in the Turkish population. In another recent study, AIP revealed that increases in monocyte/lymphocyte ratio and triglyceride-glucose index were strong markers and indices associated with subclinical CAD (31). In a previous study, we revealed that the AIP value might be an indicator of the level of collateral development in patients with chronic coronary occlusion (32). In the light of all these findings, the result we obtained in the study is compatible with the data in the literature. In addition, in a previously published study, we demonstrated a strong correlation between HbA1c value and FFR lesion severity (33). These parameters are important in terms of showing them as predictors in the process of atherosclerosis, since they are inexpensive and easily accessible and they are obtained from blood tests. Researching these markers in newly defined indexes

Table 4. Coronary angiography results

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
LMCA	2 (4.8)	2 (2.6)	4 (3.4)	0.58
LAD proximal	12 (28.6)	22 (28.5)	34 (28.6)	1.0
LAD mid	16 (38.1)	30 (39)	46 (38.7)	0.92
LAD distal	1 (2.4)	5 (6.5)	6 (5)	0.32
Cx proximal	5 (11.9)	5 (6.5)	10 (8.4)	0.30
Cx mid	3 (7.1)	5 (6.5)	8 (6.7)	0.89
Cx distal	1 (2.4)	0	1 (0.8)	0.17
RCA proximal	1 (2.4)	4 (5.2)	5 (4.2)	0.46
RCA mid	1 (2.4)	3 (3.9)	4 (3.4)	0.66
RCA distal	0	1 (1.3)	1 (0.8)	0.45

LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, Group I: FFR>0.8, Group II: FFR<0.8

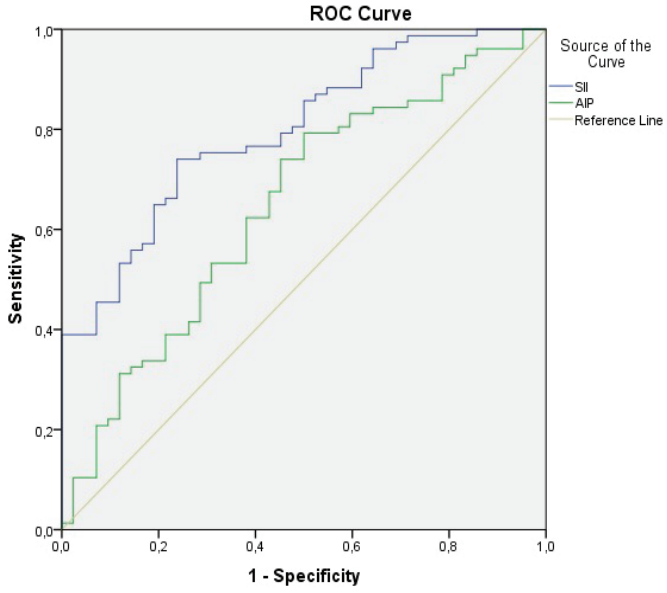

Figure 1. The cut-off values of SII and AIP associated with FFR in the ROC curve analysis

SII: Systemic immune inflammation index, AIP: Atherogenic plasma index, FFR: Fractional flow reserve

Table 5. Univariable and multivariable regression analyses for determining predictor of FFR lesion severity

Parameters	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.006 (0.96-1.04)	0.76	-	-
Gender	1.42 (0.63-3.22)	0.39		
Hypertension	0.7 (0.32-1.5)	0.36	-	-
Hyperlipidemia	1.2 (0.6-2.7)	0.49	-	-
LVEF	1.02 (0.97-1.07)	0.35	-	-
HbA1c	10 (3.2-3.5)	**<0.001**	9.41 (1.89-46.73)	**0.006**
Monocyte	273.8 (24.8-3015.3)	**<0.001**	108.2 (6.8-1726.2)	**0.001**
MPV	0.6 (0.39-0.91)	**0.02**	0.85 (0.45-1.58)	0.600
SII	1.06 (1.03-1.09)	**<0.001**	1.005 (1.002-1.008)	**0.004**
AIP	3.7 (1.6-10)	**0.01**	6.73 (0.68-66.70)	0.103

LVEF: Left ventricular ejection fraction, HbA1C: Hemoglobin A1c, MPV: Mean platelet volume, SII: Systemic immune inflammation index, AIP: Atherogenic plasma index, OR: Odds ratio, CI: Confidence interval, FFR: Fractional flow reserve

instead of evaluating them separately increases the power of studies in this field.

Study Limitations

Our study has some limitations as well as strengths. The study was designed retrospectively. The number of patients included in the study was relatively small. Prospective studies with larger numbers of patients are needed. Many other important markers of inflammation, such as CRP and albumin, were not used in this study (it is unlikely to conduct a study that could include and examine all types of inflammation markers). Our analyses were based on a single value of platelets, neutrophils, lymphocytes, triglycerides, and HDL. In other words, we did not examine temporal changes and variations in these inflammatory parameters.

Conclusion

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

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Ethics

Ethics Committee Approval: Our clinical study received ethics committee approval on 29.04.2021 from İzmir Bakırçay University, with the number 264.

Informed Consent: Verbal and written consent was obtained from all patients.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.G., Concept: T.G., Design: M.K., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., Literature Search: T.G., Writing: T.G.

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