DOI: 10.4274/terh.galenos.2022.36675
J Tepecik Educ Res Hosp 2023;33(2):203-9

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Relationship Between Systemic Immune-inflammation Index and Coronary Slow Flow

Sistemik İmmün-enflamasyon İndeksi ile Koroner Yavaş Akım Arasındaki İlişki

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Cite as: Duran M. Özen MB. Relationship Between Systemic Immune-inflammation Index and Coronary Slow Flow. J Tepecik Educ Res Hosp 2023;33(2):203-9

Abstract

Objective: The coronary slow flow (CSF) phenomenon is frequently observed during coronary angiography (CAG) and is associated with adverse cardiac events. Despite various known underlying factors, the pathophysiology is still poorly understood. The previously documented systemic immune-inflammation index (SII) is an infallible predictor of adverse events in multiple cardiovascular conditions. However, the relationship between SII and CSF has yet to be determined. Herein, we aimed to elucidate the relationship between SII and CSF.

Methods: The records of 162 patients who underwent CAG with the preliminary diagnosis of stable angina pectoris and detected CSF between January 1, 2021 and December 31, 2021 and 272 patients who did not detect CSF after CAG were retrospectively reviewed. For each group; demographic and clinical characteristics, laboratory values, and two-dimensional quantitative coronary angiographic measurements were analyzed. Epicardial coronary blood flow was quantified visually using the thrombolysis in myocardial infarction frame count method.

Results: According to our data, the calculated SII score was significantly higher in patients with CSF compared with control subjects (719±20 vs 590±2, p<0.01). Regarding the receiver operating characteristic curve, the optimal cut-off value was calculated as 612.4 using the Youden index (area under the curve: 0.751, 95% confidence interval: 0.699-0.804, p<0.001). The multivariate Cox regression model also showed that in the calculated predictors, SII was the best predictor of CSF.

Conclusion: Our data showed that SII is an independent predictor of CSF among patients with stable angina pectoris.

Keywords: Coronary slow flow, thrombolysis in myocardial infarction frame count, systemic immune-inflammation index

Öz

Amaç: Koroner yavaş akım (KYA) fenomeni, koroner anjiyografi (KAG) sırasında sıklıkla gözlemlenen ve olumsuz kardiyak olaylarla ilişkili bir durumdur. Altta yatan faktörlere rağmen, hastalığın patofizyolojisi hala tam olarak anlaşılamamıştır. Son zamanlarda tanımlanan sistemik immün-enflamasyon indeksinin (Sİİ), çeşitli kardiyovasküler durumlarla ilişkili olumsuz sonuçların güvenilir bir göstergeci olduğu bildirilmektedir. Bununla birlikte KYA ve Sİİ arasındaki ilişki tam olarak belirlenmemiştir. Bu çalışmada, KYA ve Sİİ arasındaki ilişkiyi aydınlatmaya çalıştık.

Yöntem: 1 Ocak 2021 ile 31 Aralık 2021 tarihleri arasında stabil anjina pektoris ön tanısı ile KAG uygulanan ve KYA saptanan 162 hasta ile KAG sonrası KYA saptanmayan 272 hastanın kayıtları retrospektif olarak incelendi. Her grup için; demografik ve klinik özellikler, laboratuvar değerleri ve iki boyutlu kantitatif

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Received/Geliş tarihi: 22.01.2022
Accepted/Kabul tarihi: 14.04.2022

Öz

koroner anjiyografik ölçümleri analiz edildi. Epikardiyal koroner kan akımı, miyokard enfarktüsünde tromboliz çerçeve sayımı (TIMI) yöntemi kullanılarak görsel olarak ölçüldü.

Bulgular: Verilerimize göre hesaplanan Sİİ skoru KYA tespit edilen hastalarda kontrol grubuna göre anlamlı derecede yüksekti (719±20 vs 590±2, p<0,01). Alıcı işletim karakteristiği eğrisi ile bakıldığında, en iyi kestirim değeri Youden indeksi kullanılarak 612,4 olarak belirlenmiştir (eğri altındaki alan: 0,751, %95 güven aralığı: 0,699-0,804, p<0,001). Cox çok değişkenli regresyon analizi de hesaplanan parametreler arasında Sİİ'nin KYA'yı en iyi öngörücüsü olduğunu gösterdi.

Sonuç: Verilerimiz stabil anjina pektorisli hastalarda Sİİ'nin KYA'yı bağımsız bir belirleyicisi olduğunu göstermektedir.

Anahtar Kelimeler: Koroner yavaş akım, miyokard enfarktüsünde tromboliz çerçeve sayısı, sistemik immün-enflamasyon indeksi

Introduction

Coronary slow flow (CSF) is defined as the visibly decreased flow rate of contrast opacification in one or more specified segments of the coronary arterial circulation without angiographic evidence of epicardial vessel obstruction[1,2]. This phenomenon is quantitatively assessed using the corrected thrombolysis in myocardial infarction (TIMI) frame count[3]. In addition, secondary conditions that complicate the process of diagnosis such as valvular heart disease, coronary artery spasm and ectasia, connective tissue disorders, and heart failure must be excluded[2,4,5]. Previous studies have shown that the incidence of CSF ranged between 1 % and 5.5% among patients who underwent coronary angiography (CAG) and was associated with adverse cardiac events including recurrent angina, unnecessary hospital admissions, prolongation of QT interval, and life-threatening ventricular arrhythmias[6-9]. Although the underlying factors contributing to the development of CSF are still poorly understood, endothelial dysfunction, thrombocyte dysfunction, oxidative stress, vasomotor dysfunction, and systemic and local inflammation play a substantial role in the pathogenesis of CSF[10,11].

Recently, a new prognostic biomarker has been identified to determine the inflammatory and immune status of patients: "the systemic immune-inflammation index (SII)", calculated based on platelet count neutrophil/lymphocyte ratio[12]. SII was reported to be a reliable indicator of poor outcomes in malignant diseases and associated with adverse outcomes in various cardiovascular conditions[13-16]. However, the relationship between SII and CSF has yet to be determined. Therefore, in this study, we aimed to elucidate the relationship between SII and CSF.

Materials and Methods

Study Population

We reviewed the database of our hospital and enrolled 864 patients who underwent CAG between January 1, 2021 and December 31, 2021 due to stable angina pectoris. All patients had chest pain and CAG was indicated due to an objective evidence of ischemia, including a positive exercise stress test or radionuclide study positive noninvasive test. Demographic and clinical characteristics of patients and indications for the procedure were retrospectively analyzed. Patients with a prior history of congestive heart failure, moderate to severe valvular heart disease, hypertrophic, restrictive, and dilated cardiomyopathy, left ventricular hypertrophy, vasculitis, history of end-stage renal failure, liver failure, coagulopathy, malignancy, inflammatory disease, cardiogenic shock, pregnancy, and patients presenting with acute coronary syndrome were excluded. Patients with inadequate image quality, coronary ectasia, or coronary spasm were also excluded from the study.

All patients underwent a comprehensive transthoracic echocardiographic examination using a GE Vingmed Vivid 5 echocardiography device (GE Vingmed Ultrasound, Horten, Norway) before the planned procedure. During echocardiographic examination, parasternal long-axis, short-axis, and apical 4-chamber and 2-chamber images were obtained and evaluated using M-mode, 2-D, continuous-wave Doppler, pulse wave Doppler, and tissue Doppler methods. All echocardiographic examinations performed before hospital discharge and outcomes of echocardiographic findings were obtained from our hospital database. Informed consent was obtained from all patients in accordance with a protocol approved by the Ethics Committee of Konya City Hospital (decision no: 01-33, date: 06.01.2022).

The Assessment of Coronary Angiograms

CAG was performed through the femoral or radial arteries using 6 or 7 Fr sheaths. At least 4 and 2 images, respectively, were obtained for the left and right coronary arteries. Iopromide (Ultravist-370, Schering AG, Berlin, Germany) was used as the contrast agent at a rate of 3-4 mL/s for the left anterior descending coronary artery (LAD), left circumflex artery (LCx), and 2-3 mL/s for the right coronary artery (RCA). CAG was performed at a rate of 30 frames. In all patients, the injection of radiopaque contrast agent during CAG was utilized manually. Epicardial coronary blood flow was quantified visually using the TIMI frame count method. The initial frame was defined by a column of contrast extending across >70% of the arterial lumen in an antegrade fashion[3]. The final frame was accepted as the leading edge of the contrast column appeared at the distal end. The distal coronary landmark was defined as the distal bifurcation for the LAD, the distal bifurcation of the segment with the longest total distance for the LCx, and the first branch of the posterolateral artery for the RCA. The corrected TIMI frame count for the LAD was derived from the original value after dividing it by 1.7[17]. The cut-off values of the TIMI frame count for the normal filling of epicardial coronary arteries were 36.2±2.6 for LAD (corrected cut-off value for LAD was 21.1±1.5), 22.1±4.1 for LCX, and 20.4±3 for the RCA[3]. According to our study, patients presenting at least one coronary artery with a TIMI frame count above this criterion were defined as the CSF group. Patients presenting with values below this criterion with luminal narrowing of 30% or more of its reference diameter in any coronary artery were defined as the control group. The TIMI frame counts were measured using the two-dimensional quantitative CAG software CAAS (Version 5.1, Pie Medical Imaging B.V., Maastricht, The Netherlands). All angiograms were evaluated by two interventional cardiologists blinded to the patients' clinical and laboratory data.

The Assessment of SII

Peripheral venous blood samples were taken from the forearm vein after 12 h of fasting before CAG. Total blood cell counts including platelets, neutrophils, and lymphocytes were analyzed. with an Auto Analyzer. An automated hematology analyzer (Sysmex, XT-2000i) was used for total blood counts. SII was calculated as total peripheral platelet count neutrophil/lymphocyte ratio (p x n/L ratio)[12].

Statistical Analysis

Data were analyzed with SPSS software version 21.0 for Windows (IBM SPSS Statistics for Windows Version 21.0. Armonk, NY: IBM Corp., USA In this study, data are expressed as mean ± SD for continuous variables and as counts and percentages for categorical variables. The Kolmogorov-Smirnov and Shapiro-Wilk test's were used to evaluate the distribution of continuous variables. The χ^2 test and Fisher's exact test were used to analyze categorical variables. The student t-test was used for continuous variables with a normal distribution, and the values were presented as mean ± SD. Comparison of intergroup continuous variables without a normal distribution was analyzed using Mann-Whitney U test. A 2-tailed p-value <0.05 was considered statistically significant during the study. The receiver operating characteristic (ROC) curve was used to determine the cut-off value of SII to predict CSF. The effect of various variables on CSF was calculated by univariate regression analysis. In these analyzes variables with unadjusted p<0.05 were identified as confounding factors and were included in multivariate regression analyzes to determine the independent predictors of CSF.

Results

After the exclusion of ineligible subjects, 162 patients with CSF and 272 without CSF were enrolled. The baseline demographic, clinical and laboratory characteristics of the study population are summarized in Table 1. There was no statistically significant difference between the two groups in terms of clinical characteristics. On the other hand, there was a significantly higher prevalence of male gender and smoking history among patients with CSF compared with control subjects (53.1% vs 36.8% & 48.1% vs 41.1%, p<0.05 respectively). In addition, patients with CSF were found to be older and had lower levels of estimated LVEF compared with patients without CSF (67.4±11.7 vs 65.6±10.6 & 53.4±12.0 vs 55.6±10.8, p<0.05 respectively). When the previous coronary interventions were examined, it was seen that both groups showed similar characteristics (36.4% vs 31.9%, p>0.05).

Regarding baseline biochemical and hematological parameters, patients with CSF had significantly higher levels of serum creatinine, uric acid, and neutrophil counts than patients without CSF (p<0.05). Additionally, compared to control subjects, patients with CSF had significantly increased levels of estimated NLR and SII scores (2.55±0.80 vs 2.29±0.11 & 719±20 vs 590±2, p<0.01 respectively).

There were no significant differences in other biochemical parameters between the two groups.

Angiographic characteristics of patients with CSF are summarized in Table 2. In this study, 84 patients showed CSF in the LAD, 16 patients in the LCX, and 102 patients in the RCA. Twenty four (14.8%) patients showed CSF in 3 main coronary arteries, 68 (41.9%) in 2, and 70 (43.2%) in 1.

Various variables such as age, gender, smoking history, LVEF, serum creatinine level, uric acid level, neutrophil count, NLR, and SII score were included in the univariate Cox regression analysis to determine the prognostic parameters of CSF. After the exclusion of parameters that showed no effect on CSF in univariate analysis, Cox multivariate regression analysis was performed, which described sex, LVEF, and SII score as independent determinants of CSF (Table 3). According to our findings, SII was the best parameter to predict CSF. The ROC curve was plotted to determine the SII cut-off value to estimate CSF, and the optimal cut-off value was calculated as 612.4 using the Youden index (area under the curve: 0.751, 95% confidence interval: 0.699-0.804, p<0.001), (Figure 1). Above this cut-off value, CSF could be determined by sensitivity of 84.4% and specificity of 54.6%.

Discussion

In the present study, we evaluated the association between SII and CSF and observed that SII was a strong predictor

Table 1. Baseline characteristics of the patients

Variables	CSF + (n=162)	CSF - (n=272)	p-value
Age (years)	67.4±11.7	65.6±10.6	**0.043**
Sex (male, %)	86 (53.1%)	100 (36.8%)	**0.001**
DM (n, %)	64 (39.5%)	80 (29.4%)	0.069
HT (n, %)	106 (65.4%)	162 (59.6%)	0.180
COPD (n, %)	68 (42.0%)	126 (46.3%)	0.220
Previous coronary intervention (n, %)	59 (36.4%)	87 (31.9%)	0.095
Smoking (n, %)	78 (48.1%)	112 (41.1%)	**0.041**
Positive exercise stress test	103 (63.5%)	169 (62.1%)	0.871
Positive radionuclide study	59 (36.4%)	103 (37.8%)	0.898
LVEF (%)	53.4±12.0	55.6±10.8	**0.001**
Total cholesterol (mg/dL)	168.1±21.5	144.1±32.6	0.143
LDL (mg/dL)	138.6±25.9	127.6±15.6	0.246
HDL (mg/dL)	34.3±9.5	37.7±1.3	0.097
Triglycerides (mg/dL)	136.9±45.8	123.8±38.9	0.232
Blood glucose (mg/dL)	125±31.9	121.3±41.8	0.213
Creatinine (mg/dL)	0.89±0.92	0.87±0.56	**0.048**
Urea (mg/dL)	34.4±4.5	33.4±3.8	0.082
Uric acid (mg/dL)	5.67±1.98	5.12±0.67	**0.001**
Hemoglobin (g/dL)	13.4±1.5	13.9±1.6	0.211
WBC (10^3/µL)	9.21±2.73	8.53±2.75	0.078
Neutrophil (10^3/µL)	5.73±0.67	4.72±0.34	**<0.001**
Lymphocyte (10^3/µL)	2.24 ± 0.66	2.06±0.86	0.193
Platelets (10^3/µL)	282±25	258±17	0.112
NLR	2.55±0.80	2.29±0.11	**<0.001**
PLR	125±37	124±19	0.345
SII	719±20	590±2	**<0.001**

DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease,
LVEF: Left ventricular ejection fraction, LDL: Low-density lipoprotein, HDL: High-density,
Lipoprotein, WBC: Wight blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune-inflammation index, CSF: Coronary slow flow

of CSF. To our knowledge, this is the first research in the literature that evaluates the relationship between SII and CSF in patients who underwent CAG.

The CSF phenomenon is frequently observed during CAG and is associated with various clinical manifestations including myocardial ischemia, life-threatening arrhythmias, sudden cardiac death, and recurrent acute coronary syndromes[8,18,19]. According to previous studies, coronary microvascular disease, diffuse atherosclerosis, endothelial dysfunction, chronic inflammation, and oxidative stress are underlying pathologies that contribute to the development of CSF[20-22]. Despite various known risk factors, the pathophysiology of CSF remains unclear.

Table 2. Angiographical characteristics of the patients with coronary slow flow

TIMI frame count in each artery	
TIMI FC (LAD)	43.7±11.9
Corrected TIMI FC (LAD)	25.7±7.0
TIMI FC (LCX)	31.5±10.2
TIMI FC (RCA)	35.6±12.4
Mean TIMI FC	36.9±11.5
Number of coronary vessel involvement	
One (n, %)	70 (43.2)
Two (n, %)	68 (41.9)
Three (n, %)	24 (14.8)
Coronary artery involvement	
LAD (n, %)	84 (51.8)
LCX (n, %)	16 (47.5)
RCA (n, %)	102 (62.9)

LAD: Left anterior descending, LCX: Left circumflex, RCA: Right coronary artery, FC: Frame count, TIMI: Thrombolysis in myocardial infarction

Table 3. Logistic regression analysis for CSF

	B	p	OR	95.0% CI for OR	
				Lower	Upper
Age	0.20	0.662	0.82	0.34	1.98
Sex	1.48	0.035	0.23	0.06	0.90
Smoking	0.65	0.292	1.91	0.57	6.36
LVEF (%)	1.92	0.01	0.15	0.03	0.63
Uric acid (mg/dL)	0.16	0.248	1.17	0.90	1.54
Creatinine (mg/dL)	0.13	0.899	0.88	0.13	6.22
Neutrophil (10^3/µL)	-0.02	0.363	0.99	0.96	1.02
NLR	0.14	0.04	1.15	0.76	1.73
SII	0.08	0.001	1.09	1.03	1.14

LVEF: Left ventricular ejection fraction, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CI: Confidence interval, OR: Odds ratio, CSF: Coronary slow flow

In our study, male gender reduced LVEF, and higher SII score were independent predictors of CSF. We also observed a higher prevalence of CSF compared with previous reports (18.7% vs 1-5.5%). The the inclusion of patients whose CAG revealed at least one coronary artery with a TIMI frame count above the accepted criterion may cause this outcome. Moreover, all patients had chest pain, and CAG was indicated due to an objective evidence of ischemia. Last but not least, the population of Konya province has a higher atherosclerotic burden. According to a survey conducted by the Public Health Agency of the Turkish Ministry of Health, patients living in Konya province had a higher prevalence of CAD, family history, and smoking status compared to previous well-known population-based studies and the rest of the Turkish population[23]. It has been well established that male gender and impaired ventricular functions are strongly associated with subclinical atherosclerosis and endothelial dysfunction, which are proven to be underlying causes of CSF[10,11]. Although our study confirmed the outcomes of previous studies, we also revealed a strong relationship between CSF and increased SII.

Previous reports revealed a strong link between hematological parameters, including neutrophils, platelets, lymphocytes, and atherogenesis. They also uncovered the adverse effects of these hematological parameters on

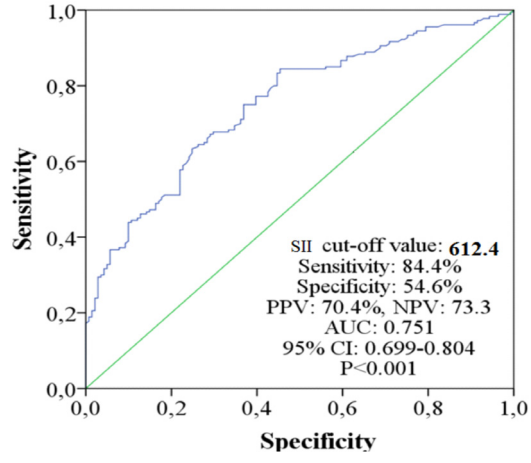

Figure 1. ROC analysis for predicting coronary slow flow

ROC: Receiver operating characteristic, CI: Confidence interval, AUC: Area under the curve

various cardiovascular conditions[24,25]. Moreover, they combined these hematological parameters such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) and used them as new risk scores to predict poor outcomes in patients with known coronary artery disease[26,27]. Apart from risk scores, a new index called SII has entered clinical practice. This index is a simple and useful biomarker that combines these hematological indices and has a better predictive value in determining the inflammatory status of the patient. The results of previous reports have proven the predictive value of this index in multiple cardiac conditions such as congestive heart failure, atherosclerotic heart disease, and severe aortic stenosis[28,29]. In our study, patients with CSF had a higher SII score than patients without CSF. Considering the complex interplay between atherosclerosis and inflammation, our findings comply with the results of previous reports. In addition, this index, which combines NLR and platelet counts, confirmed the proven role of these parameters not only in the severity of inflammation but also in atherogenesis. However, we demonstrated that this index had a better predictive value compared with well-known inflammatory indexes including NLR and PLR.

Study Limitations

There are some limitations to our study. First, this was a single-center retrospective study with a limited number of patients. Although multiple studies have investigated the prognostic value of SII in terms of determining adverse cardiovascular events in various conditions, we did not follow our patients regarding those poor cardiac outcomes. Therefore, prospective and multicenter studies with larger sample sizes investigating the prognostic value of SII for predicting adverse cardiac outcomes in patients with CSF are needed. Second, the injection of radiopaque contrast agents during CAG was utilized manually instead of automated contrast injection. This may result in miscalculation in assessments of TIMI frame counts of epicardial coronary arteries. Third, although we investigated the relationship between the common hematological indices and CSF, we did not investigate the association between the well-known acute phase reactants, including C-reactive protein, fibrinogen, plasminogen, PAI-1, t-PA, and the presence of CSF. Considering the strong relationship between acute phase reactants and CSF, this decreased the power of the study.

Conclusion

SII is an independent predictor of CSF, especially in patients presenting with stable angina pectoris. Considering the strong association between the presence of CSF and systemic inflammation, this non-invasive and easily calculable index can be used in daily practice.

Ethics

Ethics Committee Approval: The approval was obtained from the Ethics Committee of Konya City Hospital (decision no: 01-33, date: 06.01.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D., M.B.Ö., Concept: M.D., M.B.Ö., Design: M.D., Data Collection or Processing: M.D., M.B.Ö., Analysis or Interpretation: M.B.Ö., Literature Search: M.D., M.B.Ö., Writing: M.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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