

## Atherogenic indexes versus hematologic inflammatory indexes: What is the most useful predictor of coronary slow flow?

Atherogenic and hematologic inflammatory indexes in coronary slow flow

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### Abstract

**Aim:** Previous studies reported that inflammation and atherosclerosis are linked to coronary slow flow (CSF). The predominant pathological mechanism has not been elucidated yet. Hence, we aimed to compare hematologic inflammatory and atherogenic indexes simultaneously between patients with normal coronary flow (NCF) and CSF.

**Material and Methods:** In a single-center retrospective analysis, 91 consecutive NCF patients and 90 consecutive CSF patients constituted two groups according to Thrombolysis in Myocardial Infarction frame count (TFC). Hematological indexes consist of the neutrophil-lymphocyte ratio (NLR), the lymphocyte to monocyte ratio (LMR), and the platelet-lymphocyte ratio (PLR), and the atherogenic indexes consist of an atherogenic index of plasma (AIP), atherogenic coefficient (AC), and Castelli's risk index (CRI). Baseline clinical parameters were compared beside the indexes.

**Results:** NLR, LMR, PLR were similar in groups. AIP, AC and CRI were significantly higher in the CSF group ( $p < 0.05$ ). In correlation analysis, only CRI has a significantly positive correlation with mean TFC ( $r: 0.419$   $p < 0.001$ ). In multivariate regression analysis, CRI was found as independently predictor of CSF (Odds ratio = 2.74, 95% CI = 1.21-6.207;  $p = 0.016$ ). **Discussion:** An elevated CRI may be an independent predictor for the presence of CSF. Additionally, it can be said that the inflammatory activity in CSF is transformed into atherosclerotic structures.

### Keywords

Coronary Circulation; Inflammation; Coronary Atherosclerosis; Dyslipidemias

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## Introduction

Coronary slow flow (CSF), classified as heart syndrome Y or non-obstructive coronary artery disease (INOCA), is an angiographic phenomenon characterized by late dye transfer to the distal coronary vascular bed during angiography in patients without obstructive coronary lesions [1,2]. CSF is a considerable clinical entity because it causes acute cardiac ischemic effects as well as complaints reminiscent of myocardial ischemia in general [3]. CSF has well-established mechanisms based on inflammation, atherosclerosis, endothelial dysfunction, and microvascular resistance [4]. However, the proportion of this relationship between the factors involved in the pathological mechanism is still unclear.

Hematological inflammatory indexes consisting of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR), associated with inflammation in cardiovascular diseases have been previously specified [5,6]. Studies have shown that there is a significant association between decreased density lipoprotein cholesterol (HDL-c) level, increased low-density lipoprotein cholesterol (LDL-c) level, and the incidence of cardiovascular diseases and adverse events [7,8]. Recently, researchers have defined atherogenic indexes, consisting of the Atherogenic plasma index (AIP), the Atherogenic coefficient (AC), and Castelli's risk index (CRI) to better define cardiovascular diseases based on atherosclerosis [9, 21-23].

Although many studies have been conducted on patients with CSF, as far as we know, no studies have been conducted comparing these hematologic inflammatories and atherogenic indexes in slow coronary flow. We aimed to compare the possible roles of atherogenic and hematological indexes in CSF, which includes both inflammation and atherosclerosis in its basic pathology.

## Material and Methods

### Patient selection

The present study was a retrospective and single-center study. Patients who admitted to cardiology clinic for stable angina pectoris between January 2015 and December 2018, who underwent coronary angiography and had angiographically normal or close to normal coronary arteries were retrospectively analyzed [4]. At the beginning of our study, 129 patients with coronary slow flow (CSF) were detected. Exclusion criteria are as follows: left ventricular ejection fraction <50%, history of the previous revascularization, acute coronary syndrome, obstructive coronary lesion (>20%), myocardial bridging, coronary ectasia, coronary spasm, infection, current anti-inflammatory and lipid-lowering medication usage, autoimmune disease, renal failure, anemia, hematological disease, and malignancy. After exclusion criteria, 181 patients were included in the final analysis, 90 consecutive patients with slow flow in either of their coronary arteries, versus 91 consecutive patients with normal coronary flow (NCF). Hypertension was defined as diastolic blood pressure  $\geq$  90 mm Hg or systolic blood pressure  $\geq$  140 mm Hg or with the use of any reported antihypertensive therapy. Diabetes mellitus (DM) was defined as the use of any antidiabetic agent. The study was in compliance with the principles in the Declaration of Helsinki and approved by the Local Institutional

Ethics Committee (Ethics committee approval code numbered 2020-16/07 was obtained on 17.06.2020).

Angiographic Data and Determination of Slow Coronary Flow  
Coronary angiography of all patients included in the study was performed using the Judkins technique and 6-French catheters from the femoral or radial artery. All angiographic images were recorded in Philips Allura Xper Percutaneous Coronary Intervention digital system at our cardiology clinic. Iopromide contrast (Omnipaque; GE Healthcare) was used in all study patients. Coronary flow of Angiograms was measured according to Thrombolysis in Myocardial Infarction (TFC) described by two cardiologists who were previously blinded to details of the study [10]. The first frame count was determined as the anterograde movement of the contrast material touching both borders of the coronary lumen [10]. The final frame count was determined as the first branch of posterolateral for right coronary artery (RCA), distal bifurcation for left anterior descending (LAD), and circumflex (CX) [10]. The obtained frame results were doubled since the angiographic filming speed was 15 frames/second. Since the LAD artery is naturally long as described previously, the corrected TFC was obtained by dividing it by 1.7 [10]. The mean TFC (mTFC) was calculated by summing the TFCs for the corrected LAD, CX, and RCA, and then dividing the sum by three [10]. Patients with TFC greater than two standard deviations (SD) from the published normal range for any of the three vessels were considered patients with CSF ( $36.2 \pm 2.6$  frames for LAD,  $22.2 \pm 4.1$  frames for CX, and  $20.4 \pm 3$  frames for the RCA) [10].

### Laboratory Measurements and Definition of Indexes

Blood samples were taken in the morning after 8-12 hours of overnight fast then examined within one hour of arrival at the central laboratory. Complete blood cell counts in blood samples were analyzed using a Beckman Coulter automated hematology device (Beckman Coulter Brea, CA, USA). Serum levels of total cholesterol, triglyceride (TG), and HDL-c were measured with standard enzymatic methods (Abbot GmbH Co, Germany) using a fully automated analyzer (Abbott Architect c16000) with original reagents. LDL-c concentrations were determined by the Friedewald method [11]. Body mass index (BMI) was calculated by dividing weight by the square of the height ( $\text{kg} / \text{m}^2$ ). The estimated glomerular filtration rate (eGFR) was calculated by the Cockcroft Gault Calculator. Smoking was defined as one pack per day.

Hematological inflammatory indexes were calculated as follows [5,6]

Neutrophil lymphocyte ratio (NLR): Neutrophil counts/ Lymphocyte counts

Lymphocyte monocyte ratio (LMR): Lymphocyte counts/ Monocyte counts

Platelet lymphocyte ratio (PLR): Platelet counts / Lymphocyte counts

The Atherogenic indexes were calculated as follows [9,12]

Atherogenic Index of Plasma (AIP) =  $\log(\text{TG} / \text{HDL-c})$

Atherogenic Coefficient (AC) =  $(\text{Total cholesterol} - \text{HDL-c}) / \text{HDL-c}$

Castelli's Risk Index (CRI) =  $\text{LDL-c} / \text{HDL-c}$

### Statistical Analysis

All analyses were performed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). The compliance of the data

to normal distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean  $\pm$  standard deviation, while continuous variables that were not normally distributed were specified as median with interquartile range (25–75th percentiles). Categorical variables were specified as the number with a percentage. Student's t-tests were used to compare parametric continuous variables, and the Mann-Whitney U test was used to compare nonparametric continuous variables. Chi-square analysis was used to compare categorical variables. The correlation between CRI and mTFC was tested with the Spearman rho analysis. Logistic regression analysis was performed to assess the association of clinical and laboratory parameters with the presence of CSF. Univariate analyses were performed by including parameters that were significantly different between the groups. The Hosmer-Lemeshow test was used to determine sufficient goodness of fit for the regression model. Then, all significant parameters in univariate analysis were evaluated individually in a multivariate model with possible confounding factors (mTFC, age, gender, hypertension, smoking). All odds ratios were presented with their respective 95% confidence intervals (CI). A two-sided  $p < 0.05$  was considered significant.

## Results

The comparison of the main clinical characteristics and laboratory findings of the groups are shown in Table 1. There was no significant difference between the groups with respect to BMI, family history of premature coronary artery disease (CAD), DM, systolic blood pressure. Age ( $55.76 \pm 12.16$  years;  $52.03 \pm 11.94$  years,  $p = 0.047$ ), female gender ( $n=27$  [30.3%];  $n=61$  [67%],  $p < 0.001$ ), smoking ( $n=26$  [28.9%];  $n=14$  [15.4%],  $p = 0.022$ ), hypertension ( $n=41$  [45.6%];  $n=27$  [29.7%],  $p = 0.020$ ) were significantly higher in patients with CSF. When the CSF and NCF groups were compared with the laboratory parameters, there was no significant difference between the CRP and glomerular filtration rate. In complete blood count, hemoglobin was significantly higher in patients with CSF ( $14.66 \pm 1.8$  g/dL,  $13.91 \pm 1.7$  g/dL,  $p = 0.003$ ). On the other hand, platelet count was significantly higher in the NCF group ( $244.69 \pm 73.52 \times 10^3/\text{mm}^3$ ,  $265.66 \pm 63.57 \times 10^3/\text{mm}^3$ ,  $p = 0.008$ ). Neutrophil count, monocyte count and lymphocyte count were similar among groups. On a lipid scale, the TG levels were similar in the groups. Total cholesterol ( $134$  [100.75-216] mg/dL,  $123.5$  [93-175.75] mg/dL,  $p < 0.001$ ) and LDL-c ( $116.98 \pm 41.71$  mg/dL,  $90.42 \pm 29.81$  mg/dL,  $p < 0.001$ ) were higher in patients with CSF. HDL-c ( $40$  [34-48] mg/dL,  $50.5$  [40.25-62] mg/dL,  $p < 0.001$ ) was lower in CSF group. As expected, the mTFC ( $31$  [25-37],  $14$  [12-16],  $p < 0.001$ ) was significantly higher in the CSF group.

Comparisons of the hematological inflammatory indexes and atherogenic indexes are shown in Table 1. NLR, LMR, and PLR were similar between the groups. AIP ( $3.4$  [2.1-5.4],  $2.2$  [1.8-3.8],  $p = 0.027$ ), AC ( $3.59 \pm 1.66$ ,  $2.34 \pm 1.19$ ),  $p < 0.001$ ), and CRI ( $2.92$  [1.94-3.84],  $1.72$  [1.17-2.53],  $p < 0.001$ ) were significantly higher in the CSF group. Univariate and multivariate logistic regression analyses were used to evaluate independent predictors of CSF and are shown in Table 2. In multivariate regression analysis, total cholesterol (OR = 1.946; 95% CI =

**Table 1.** Comparison of baseline clinical, laboratory parameters and indexes of study groups

	Patient with CSF (n=90)	Patient with NCF (n=91)	p
<b>Clinical parameters</b>			
Age, years	55,76 $\pm$ 12,16	52,03 $\pm$ 11,94	0.047
Female gender	27(30.3 %)	61(67 %)	<.001
BMI, kg/m <sup>2</sup>	27.1(25-30.1)	26.6(2.7-31,2)	0.671
Smoking	26(28.9 %)	14(15.4 %)	0.022
Family history premature CAD	20(22.2 %)	14(15.4 %)	0.162
Diabetes mellitus	10(11.1 %)	14(15.4 %)	0.265
Hypertension	41(45.6 %)	27(29.7 %)	0.020
Systolic blood pressure, mmHg	127.5(120-140)	125(110-130)	0.140
<b>Laboratory parameters</b>			
eGFR, mL/min	90(83.8-90)	90(85.8-90)	0.247
CRP, mg/L	3,4(2,25-6,7)	3,2(1,93-5,35)	0.176
Hemoglobin, g/dL	14,66 $\pm$ 1.8	13,91 $\pm$ 1.7	0.003
Platelet, X 10 <sup>3</sup> /mm <sup>3</sup>	244.69 $\pm$ 73.52	265.66 $\pm$ 63.57	0.008
Neutrophil, X 10 <sup>3</sup> $\mu$ L	4.7(3.61-5.72)	4.52(3.58-6.09)	0.627
Monocyte, X 10 <sup>3</sup> $\mu$ L	0.48(0.36-0.64)	0.48(0.38-0.62)	0.989
Lymphocyte, X 10 <sup>3</sup> $\mu$ L	2.15(1.68-2.56)	2.32(1.93-2.68)	0.100
Triglyceride mg/dL	134(100.75-216)	123.5(93-175.75)	0.191
Total cholesterol, mg/dL	187.11 $\pm$ 52.65	154.64 $\pm$ 38.36	<.001
LDL-c, mg/dL	116.98 $\pm$ 41.71	90,42 $\pm$ 29.81	<.001
HDL-c, mg/dL	40(34-48)	50,5(40.25-62)	<.001
mTFC	31(25-37)	14(12-16)	<.001
<b>Hematological inflammatory indexes</b>			
NLR	2.17(1.60-3.01)	2.10(1.59-2.81)	0.342
LMR	4.37(3.10-5.66)	4.40(3.33-5.95)	0.261
PLR	120.6(93.0-151.2)	118.8(90.2-140.0)	0.066
<b>Atherogenic indexes</b>			
AIP	3.4(2.1-5.4)	2.2(1.8-3.8)	0.027
AC	3.59 $\pm$ 1.66	2.34 $\pm$ 1.19	<.001
CRI	2.92(1.94-3.84)	1.72(1.17-2.53)	<.001

Abbreviations: AC, atherogenic coefficient; AIP, atherogenic index of plasma; BMI, body mass index; CAD, coronary artery disease; CRI, Castell's risk index; CRP, C-reactive protein; CSF, coronary slow flow; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LMR, lymphocyte to monocyte ratio; mTFC, mean TIMI frame count; NCF, normal coronary flow; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; TIMI, thrombolysis in myocardial infarction.

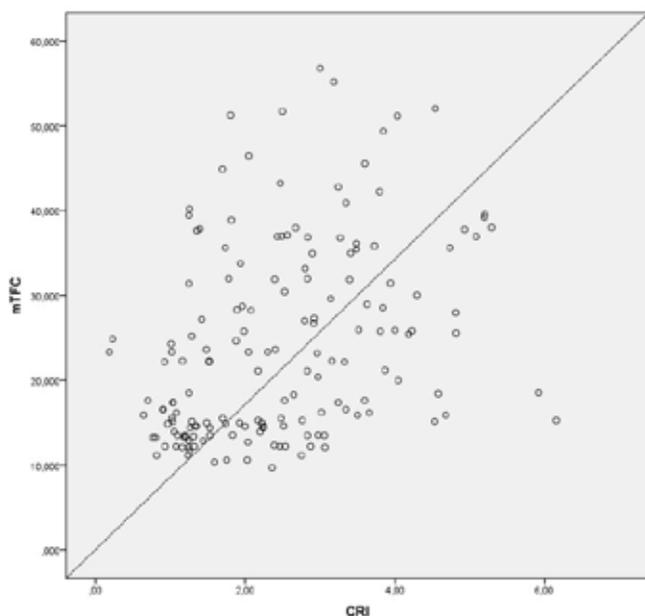
**Table 2.** Univariate and multivariate logistic regression analyses of independent variables of SCF

Variables	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis*		
	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Hemoglobin	1.302	1.091-1.553	0.003			
Platelet	0.995	0.991-1.000	0.035			
Total cholesterol	1.012	1.004-1.020	0.002	1.946	1.359-2.787	0.024
LDL-C	1.017	1.008-1.026	<0.001	1.032	1.005-1.059	0.018
HDL-C	0.984	0.964-1.003	0.103			
AIP	1.101	0.97-1.251	0.138			
AC	1.662	1.269-2.177	<0.001			
CRI	1.94	1.44-2.61	<0.001	2.74	1.21-6.207	0.016

Abbreviations: AC, atherogenic coefficient; AIP, atherogenic index of plasma; CRI, Castell's risk index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol. \* Multivariate logistic regression analyses were performed for each parameter adjusted for mTFC, age, sex, hypertension, and smoking coefficients, and only significant results were presented.

1.359 - 2.787,  $p = 0.024$ ), LDL-c (OR = 1.032, 95% CI = 1.005-1.059,  $p = 0.018$ ), CRI (OR = 2.74, 95% CI = 1.21-6.207,  $p = 0.016$ ) were significant independent predictors of the presence of CSF. Also, there was a moderate positive correlation between mFC and CRI ( $r = 0.419$ ,  $p < 0.001$ ) (Figure 1).

## Discussion



**Figure 1.** Correlation between mFC and CRI ( $r = 0.419$ ,  $p < 0.001$ )

In the present study, we found that CRI, LDL-c, and total cholesterol were independent predictors of the presence of CSF. We also found that CRI activity was moderately correlated with mTFC.

CSF is a term professionally known to interventional cardiologists that delays opacification in distal segments without >40% angiographic lesions in main epicardial coronary arteries [1]. Previous studies have shown that CSF is a condition involving systemic inflammatory factors rather than just locally acting inflammation [13]. Systemic inflammatory effects can alter the parameters and rates of blood count. PLR, LMR, and NLR are inexpensive systemic inflammatory markers. Considering the relationship between many cardiovascular diseases in which cardiovascular risk factors are well documented by various previous studies, these parameters can be used as markers for conditions involving an inflammatory process [5,6]. PLR, NLR, and LMR were similar between groups in our study. Inflammatory infrastructure pattern was recessive in CSF. These results may be explained by the presence of near-normal coronary arteries in our patient selection, because inflammation has been blamed in the initial stage rather than the advanced stage of the atherosclerotic process [15].

The benefits of increasing HDL-c level as well as lowering LDL-c level for the prevention of atherosclerotic cardiovascular disease are well known and potential benefits have been reported in patients at an early age [16]. Besides, it has been reported that statin therapy reduces CSF and increases coronary flow reserve in patients with CSF [17]. Decreased coronary reserve in CSF required a new definition as INOCA [2]. The increased

microvascular tone has been blamed in the CSF examined in the INOCA subgroup. In the increase of coronary microvascular tone, oxidative stress and pro-inflammatory process in which adipokines are blamed together with sympathetic hyperactivity [18]. Recent adipokine gene studies have found significant regulatory and correlative effects of adipokines on LDL-c and total cholesterol in obese male and female patients [19]. According to the results of our study, the increased LDL-c and total cholesterol level associated with atherosclerosis and increased microvascular tone is an independent predictor of CSF.

CSF may include diffuse atherosclerosis not only in the epicardial coronary arteries but also in the coronary microvascular circulation [20]. The relationship of atherogenic indexes with cardiovascular diseases and cardiovascular death based on atherosclerosis has been defined [9,12]. A recent study found that the SYnergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score, which indicates the severity of obstructive coronary artery disease, is associated with AIP [21]. Besides, saphenous vein graft stenosis associated with distal flow insufficiency, endothelial damage, and accelerated atherosclerosis has been associated with AIP and AC [22]. Furthermore, in a study based on intracoronary imaging in CAD, there was a significant relationship between plaque lipid content and plaque sensitivity and CRI [23].

In our comparison of the CSF group with the NCF group, AIP, AC, and CRI were found to be significantly higher in the CSF group. CRI, the equivalent of LDL-c/HDL-c, was an independent predictor of CSF.

The present study has some limitations that need to be mentioned. First, this study used a retrospective study design with a relatively small sample size based on single-center experience. Second, since we used a single CRI value and a limited number of patients for our analysis, rather than a transient trend, no prognostic values were determined on cardiovascular outcomes. Third, Cohen's kappa value was not determined to detect inter-observer and intra-observer variations in TFC measurements. Finally, we did not evaluate for endothelial dysfunction and microvascular tone.

Our findings suggested that higher total cholesterol level, LDL-c level, and CRI were independently related to the presence of CSF. In addition to that, CRI was significantly positively correlated with mTFC. The findings of our study also confirmed that CRI had a moderate positive correlation with mTFC. Studying these markers may provide more informative data about the pathogenesis of microvascular atherosclerosis in patients with CSF. Additionally, it can be said that the inflammatory activity in CSF changes into atherosclerotic structures but more studies are needed to confirm our findings in CSF.

### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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**Conflict of interest**

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