

Systemic Immune-Inflammation Index Levels in Patients with Coronary Slow Flow: A Case-Control Study

Okan Tanriverdi^a, Husna Sengul Askin^b, Lutfu Askin^c, Mustafa Polat^d, Esra Polat^d

^a Department of Cardiology, Adiyaman Education and Research Hospital, Merkez/Adiyaman, Turkey

^b Department of Infectious Disease, Gaziantep City Hospital, Gaziantep, Turkey

^c Department of Cardiology, Gaziantep Islamic Science and Technology University, Gaziantep, Turkey

^d Department of Cardiology, Gaziantep City Hospital, Gaziantep, Turkey

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SOUHRN

Kontext: Termínem pomalý koronární průtok (coronary slow flow, CSF) se při angiografickém vyšetření označuje protrahovaná distální opacifikace koronárních tepen v nepřítomnosti významné stenózy. I když přesná patogenese tohoto jevu dosud nebyla zcela objasněna, přibývající důkazy ukazují na jistý podíl systémového zánětu a mikrovaskulární dysfunkce. Za spolehlivý ukazatel systémového zánětu je v poslední době uznáván index systémového zánětu a imunitní odpovědi (systemic immune-inflammation index, SII), založený na počtech buněk v periferní krvi.

Cílem této studie bylo zhodnotit korelaci mezi hodnotami SII a pomalým koronárním průtokem u pacientů s pocitem tlaku či bolesti na hrudi.

Metody: Do studie bylo zařazeno celkem 300 pacientů ve věku 30 až 70 let, kteří byli dopraveni na urgentní příjem nebo na ambulanci s bolestí na hrudi. Na základě výsledku koronarografického vyšetření byli pacienti rozděleni do dvou skupin: skupina s CSF (n = 150) a skupina s normálním koronárním průtokem (n = 150). Ze studie byli vyřazeni pacienti s významnou stenózou koronární tepny, chlopenní vadou, nádorovým onemocněním nebo se systémovým zánětem. Hodnota SII se vypočítávala jako (počet neutrofilů × počet trombocytů) / počet lymfocytů. Statistické analýzy se prováděly s použitím softwaru SPSS verze 25.0.

Výsledky: Průměrné hodnoty SII byly ve skupině CSF vyšší než u kontrol (728 ± 242 vs. 418 ± 165 ; $p < 0,001$). Pacienti s CSF vykazovali zvýšené poměry neutrofilů k lymfocytům (neutrophil-to-lymphocyte ratio, NLR) a trombocytů k lymfocytům (platelet-to-lymphocyte ratio, PLR). V multivariační logistické regresní analýze představovala zvýšená hodnota SII nezávislý prediktor CSF (OR = 2,41; 95% CI 1,64–3,53; $p < 0,001$). Analýza křivky operační charakteristiky přijímače (receiver operating characteristic, ROC) prokázala vhodnou mezní hodnotu SII ve výši 560 s výslednou 80% senzitivitou a 75% specifitou (AUC = 0,84).

Závěr: Zvýšené hodnoty SII statisticky významně korelují s pomalým koronárním průtokem, což ukazuje na zásadní roli systémového zánětu v patofyziologii uvedeného jevu. Hodnoty SII tak mohou představovat nákladově účinný a snadno dostupný biomarker pro stanovení rizika u pacientů s podezřením na CSF.

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ABSTRACT

Background: Coronary slow flow (CSF) is an angiographic occurrence marked by the protracted distal opacification of coronary arteries without the presence of substantial stenosis. While its precise pathogenesis is not fully elucidated, mounting evidence substantiates the involvement of systemic inflammation and microvascular dysfunction. The Systemic Immune-Inflammation Index (SII), based on peripheral blood counts, has lately been recognised as a reliable indicator of systemic inflammation.

The objective of this study was to assess the correlation between SII levels and coronary sluggish flow in patients experiencing chest discomfort.

Methods: A total of 300 patients, aged 30 to 70 years, presenting to the emergency department or outpatient clinic with chest pain were enrolled. All individuals underwent coronary angiography and were categorised into two groups: the CSF group (n = 150) and the normal coronary flow group (n = 150). Patients with substantial coronary stenosis, valve disease, cancer, or systemic inflammatory conditions were excluded. The SII was computed as (Neutrophil count × Platelet count) / Lymphocyte count. Statistical analyses were conducted with SPSS version 25.0.

Address: Lutfu Askin, MD, Gaziantep Islamic Science and Technology University, 2700 – Gaziantep, Turkey, e-mail: lufuaskin23@gmail.com

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Results: Mean SII levels were markedly elevated in the CSF group relative to controls (728 ± 242 vs. 418 ± 165 , $p < 0.001$). Patients with CSF exhibited elevated neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). In multivariate logistic regression, increased SII was an independent predictor of CSF (OR = 2.41, 95% CI: 1.64–3.53, $p < 0.001$). An examination of the receiver operating characteristic (ROC) curve indicated an appropriate SII cutoff of 560, resulting in 80% sensitivity and 75% specificity (AUC = 0.84).

Conclusion: Increased SII levels are significantly correlated with coronary sluggish flow, indicating that systemic inflammation is crucial in its pathophysiology. The SII may function as a cost-effective and readily available biomarker for risk evaluation in patients with suspected CSF.

Introduction

Coronary slow flow (CSF) is delayed opacification in the coronary arteries without occlusion. Initially documented by Tambe et al. in 1972.¹ The incidence varies from 1% to 5% in angiograms, although the underlying mechanisms are not fully comprehended.² Proposed aetiologies encompass microvascular dysfunction, endothelial inflammation, and heightened small-vessel resistance.^{3,4} The Systemic Immune-Inflammation Index (SII) is a composite biomarker derived from the counts of neutrophils, lymphocytes, and platelets. It harmonises the equilibrium between inflammatory and immunological responses.⁵ Originally established as a prognostic marker in oncology,⁶ the SII has lately been linked to several cardiovascular disorders, including cardiovascular diseases (CVDs).^{7–9} Considering that CSF is regarded as a low-grade inflammatory condition, evaluating the role of SII may yield new insights into its pathophysiology and clinical applicability.¹⁰ This study sought to assess SII levels in CSF patients relative to people with normal coronary flow.

Materials and methods

Study design and population

This case-control study was performed from January 2024 to June 2025 at a tertiary cardiology centre. Three hundred individuals aged 30 to 70 years, who reported with chest discomfort and had coronary angiography, were included in the study. The minimal required sample size, calculated using G*Power 3.1, was determined to be 270 for an effect size of 0.35, $\alpha = 0.05$, and power = 0.90.

Inclusion criteria: Individuals aged 30 to 70 years presenting with chest pain warranting coronary angiogra-

phy, with angiographic findings of normal coronary anatomy or coronary spasm (Table 1).

Exclusion criteria: Substantial coronary stenosis (>20%), valvular heart disease, heart failure (ejection fraction <50%), malignancy, autoimmune or inflammatory disorders, acute infection, chronic renal or hepatic impairment. Coronary angiography was conducted using the usual Judkins procedure. The TIMI frame count was utilised to establish CSF as a corrected TIMI frame count (CTFC) above 27 frames for a minimum of one major coronary artery.¹¹

Laboratory measurements and SII calculation

Venous blood specimens were obtained following an 8-hour fast. The complete blood count was evaluated by an automated haematology analyser. SII = (neutrophil count multiplied by platelet count) divided by lymphocyte count. Routine biochemical parameters were documented as well (Table 2).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA). The minimal sample size was determined using G*Power 3.1.9.7. For a medium effect size (Cohen's $d = 0.35$), $\alpha = 0.05$, and power ($1-\beta$) = 0.90, a minimum sample size of 270 people was calculated. To reduce attrition and improve statistical robustness, 300 participants were included. Data normality was determined using Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables with normal distribution were represented as mean $\pm$ SD, whereas non-normally distributed data were presented as median (IQR). Categorical variables were reported as numbers and percentages. Both groups were compared using the Student's t-test for normally distributed variables and

Table 1 – Baseline demographic and clinical characteristics of the study population

Parameter	CSF (n = 150)	Control (n = 150)	Total (n = 300)	t / χ^2	p-value
Age (years)	54.8 $\pm$ 9.6	53.6 $\pm$ 10.1	54.2 $\pm$ 9.8	1.01	0.31
Male gender, n (%)	85 (56.7%)	77 (51.3%)	162 (54%)	0.85	0.36
Hypertension, n (%)	72 (48%)	68 (45.3%)	140 (46.7%)	0.22	0.64
Diabetes mellitus, n (%)	36 (24%)	33 (22%)	69 (23%)	0.16	0.69
Smoking, n (%)	65 (43.3%)	60 (40%)	125 (41.7%)	0.30	0.58
BMI (kg/m ²)	27.9 $\pm$ 3.5	27.5 $\pm$ 3.7	27.7 $\pm$ 3.6	0.88	0.38

BMI – body mass index; CSF – coronary slow flow.

Continuous variables were analyzed using Student's t-test; categorical variables were analyzed using the Chi-square (χ^2) test.

Table 2 – Laboratory parameters and inflammatory indices in study groups

Parameter	CSF (mean ± SD)	Control (mean ± SD)	t-value	p-value
Neutrophils ($\times 10^9/L$)	6.4 ± 1.8	4.8 ± 1.5	5.12	<0.001
Lymphocytes ($\times 10^9/L$)	1.9 ± 0.6	2.5 ± 0.7	-6.42	<0.001
Platelets ($\times 10^9/L$)	274 ± 55	252 ± 50	3.38	0.001
SII ([Neut $\times$ PLT]/Lymph)	728 ± 242	418 ± 165	9.56	<0.001
NLR	3.1 ± 1.2	2.0 ± 0.8	8.01	<0.001
PLR	145 ± 48	110 ± 40	6.12	0.002
CRP (mg/L)	4.8 ± 1.7	2.9 ± 1.3	8.40	<0.001

CRP – C-reactive protein; NLR – Neutrophil-to-Lymphocyte Ratio; PLR – Platelet-to-Lymphocyte Ratio; SII – Systemic Immune-Inflammation Index.

Continuous variables were analyzed using Student's t-test. A p -value <0.05 was considered statistically significant. Significance levels: p <0.05. Values are expressed as mean ± standard deviation (SD).

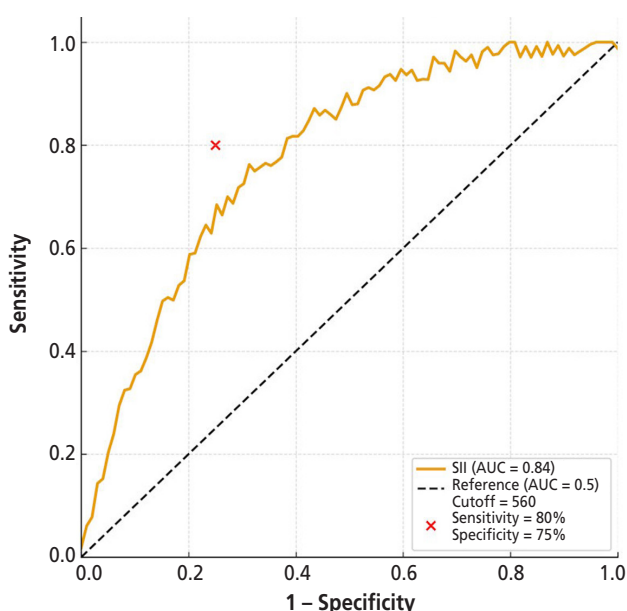


Fig. 1 – ROC curve for SII in predicting coronary slow flow.

the Mann–Whitney U test for non-parametric variables. Categorical data were analysed using chi-square (χ^2) or Fisher's exact test.

SII, TIMI frame count, NLR, PLR, and CRP were correlated. CSF-independent factors were found using binary logistic regression. Variables with a p -value <0.10 in univariate analysis were included in the multivariate model. The results were given as ORs with 95% CIs. SII's CSF prediction accuracy was assessed using ROC curve analysis (Fig. 1). AUC, optimum cutoff value, sensitivity, and specificity were calculated using the Youden index ($J = \text{sensitivity} + \text{specificity} - 1$). All statistical tests are two-tailed, and p -values under 0.05 are significant.

Results

Three hundred patients were analysed, evenly divided into the CSF group ($n = 150$) and the control group ($n =$

150) exhibiting normal coronary flow. The average age of the entire group was 54.2 ± 9.8 years, with 162 individuals (54%) being male. The baseline demographics, encompassing hypertension, diabetes mellitus, and smoking prevalence, were comparable between the two groups ($p > 0.05$). Laboratory results indicated markedly elevated inflammatory markers in CSF patients. The average SII was 728 ± 242 in the CSF group compared to 418 ± 165 in the control group ($p < 0.001$). The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were elevated in the CSF group (NLR: 3.1 ± 1.2 vs. 2.0 ± 0.8 , $p < 0.001$; PLR: 145 ± 48 vs. 110 ± 40 , $p = 0.002$).

A correlation study revealed a strong positive association between TIMI frame count and SII ($r = 0.46$, $p < 0.001$). Multivariate logistic regression revealed SII (OR = 2.41, 95% CI: 1.64–3.53, $p < 0.001$) and NLR (OR = 1.83, 95% CI: 1.21–2.78, $p = 0.004$) were independent predictors of CSF. ROC curve research determined an appropriate SII threshold of 560, resulting in 80% sensitivity and 75% specificity (AUC = 0.84, $p < 0.001$).

Discussion

The current investigation revealed that patients with CSF display markedly elevated levels of the SII, NLR, and PLR in comparison to persons with normal coronary flow. These findings corroborate the concept that systemic inflammation and microvascular endothelial dysfunction are pivotal in the pathogenesis of CSF.^{12,13}

Our findings align with numerous other studies that have associated inflammatory indicators with CSF. Increased levels of C-reactive protein and soluble adhesion molecules correlate with compromised coronary flow. Akboga et al.¹⁵ determined that PLR forecasts both the existence and intensity of CSF, whereas Li et al.¹⁴ emphasised NLR as a sensitive marker of microvascular impairment. In our investigation, SII surpassed both NLR and PLR in discriminative capability, indicating that it may offer a more thorough depiction of immunological and inflammatory equilibrium. The increase of SII in CSF can be elucidated through multiple interrelated processes.¹⁶ Activated neutrophils discharge reactive oxygen species (ROS) and proteolytic enzymes, resulting in endothelial damage and

diminished nitric oxide bioavailability, hence elevating microvascular resistance.^{17,18}

Concurrently, platelets secrete thromboxane A2, serotonin, and adhesion molecules, thereby enhancing endothelial activation and microvascular constriction.²⁰ Decreased lymphocyte levels indicate a reduction of the adaptive immune response, leading to an uncontrolled proinflammatory environment.²¹ Collectively, these pathways create a detrimental inflammatory loop that may contribute to CSF. This work builds upon prior findings by using SII as a new haematological biomarker in the evaluation of CSF. In our logistic regression study, SII independently predicted CSF (OR = 2.41, 95% CI 1.64–3.53), even after controlling for confounding variables like hypertension, diabetes, and smoking. The ROC analysis exhibited exceptional diagnostic accuracy (AUC = 0.84), akin to values documented in acute coronary syndromes and subclinical atherosclerosis.^{19–22}

These findings underscore SII as an accessible, cost-effective, and dependable inflammatory indicator that may be integrated into the clinical risk assessment of chest pain patients with normal angiograms. Our data, moreover, furnish indirect evidence corroborating the continuum between microvascular inflammation and early atherosclerosis. Kaya et al.¹⁷ and Taşolar et al.¹⁸ identified endothelial dysfunction and low-grade inflammation as common mechanisms linking CSF and coronary artery disease (CAD). Oflar et al.²¹ and Candemir et al.¹⁹ have shown that SII is associated with atherosclerotic plaque load and instability.

Consequently, CSF may not be a benign angiographic observation, as previously proposed by Ahmed et al.,²⁵ but instead an early indicator of systemic vascular inflammation and a potential precursor to future coronary events. Clinically, the identification of increased SII in CSF patients may impact therapy options. Anti-inflammatory treatments, including colchicine, statins, and IL-1 inhibitors, have demonstrated efficacy in diminishing vascular inflammation and enhancing endothelial function.²² The incorporation of SII into standard clinical practice may assist in informing therapeutic choices, assessing treatment response, and stratifying cardiovascular risk in this patient demographic.^{23,24}

Notwithstanding its merits – sufficient sample size, exclusion of confounding inflammatory diseases, and standardised angiographic evaluation – this study possesses multiple limitations. The study has a single-centre, cross-sectional design, which prevents causal inference. Secondly, specific inflammatory mediators such as IL-6, TNF- α , and hs-CRP were not assessed. Third, long-term follow-up data about cardiovascular outcomes were unavailable. Future multicentre longitudinal investigations are essential to evaluate the predictive significance of SII and ascertain whether therapies aimed at systemic inflammation can enhance coronary microvascular perfusion and outcomes in CSF patients.

In conclusion, our findings robustly endorse the notion that systemic immune-inflammatory activation plays a substantial role in coronary sluggish flow. The SII is a reliable and effective biomarker for evaluating inflammatory status and forecasting the presence of CSF. Prompt diagnosis of patients with increased SII may provide

timely treatment measures to mitigate inflammation, enhance endothelial function, and avert progression to overt atherosclerotic disease.

Conflict of interest

No conflicts of interest

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The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

Ethical statement

All procedures in this study comply with ethical standards and are consistent with the Declaration of Helsinki. The Ethics Committee for Clinical Research accepted the study protocol (2024-478).

Informed consent

All participants gave informed permission before the trial.

Contributions of authors

All authors contributed equally to the work, encompassing data collection and analysis, manuscript composition and revision, culminating in final approval of the version for publication. We collectively accept responsibility for all technical and ethical dimensions of the activity.

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