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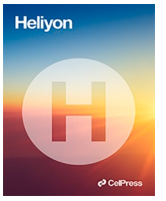

Research article

Systemic immune inflammation index is associated with in-stent neoatherosclerosis and plaque vulnerability: An optical coherence tomography study

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ABSTRACT

Background: In-stent neoatherosclerosis (ISNA) is identified as the primary cause of in-stent restenosis (ISR). The systemic immune inflammation index (SII), shows promise for predicting post-percutaneous coronary intervention (PCI) adverse cardiovascular events and is associated with coronary stenosis severity; however, its specific relationship with ISNA remains unclear. This study aimed to investigate the association between the SII and ISNA after drug-eluting stent (DES) implantation.

Methods: This cross-sectional study included 195 participants with 195 ISR lesions who underwent optical coherence tomography (OCT)-guided PCI between August 2018 and October 2022. Participants were categorized based on the SII levels into Tertile 1 (SII $<$432.37, n = 65), Tertile 2 (432.37 $\leq$ SII $\leq$751.94, n = 65), and Tertile 3 (SII $>$751.94, n = 65). Baseline Clinical, angiographic, and OCT characteristics were analyzed. The association of the SII with ISNA and thin-fibroatheroma (TCFA) was investigated using univariate and multivariate logistic regression analyses. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of the SII in detecting ISNA and TCFA.

Results: Patients in Tertile 3 had a significantly higher incidences of ISNA and TCFA than did those in Tertile 1. Logistic regression analysis revealed the SII is an independent indicator of ISNA and TCFA in ISR lesions ($P = 0.045$ and $P = 0.002$, respectively). The areas under the ROC curves for ISNA and TCFA were 0.611 and 0.671, respectively.

Conclusion: The SII is associated with ISNA and TCFA and may serve as an independent indicator in patients with ISR.

1. Introduction

In-stent restenosis (ISR) after drug-eluting stents (DES) implantation and late thrombosis in patients with coronary artery disease (CAD) following percutaneous coronary intervention (PCI) can result in serious cardiovascular events. Recent imaging and

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Abbreviations and acronyms

SII = systemic immune inflammation index
ISNA = in-stent neoatherosclerosis
DES = drug-eluting stent
ISR = in-stent restenosis
OCT = optical coherence tomography
TCFA = thin fibrous caps
AUC = area under the receiver operating characteristic curve
CAD = coronary artery disease
HDL = high-density lipoprotein cholesterol
SES = sirolimus-eluting stent
STEMI = ST-elevation myocardial infarction
MSA = minimal stent area
ACS = acute coronary syndrome
MLA = minimum lumen area
FCT = fiber cap thickness
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
TC = total cholesterol
ox-LDL = oxidized low-density lipoprotein
LDL = low-density lipoprotein
CHD = coronary heart disease
CAG = coronary angiography
NIH = neointimal hyperplasia
AS = atherosclerosis

pathological findings suggest that in-stent neoatherosclerosis (ISNA) plays a significant role in late stent failure [1,2]. The development of ISNA mirrors that of primary atherosclerosis (AS), which is characterized by chronic inflammation and the accumulation of various inflammatory cells, including macrophages, neutrophils, lymphocytes, and platelets [3,4]. Both conditions exhibit features such as necrotic cores, intraplaque hemorrhage, and thin-cap fibroatheroma (TCFA) with foam cell infiltration. However, unlike AS, which requires decades to develop, ISNA progresses rapidly after stent implantation [5]. Neutrophils-to-lymphocytes and platelets-to-lymphocytes ratios have emerged as important indicators for assessing inflammation and immune status, aiding in the early detection of adverse clinical events [6,7]. These ratios have shown promise in predicting coronary artery stenosis and are correlated with poor prognosis in myocardial infarction cases [8,9]. For instance, Karabağ et al. found that the C-reactive protein/albumin ratio (CAR) was associated with CAD severity in patients with stable angina, suggesting its prognostic potential [10]. Similarly, Karakayali et al. identified the HALP (hemoglobin, albumin, lymphocytes, and platelets) score as a predictor of in-hospital mortality in ST-segment elevation myocardial infarction (STEMI), highlighting the importance of inflammation and nutrition in cardiovascular outcomes [11]. Routine blood tests, such as the systemic immune-inflammation index (SII), calculated from neutrophil, lymphocyte, and platelet counts, are cost-effective and accessible. The SII is associated with atherosclerosis and predicts coronary artery stenosis [12,13]. The early detection of ISNA is crucial for improving patient management and reducing cardiovascular events. The correlation between the SII and inflammation makes it a promising candidate for early detection. However, the association of the SII with ISNA and TCFA in patients with ISR, assessed using optical coherence tomography (OCT), remains unexplored. Therefore, this study aims to use OCT to explore the relationship between the SII and ISNA in patients with DES-ISR, enhancing our understanding of this disease.

2. Materials and methods

2.1. Study population and procedures

A retrospective analysis was conducted on 195 patients with ISR after PCI who were admitted to the Department of Cardiology at Zunyi Medical University Affiliated Hospital between August 2018 and October 2022. These patients underwent coronary angiography (CAG) and OCT. The inclusion criteria were previous DES implantation and CAG revealing in-stent restenosis, followed by OCT examination. The exclusion criteria included acute heart failure, cardiogenic shock, severe arrhythmia during surgery, heavy thrombus load, tortuous vessels in the stent segment, and severe vascular calcification, all of which could impede OCT imaging. Additionally, patients with newly implanted stents (within the previous 6 months), missing medical record data, unclear OCT images, poor imaging quality, chronic inflammatory diseases, tumors, hematologic disorders, and severe liver or renal diseases were excluded. This study was approved by the Human Research Committee of the Affiliated Hospital of Zunyi Medical University (approval number: [2024] No. 1–205).

ISR is diagnosed using CAG, which identifies lumen stenosis ≥50 % within a stent or within 5 mm of its proximal and distal ends. Neoatherosclerosis, assessed by OCT, includes lipid-rich plaques such as TCFAs, with or without intimal rupture and/or thrombus. It also encompasses calcified plaques that may or may not exhibit neovascularization and/or macrophage accumulation. Following the application of strict inclusion and exclusion criteria, this study included 195 ISR patients with 195 lesions, all of whom underwent OCT-guided intervention (Fig. 1). The 195 patients with ISR were divided into three groups based on the SII tertiles: Tertile 1 (SII <432.37, n = 65), Tertile 2 (432.37 ≤ SII ≤751.94, n = 65), and Tertile 3 (SII >751.94, n = 65).

2.2. Patient characteristics and angiographic analysis

Patient demographic data, such as gender, age, and past medical history, were collected. Clinical data, including white blood cell count, lymphocyte count, platelet count, and neutrophil counts, endogenous creatinine clearance rate, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and albumin, were also recorded. Blood samples were collected from patients after a 12-h fast and analyzed in the central laboratory of the Affiliated Hospital of Zunyi Medical University using standard procedures. The SII was calculated based on the collected data as SII = PLT × NEU/LYM, where PLT represents platelet count, NEU represents neutrophil count, and LYM represents lymphocyte count.

CAG was performed by skilled cardiovascular interventionalists via the radial artery using the Seldinger technique to puncture and insert a 6F sheath. Coronary vessels stenosis was assessed from various angles, and the CAG findings were evaluated by two interventionalists using computer quantification. QAngio XA software (https://medicalit.hr/solutions/medis) was used for the analysis.

2.3. OCT image acquisition and analysis

OCT examination of the patient's restenotic vessel in the stent was conducted using the ILUMIENTMOPTIS system and the DragonflyTM image pipeline. ISR imaging was performed at a retraction speed of 20 mm/s using an automatic pullback device to capture detailed images of the narrowed blood vessels. The acquired images were measured and analyzed using a C7-XRTM OCT Intravascular Imaging System. Two technicians, blinded to the clinical data and CAG results, conducted offline software (Illumina Optis, St. Jude Medical) analysis to identify plaque types and coronary artery wall microstructures, such as fibrous, lipid, stratified, and calcified plaques, plaque rupture, TCFA, macrophage infiltration, microvessels, thrombus, and late stent malapposition (Fig. 2). Late stent malapposition was defined as stents implanted for over 1 year with a gap between the stent struts and the vessel wall of >200 μm (0.2 mm) and no neointimal tissue covering the stent struts. TCFA was defined as a fibrous cap thickness ≤65 μm and lipid curvature ≥180°. Two experienced technicians who were blinded to the patients' clinical and angiographic details independently evaluated the OCT images. Any disagreements were resolved by a third physician, who re-examined the original OCT images using an offline review workstation (Illumina Optis, St. Jude Medical).

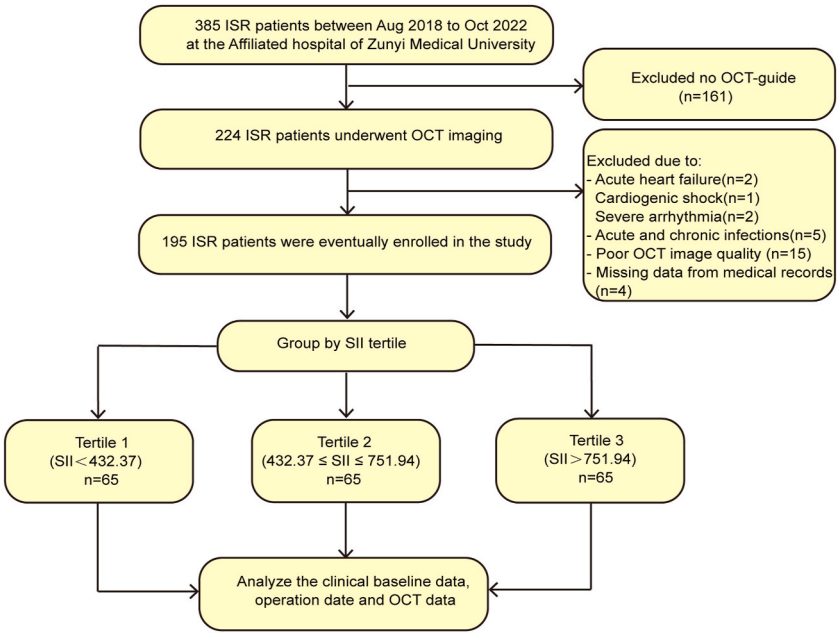


Fig. 1. Study flowchart A total of 195 ISR lesions in 195 patients were included in the final analysis. According to their SII tertile, the patients were divided into three groups (Tertile 1: SII<432.37, n = 65; Tertile 2: 432.37≤SII≤751.94, n = 65; or Tertile 3: SII>751.94, n = 65). ISR = in-stent restenosis; CAG = coronary angiography; OCT = optical coherence tomography.

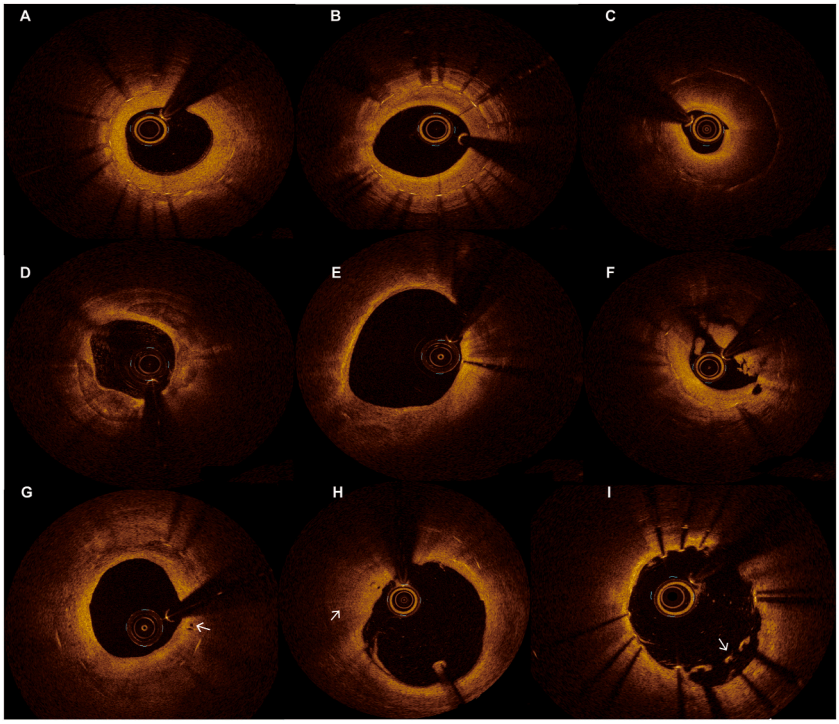


Fig. 2. Typical optical coherence tomography images showcasing various vascular morphologies Various classical images of OCT. (A) Homogenous hyperplasia, high intensity. (B) Heterogeneous, low-intensity. (C) Layered, low-intensity. (D) Calcified plaque. (E) Lipid plaques, TCFA. (F) Thrombus. (G) Microvessels (arrow). (H) Macrophages(arrow). (I) Late stent Malapposition (arrow). OCT = optical coherence tomography; ISR = in-stent restenosis; TCFA = thin-cap fibroatheroma.

2.4. Statistical analysis

Data were analyzed using SPSS (version 29.0; IBM Corp., Armonk, NY, USA). Normally distributed quantitative data were presented as means ± standard deviations and were compared using independent samples t-tests. Non-normally distributed quantitative data were presented as medians (P25, P75) and were compared using the Mann-Whitney *U* test. Categorical data were expressed as

Table 1
Baseline characteristics.

	Tertile 1[a] (n = 65) (< 432.37)	Tertile 2[a] (n = 65) (432.37–751.94)	Tertile 3[a] (n = 65) (> 751.94)	P Value
Age, M(SD), years	64.28(10.68)	64.09(10.93)	63.29(9.92)	0.852
Male, n(%)	51(78.5)	52(80)	49(75.4)	0.812
Current smoker, n(%)	24(36.9)	29(44.6)	25(38.5)	0.638
Hypertension, n(%)	40(61.5)	41(63.1)	44(67.7)	0.748
Diabetes, n(%)	17(26.2)	19(29.2)	14(21.5)	0.600
Hyperlipidemia, n(%)	16(24.6)	15(23.1)	18(27.7)	0.826
Laboratory fingdings				
White blood cells, M(IQR), × 109/L	5.60 (4.77, 6.58)	4.70 (4.01, 5.53)	6.27 (5.27 , 8.47)	< 0.001
Neutrophil, M(IQR), × 109/L	3.33 (2.64, 3.96)	4.44 (3.91, 5.01)	6.77 (5.59, 8.79)	< 0.001
Hemoglobin, M(SD), g/L	137.03(17.02)	140.06(18.74)	139.98(19.18)	0.563
Platelet, M(IQR), × 109/L	163.23(57.81)	205.94 (51.69)	235.34 (81.24)	< 0.001
Total cholesterol, M(IQR), mmol/L	3.74 (3.23, 4.71)	3.88 (3.21, 4.84)	4.21 (3.67, 5.38)	0.007
Triglycerides, M(IQR), mmol/L	1.58 (1.16, 2.25)	2.41 (1.49, 3.74)	1.72 (1.17, 2.59)	0.807
HDL-C, M(IQR), mmol/L	1.11 (0.94, 1.24)	1.06 (0.89, 1.19)	1.13 (0.94, 1.28)	0.238
LDL-C, M(IQR), mmol/L	2.07 (1.75, 2.68)	2.31 (1.87, 2.82)	2.51 (2.08, 3.16)	0.005
eGRF, M(IQR), ml/min/1.73m2	77.75 (24.79)	74.29 (27.73)	80.56 (28.26)	0.756
Medicine use				
Aspirin, n(%)	61(93.8)	64(98.5)	60(92.3)	0.254
Clopidogrel, n(%)	58(89.2)	60(92.3)	58(89.2)	0.792
Statin, n(%)	57(87.7)	58(89.2)	59(90.8)	0.852

[a] Tertiles 1, 2, and 3 are determined based on the Systemic immune inflammation index (SII, platelets × neutrophils/lymphocytes). M(SD) = mean (stand deviation); M(IQR) = median (interquartile range); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate.

numbers (percentages) and compared using the chi-square test. The association of the SII with ISNA and TCFA was analyzed using Spearman's correlation analysis. Univariate and multivariate logistic regression analyses were conducted to investigate the independent factors influencing ISNA and TCFA in patients with ISR. The predictive ability of the SII for ISNA and TCFA was evaluated using the receiver operating characteristic (ROC) curves. A *P*-value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

We excluded 161 patients who lacked complete clinical data and those with infectious or autoimmune diseases that could have influenced inflammation indicators. Compared with patients in Tertile 1, those in Tertile 3 had significantly higher white blood cell count (5.60 [4.77, 6.58] vs. 8.71 [7.33, 11.07], respectively; P < 0.001), NEU (3.33 [2.64, 3.96] vs. 6.27 [5.27, 8.47], respectively; P < 0.001), PLT (163.23 [57.81] vs. 235.34 [81.24], respectively; P < 0.001), total cholesterol (3.74 [3.23, 4.71] vs. 4.21 [3.67, 5.38], respectively; P = 0.007), and LDL cholesterol (2.07 [1.75, 2.68] vs. 2.51 [2.08, 3.16], respectively; P = 0.007) (Table 1).

3.2. Angiographic results

The angiographic findings are summarized in Table 2. No significant differences were observed between the groups.

3.3. OCT findings

The OCT measurements of the neointimal indicators within the stents are presented in Table 3. Qualitative assessment revealed significant variability in the distribution of ISR stenotic tissue structure patterns among the three tertiles (Fig. 3). Tertile 3 presented more cases of heterogeneous neointima (56.9 % [n = 37] vs. 32.3 % [n = 21], *P* = 0.034), TCFA (36.9 % [n = 24] vs. 10.8 % [n = 7], *P* = 0.034), and ISNA (58.5 % [n = 38] vs. 36.9 % [n = 24], *P* = 0.045) than Tertile 1 did. The incidences of ISNA and TCFA increased with increasing SII values. Moreover, patients in tertile 3 showed a higher prevalence of lipid plaques (61.5 % [n = 40] vs. 35.4 % [n = 23]; *P* = 0.008), thrombus (52.3 % [n = 34] vs. 26.2 % [n = 17]; *P* = 0.008), plaque erosion (50.8 % [n = 33] vs. 27.7 % [n = 18]; *P* = 0.016), and neointimal macrophages (32.3 % [n = 21] vs. 9.2 % [n = 6]; *P* = 0.006), whereas fibrous plaque (38.5 % [n = 25] vs. 63.1 % [n = 41]; *P* = 0.016) was less frequently identified. Our findings indicated no statistically significant differences in calcific plaques, spotty calcifications, microvessels, or late stent malapposition among the tertiles. Notably, Tertile 3 exhibited increased macrophage infiltration (*P* < 0.05) and a higher prevalence of vulnerable plaques, suggesting an elevated risk of future cardiovascular events.

3.4. ISNA prediction through ROC analysis

Several factors associated with ISNA and plaque vulnerability were investigated using univariate and multivariate analyses. Both ISNA and TCFA showed a positive correlation with SII. After adjusting for confounding factors, the SII emerged as a significant predictor of ISNA and plaque susceptibility. Univariate analysis (odds ratio [OR], 1.021; 95 % confidence interval [CI], 1.001–1.042; *P* =

Table 2
Angiography characteristics.

	Tertile 1[a] (n = 65) (< 432.37)	Tertile 2[a] (n = 65) (432.37–751.94)	Tertile 3[a] (n = 65) (> 751.94)	*P* Value
Time since implantation, M(IQR), years	3(1, 5)	3(1, 7)	3(1, 5)	0.897
DES types[b]				ns
paclitaxel	0(0.0)	0(0.0)	0(0.0)	
sirolimus	65(100.0)	65 (100.0)	65 (100.0)	
Culprit vessel				
Left anterior descending, n(%)	44(67.7)	39(60)	43(66.2)	0.624
Circumflex, n(%)	2(3.1)	8(12.3)	6(9.2)	0.149
Right, n(%)	18(27.7)	17(26.2)	16(24.6)	0.923
Other, n(%)	1(1.5)	1(1.5)	0(0.0)	0.603
Lesion Characteristics				
Bifurcation(> 1.5 mm), n(%)	12(18.5)	19(29.2)	14(21.5)	0.324
Ostial location, n(%)	6(9.2)	5(7.7)	4(6.2)	0.805
In-stent restenosis pattern[c]				
Type I, n(%)	17(26.2)	23(35.4)	16(24.6)	0.341
Type II, n(%)	18(27.7)	11(16.9)	16(24.6)	0.324
Type III, n(%)	19(29.2)	13(20)	15(23.1)	0.456
Type IV, n(%)	11(16.9)	18(27.7)	18(27.7)	0.253

[a] Tertiles 1, 2, and 3 are determined based on the Systemic immune inflammation index (SII, platelets × neutrophils/lymphocytes). DES = Drug-eluting stents; M(IQR) = median (interquartile range).
[b] The type of DES is only sirolimus-eluting stents.
[c] In-stent restenosis pattern was defined as per Mehran's classification.

Table 3
ISR characteristics evaluated by optical coherence tomography.

	Tertile 1[a] (n = 65) (< 432.37)	Tertile 2[a] (n = 65) (432.37–751.94)	Tertile 3[a] (n = 65) (> 751.94)	*P* Value
Quantitative assessment				
Distal reference lumen area, M(IQR), mm^2	4.96 (3.61, 6.12)	4.48 (3.31, 5.31)	5.04 (3.62, 6.30)	0.131
Distal reference lumen diameter, M(IQR), mm	2.47 (2.18, 2.74)	2.32 (1.90, 2.58)	2.57 (2.12, 2.97)	0.013
Proximal reference lumen area, M(IQR), mm^2	8.57 (6.44, 9.57)	7.61 (6.77, 8.97)	7.54 (6.14, 9.30)	0.420
Proximal reference lumen diameter, M(IQR), mm	3.25 (2.87, 3.48)	3.09 (2.93, 3.38)	3.18 (2.81, 3.45)	0.645
Minimum lumen area, M(IQR), mm^2	1.78 (1.38, 2.24)	1.61 (1.35, 2.17)	1.49 (1.09, 2.26)	0.196
Minimum lumen diameter, M(IQR), mm	1.48 (1.29, 1.65)	1.40 (1.29, 1.64)	1.33 (1.13, 1.62)	0.190
Minimum stent area, M(IQR), mm^2	6.96 (5.48, 8.15)	5.98 (4.69, 7.27)	6.37 (4.68, 7.82)	0.051
Minimum stent diameter, M(IQR), mm	2.85 (2.53, 3.11)	2.65 (2.34, 2.95)	2.72 (2.35, 3.11)	0.061
Maximal NIH,%	62(95.4)	63 (96.9)	61 (93.8)	0.705
Qualitative assessment				
Neoatherosclerosis, n(%)	24(36.9)	33(50.8)	38(58.5)	0.045
Restenotic tissue structure				0.034
Homogeneous, n(%)	39(60.0)	28(43.1)	21(32.3)	
Heterogeneous, n(%)	21(32.3)	30(46.2)	37(56.9)	
Layered, n(%)	5(7.7)	7(10.8)	7(10.8)	
Lipid plaque, n(%)	23(35.4)	36(55.4)	40(61.5)	0.008
TCFA, n(%)	7(10.8)	19(29.2)	24(36.9)	0.002
Calcific plaque, n(%)	6(9.2)	5(7.7)	3(4.6)	0.584
Spotty calcification, n(%)	4(6.2)	5(7.7)	4(6.2)	0.921
Fibrous plaque, n(%)	41(63.1)	30(46.2)	25(38.5)	0.016
Thrombus, n(%)	17(26.2)	23(35.4)	34(52.3)	0.008
Neointimal macrophages, n(%)	6(9.2)	15(23.1)	21(32.3)	0.006
Microvessels, n(%)	27(41.5)	24(36.9)	22(33.8)	0.660
stent malapposition, n(%)	8(12.3)	11(16.9)	14(21.5)	0.373
plaque erosion, n(%)	18(27.7)	21(32.3)	33(50.8)	0.016

[a] Tertiles 1, 2, and 3 are determined based on the the Systemic immune inflammation index (SII, platelets × neutrophils/lymphocytes). M(SD) = mean (stand deviation); M(IQR) = median (interquartile range); NIH: neointimal hyperplasia; TCFA: thin-cap fibroatheroma.

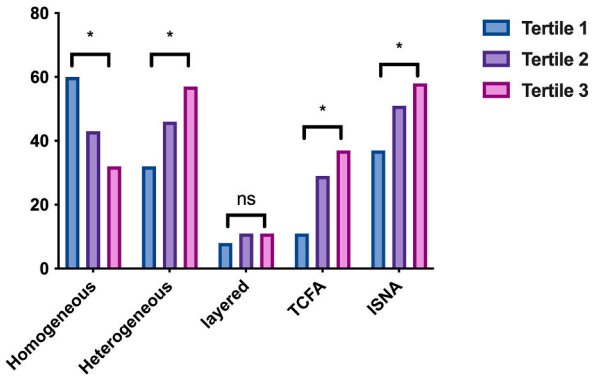


Fig. 3. Pattern of restenotic tissues
More homogeneous neointima (56.9 % vs. 43.1 % vs. 30.6 %) in the lower SII group; more TCFA (41.7 % vs. 26.4 % vs. 9.7 %) and ISNA (37.5 % vs. 47.2 % vs. 66.7 %) in the higher SII group ($p < 0.05$). TCFA: thin-cap fibroatheroma. ISNA: In-stent neoatherosclerosis. Tertiles 1, 2, and 3 are determined based on the systemic immune inflammation index (SII, platelet × neutrophil/lymphocyte ratio).

0.044) and multivariate analysis (OR, 1.010; 95 % CI, 1.001–1.018; $P = 0.025$) analyses demonstrated a significant association between SII levels and ISNA incidence (Table 4). Similarly, the SII was significantly associated with the presence of TCFA in both univariate (OR, 1.006; 95 % CI, 1.002–1.010; $P = 0.003$) and multivariate (OR, 1.003; 95 % CI, 1.001–1.005; $P = 0.002$) analyses.

The area under the curve (AUC) values for the SII in predicting ISNA and TCFA in patients with DES-ISR were 0.611 (95 % CI, 0.583–0.729; $P < 0.01$) and 0.671 (95 % CI, 0.568–0.756; $P < 0.01$), respectively. The optimal SII cut-off values for detecting ISNA and TCFA were 567.71 (sensitivity, 64.2 %; specificity, 63.0 %) and 583.65 (sensitivity, 72.0 %; specificity, 60.0 %), respectively. Additionally, our study found that patients in SII tertile 3 had greater macrophage infiltration ($P < 0.05$) and more vulnerable plaques compared to those in SII tertiles 1 and 2, indicating a higher risk of future cardiovascular events (Fig. 4).

4. Discussion

To our knowledge, this is the first study to use OCT to determine the association of the SII with ISNA and TCFA in patients with DES-

Table 4
Univariate and multivariate logistic regression analysis to determine the independent risk factors of ISNA and TCFA.

	In-stent neoatherosclerosis				Thin-cap fibroatheroma			
	Univariate ananlysis		Multivariate ananlysis		Univariate ananlysis		Multivariate ananlysis	
	Odds ration (95 % CI)	*P* Value	Odds ration (95 % CI)	*P* Value	Odds ration (95 % CI)	*P* Value	Odds ration (95 % CI)	*P* Value
Age,years	1.029 (1.001–1.058)	0.043	1.031 (0.996–1.067)	0.086	1.024 (0.992–1.057)	0.148	1.017 (0.976–1.059)	0.421
Sex	0.893 (0.453–1.759)	0.743	0.774 (0.557–2.999)	0.551	0.717 (0.316–1.623)	0.424	1.049 (0.343–2.652)	0.928
Current smoker	1.187 (0.669–2.106)	0.559	0.801 (0.625–2.495)	0.529	1.249 (0.651–2.394)	0.504	0.756 (0.597–2.930)	0.492
Hypertension	0.772 (0.430–1.388)	0.387	0.613 (0.314–1.194)	0.150	1.261 (0.637–2.496)	0.506	0.761 (0.593–2.906)	0.501
Diabetes mellitus	1.193 (0.627–2.271)	0.590	1.146 (0.563–2.331)	0.708	0.889 (0.421–1.877)	0.758	1.197 (0.364–1.919)	0.671
eGRF, M(IQR), ml/min/ 1.73m2	0.989 (0.979–1.000)	0.052	0.991 (0.979–1.004)	0.191	0.986 (0.973–0.999)	0.029	0.985 (0.970–1.000)	0.057
Triglycerides, mmol/L	0.958 (0.814–1.128)	0.606	0.946 (0.789–1.135)	0.552	0.955 (0.774–1.177)	0.665	0.913 (0.712–1.170)	0.471
Total cholesterol, mmol/ L	1.010 (0.821–1.242)	0.927	1.028 (0.654–1.615)	0.906	1.040 (0.824–1.312)	0.742	1.075 (0.661–1.751)	0.770
HDL-C, mmol/L	0.543 (0.201–1.469)	0.229	0.245 (0.064–0.936)	0.040	0.384 (0.109–1.346)	0.135	0.104 (0.018–0.619)	0.013
LDL-C, mmol/L	1.102 (0.803–1.512)	0.548	1.187 (0.614–2.295)	0.610	1.128 (0.796–1.599)	0.498	1.117 (0.550–2.267)	0.760
NIH > 50 %	1.957 (0.475–8.061)	0.352	0.371 (0.547–13.25)	0.223	0.676 (0.163–2.811)	0.591	0.499 (0.095–2.633)	0.413
Time since implantation, years	1.009 (0.945–1.077)	0.799	1.004 (0.936–1.078)	0.909	1.014 (0.943–1.091)	0.705	1.024 (0.945–1.110)	0.559
Minimum lumen area, mm2	1.043 (0.712–1.528)	0.829	1.217 (0.784–1.889)	0.381	0.856 (0.545–1.344)	0.499	0.876 (0.532–1.443)	0.604
SII	1.021 (1.001–1.042)	0.044	1.010 (1.001–1.018)	0.025	1.006 (1.002–1.010)	0.003	1.003 (1.001–1.005)	0.002

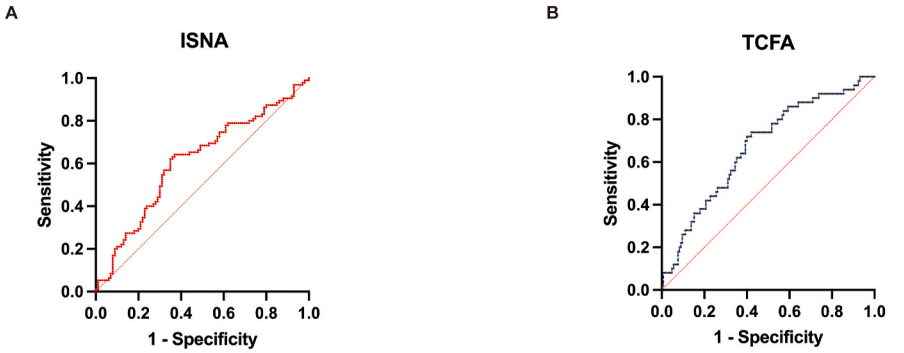
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; NIH = neointimal hyperplasia; SII = platelets × neutrophils/lymphocytes.

ISR. Our findings indicate that patients in the lowest SII tertile (Tertile 1) had significantly lower levels of inflammation and lipid-related markers than did those in the higher tertiles (Tertiles 2 and 3). Moreover, Tertile 3 was associated with a higher prevalence of lipid plaques, thrombus, neointimal macrophages, and plaque erosion, and a lower prevalence of fibrous plaques. The incidences of ISNA and TCFA were significantly higher in the Tertile 3 (Table 3). These results suggest that elevated SII levels are positively associated with increased plaque vulnerability and a higher proportion of ISNA, establishing the SII as a distinct risk factor for ISNA plaque susceptibility.

PCI is a vital treatment for ischemic heart disease; however, managing ISR remains a challenge and often leads to adverse outcomes [14]. The primary pathophysiological mechanisms underlying ISR and ISNA are chronic inflammation and delayed endothelial healing [15]. Atherosclerosis is intricately linked to the inflammatory response, in which immune processes interact with metabolic factors to initiate and propagate atherosclerotic lesions [16]. Inflammatory mediators released by neutrophils induce endothelial dysfunction and vessel wall degradation [17,18]. Platelets release chemokines, proinflammatory cytokines, and growth factors that contribute to endothelial cell dysfunction [19,20]. Neutrophils interact with platelets, proteolyze coagulation factors, release prothrombotic molecules, and facilitate monocyte infiltration, and promote atherosclerosis and thrombosis, ultimately leading to cardiovascular events [21]. In contrast, lymphocytes regulate inflammatory responses and exhibit anti-atherosclerotic effects [22]. The suppression of the inflammatory response can delay the progression of atherosclerosis and reduce cardiovascular events [23].

Several studies have shown that individual cellular components or blood biochemical indicators may not have the optimal predictive power for coronary heart disease development. Therefore, researchers have focused on the ratio of multiple indicators, such as neutrophil-to-lymphocytes and platelet-to-lymphocyte ratios. These combined indicators may offer greater value than the individual cell components or biochemical markers alone do. The CAR has been identified as an independent predictor of stent restenosis in patients with STEMI, providing a better predictive value, compared with C-reactive protein or albumin alone [24]. Similarly, the CAR has been shown to correlate with CAD severity in patients with acute coronary syndrome (ACS) [25].

Karakayali et al. demonstrated that the SII, which integrates lymphocytes, platelets, and neutrophils, is significantly associated with ischemia with non-obstructive coronary arteries (INOCA), highlighting its potential as a predictive marker [26]. The SII provides a more balanced and comprehensive evaluation of the body's immune and inflammatory responses, compared with traditional ratios involving one- or two-cell components. The SII has demonstrated predictive value and offers unique advantages over other biological markers, such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein level [27]. Liu et al. found that the SII demonstrated superior predictive ability for coronary heart disease compared with other markers, such as the



	Maximum Youden Index			
	AUC(95%CI)	Cut-offs	Sensitivity	Specificity
SII	0.611(0.583-0.729)	567.71	0.642	0.630

	Maximum Youden Index			
	AUC(95%CI)	Cut-offs	Sensitivity	Specificity
SII	0.671(0.586-0.756)	583.65	0.720	0.600

Fig. 4. ROC analysis ISNA, in-stent neoatherosclerosis; TCFA, thin-cap fibroatheroma.

neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein level [12]. The SII appears to be less influenced by fluid load, conpared with the other ratios [28]. Analyzing 669 patients undergoing CAG, Candemir et al. found that the SII was an independent predictor of severe stenosis, suggesting its potential for assessing coronary atherosclerosis severity [29]. Elevated SII levels is associated with atherosclerotic lesions and better prognosis prediction in patients with ACS, indicating a link to increased inflammatory activity. The study observed higher platelet and neutrophil counts and lower lymphocyte counts in cases of elevated SII, reflecting heightened inflammatory activity. Some studies have also found that during long-term follow-up, the SII is more closely associated with cardiovascular disease in patients with hypertension or diabetes. This relationship may be attributed to endothelial dysfunction, inflammatory infiltration, and vascular remodeling resulting from chronic inflammation in patients [30,31].

Our study revealed that patients with higher SII values exhibited higher rates of neoatherosclerosis, macrophage infiltration, plaque erosion, vulnerable plaques, and stent thrombosis, indicating a poorer prognosis. Consequently, treatment adjustment may be necessary in patients with elevated SII. Closer monitoring and potentially more aggressive anti-inflammatory treatments may be beneficial for these high-risk patients. Implementing SII measurements in clinical practice may help identify patients who would benefit from tailored therapeutic strategies to mitigate inflammation and reduce the risk of adverse outcomes. Further research is warranted to explore the optimal therapeutic interventions for patients with elevated SII and to validate the clinical benefits of such approaches.

Previous studies have clearly indicated that elevated SII values play a crucial predictive role in chronic heart failure, effectively predicting poor patient outcomes [32]. High SII has been confirmed as an independent predictor of cardiovascular events, including cardiac death, nonfatal myocardial infarction, stroke, and hospitalization for heart failure [33]. This association indicates that the SII not only has predictive value in chronic heart failure but also plays a crucial role in evaluating cardiovascular risk and forecasting related events [34,35]. Emerging inflammatory biomarkers connect the three immune cell types, delineating the balance between pro- and anti-inflammatory states in the body and providing insight into the involvement of the immune system in ISNA.

4.1. Limitations

This study has some limitations. First, we did not compare the SII with conventional inflammatory markers, such as C-reactive protein and fibrinogen. Future research should consider integrating the SII with other relevant markers for a more comprehensive analysis. Second, the lack of follow-up data for our patient cohort highlights the need for further investigation into the relationship between the SII and ISNA plaque vulnerability and their potential clinical implications. Third, our study was retrospective and single-center in nature, and despite our efforts to include as many patients as possible, the sample size was limited. Although we found an initial association of the SII with ISNA and TCFA in patients with restenosis, the predictive value of the SII in this study was limited. This limitation may stem from a small sample size or differences in the mechanisms underlying ISR and de novo atherosclerosis progression, warranting further investigation. This exploratory study suggests that the SII could serve as a predictive factor. Future large-scale, prospective, multi-center studies are crucial to validate the assciation of the SII with ISNA and TCFA and to investigate anti-inflammatory treatment strategies for patients with high SII and restenosis. Despite these limitations, our study provides valuable insights that will pave the way for future research aimed at identifying novel therapeutic targets for ISNA in chronic diseases.

5. Conclusion

Patients with ISR and with higher SII levels showed increased incidences of ISNA and plaque vulnerability. Although the SII is an independent risk factor for ISNA and TCFA, larger studies are needed to fully validate its predictive value.

Ethical approval statement

The Human Research Committee of the Affiliated Hospital of Zunyi Medical University approved the study after obtaining written informed consent from all the participants ([2024] No. 1–205).

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Data availability statement

The data associated with this study has not been deposited into a publicly available repository. However, under reasonable request, the data can be obtained by contacting the corresponding author.

CRediT authorship contribution statement

Jin Sheng: Writing – original draft, Data curation, Conceptualization. **Shuangya Yang:** Writing – original draft, Funding acquisition, Data curation, Conceptualization. **Ning Gu:** Formal analysis, Data curation, Conceptualization. **Chancui Deng:** Formal analysis, Data curation. **Youcheng Shen:** Formal analysis, Data curation. **Qianhang Xia:** Formal analysis, Data curation. **Yongchao Zhao:** Formal analysis, Data curation. **Xi Wang:** Formal analysis, Data curation. **Yi Deng:** Formal analysis, Data curation. **Ranzun Zhao:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization. **Bei Shi:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Shuangya yang reports financial support was provided by Guizhou Provincial Health Commission. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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