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The Predictive Value of the Systemic Immune-Inflammation Index for Cardiovascular Events in Chronic Total Occlusion Patients Who Prior Coronary Artery Bypass Grafting

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Background: There is limited research on the long-term prognosis of percutaneous coronary intervention (PCI) in coronary chronic total occlusion (CTO) patients who have previously undergone coronary artery bypass grafting (CABG). Additionally, the prognostic value of a novel systemic immune inflammation index (SII) in this specific patient population remains unclear.

Methods: To adjust for differences in baseline features and minimize bias, 335 pairs of patients with or without prior CABG undergone PCI were obtained after probability score matching (PSM) in a single-center cohort. The clinical characteristics were collected, and the primary outcomes were major cardiovascular events (MACE), which included all-cause death, nonfatal MI and unplanned revascularization, were recorded during the follow-up period after discharge. The group with prior CABG were divided according to the median level of SII: Lower SII group (SII ≤ 570.10, N = 167) and higher SII group (SII ≥ 570.10, N = 168).

Results: The SII values were significantly higher in the prior CABG group than in the without prior CABG group [570.10 (444.60, 814.12) vs 519.65 (446.86, 565.84), P < 0.001, respectively]. The survival Kaplan–Meier analysis showed that patients with prior CABG was significantly associated with a higher risk of MACE than patients without prior CABG (P = 0.016) in the long-term follow-up. As SII levels increased, the cumulative risk of MACE became significantly higher in the patients with prior CABG (P = 0.023) stratified by the median value of SII. The Cox proportional hazards regression model analysis indicated that the level of SII (hazard ratio = 2.035, 95% CI, 1.103–3.753, P = 0.023) emerged as independent predictors of MACE. The restricted cubic spline (RCS) analysis illustrated that the HR for MACE increased with increasing SII.

Conclusion: SII is a reliable predictor of long-term cardiovascular events after PCI in CTO patients with prior CABG, suggesting that SII may be helpful in identifying high-risk patients who need more aggressive treatment and follow-up strategies.

Keywords: systemic immune inflammation index, coronary chronic total occlusion, coronary artery bypass grafting, percutaneous coronary intervention, major adverse cardiovascular events

Introduction

Chronic total occlusion (CTO), as the most complex and challenging lesion in coronary artery, accounts for 20% of hospitalized patients undergoing non-emergency coronary angiography without previous coronary artery bypass grafting (CABG).[1] For most patients with CTO lesions, they must receive either CABG or percutaneous coronary intervention (PCI). Revascularization of CTO is associated with the improvement of quality of life, left ventricular function and long-term survival.[2,3] Although the results and techniques of CTO-PCI have been improving over time, due to the complexity of CTO lesions, most patients still choose CABG.[4]

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Previous studies have shown that CABG also has been widely used in the treatment of multi vessel CAD and left main lesions.[5,6] However, CABG itself can accelerate the progression of primary coronary atherosclerosis, resulting in up to 50% of native coronary arteries forming new CTOs after surgery.[7] Notably, patients with a new native coronary occlusion often develop recurrent symptoms and events, which necessitates revascularization in this group of patients.[8] Compared with initial CABG, repeated CABG is associated with poorer clinical outcomes, and saphenous vein graft PCI also has a higher failure rate.[9,10] For these cases, native artery CTO-PCI is preferred as the revascularization strategy. Previous studies have shown that the success rate of CTO-PCI in patients with prior CABG is lower, but there is a higher incidence of adverse events.[11,12] Therefore, it is critical to identify patients at high risk of adverse outcomes after PCI.

Atherosclerosis is considered to be an inflammatory process that plays a crucial role in the pathogenesis of cardiovascular disease.[13] The pathophysiology of atherosclerosis is influenced by circulating neutrophils, platelets, and lymphocytes, which play an important role in the chronic inflammatory process. Currently, a growing body of literature indicates that an increased inflammatory response is the cause of various complications after PCI.[14,15] The systemic immune inflammation index (SII) based on neutrophil, lymphocyte, and platelet counts has developed into a new inflammatory marker in the past decade.[16] A study reported that higher SII values are independently associated with non-fatal MI, stroke, and overall cardiovascular events, outperforming traditional markers in predicting major cardiovascular events.[17] Liu et al further demonstrated that SII offers superior predictive accuracy for CAD compared to the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR).[18] Our previous study found that SII was a better predictor of major cardiovascular events after PCI in CTO patients than traditional risk factors.

However, there have been few studies on the long-term prognosis of CTO-PCI in patients with prior CABG, and it is unclear whether the role of SII in these higher risk patients. Herein, this study aims to explore whether the SII could predict major adverse cardiovascular events (MACE) after PCI in CTO patients with prior CABG.

Methods

Subjects

This retrospective, observational study was conducted from a single center (Heart Center, Beijing Anzhen Hospital, Capital Medical University) between January 2019 and November 2021. The inclusion criteria consist of age >18 and patients who had previously received CABG were treated with CTO-PCI. CTO was defined as a thrombolysis in myocardial infarction (TIMI) grade 0 flow in coronary artery for more than 3 months. For patients who underwent multiple interventions, only the first CTO-PCI was recorded. The exclusion criteria were as follows: 1) chronic or acute infections, inflammatory diseases; 2) severe heart failure (left ventricular ejection fraction < 30%) or cardiogenic shock; 3) newly diagnosed acute coronary syndrome with positive troponin (within 1 months); 4) autoimmune diseases; 5) malignant tumor history; 6) severe liver and kidney dysfunction; 7) taking glucocorticoids or other immunosuppressants; 8) incomplete key information patients. All patients signed a written informed consent form to participate in the study prior to any procedures. The study protocol was in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Beijing AnZhen Hospital of Capital Medical University.

Laboratory Measurements

The clinical characteristics, including demographic data and medical history, were collected at the time of enrollment. All the blood samples were immediately collected from the peripheral vein after admission. The laboratory measurements, including the total white blood cell (WBC), neutrophil, lymphocyte and platelet counts and high-sensitivity C-reactive protein (Hs-CRP), hemoglobin, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, total cholesterol (TC), brain natriuretic peptide (BNP), D-dimer and serum creatinine levels, were obtained in the clinical laboratory center according to standard protocols.

The systemic immune-inflammation index (SII) was calculated as total peripheral platelets count (P) × neutrophil-to-lymphocyte ratio (N/L) (SII = P × N/L ratio × 10^9/L).[16] NLR and PLR were simultaneously calculated.

Angiography

Procedural success was defined as successful CTO revascularization, achievement of <30% residual diameter stenosis within the target lesions, and restoration of TIMI grade 3 flow without any in-hospital major adverse cardiovascular events, including death, myocardial infarction (MI), clinically driven target vessel revascularization with PCI or CABG, cardiac tamponade requiring intervention or surgery, and stroke.

The PROGRESS CTO score was calculated from four dimensions: proximal cap ambiguity, absence of interventional collaterals, moderate or severe tortuosity, and circumflex CTO. The J-CTO score was calculated from five dimensions: stump passivation, calcification, bending >45°, CTO lesion length ≥20 mm, and reattempt. The PROGRESS score and J-CTO CTO score were used to quantify the complexity of CTO lesions.

Outcomes

Patients included in the study were routinely followed up by telephone communication, medical history system, or outpatient service. The primary endpoint was the composite of major adverse cardiac events (MACE), which included all-cause death, nonfatal MI and unplanned revascularization. The definition of MI is based on the fourth general definition of myocardial infarction.[19] Unplanned repeated revascularization is defined as any unexpected PCI or CABG after surgery.

Statistical Analysis

Categorical data were expressed as numbers and percentages, and continuous data were expressed as mean ± SD or median and interquartile range (IQR) (25th–75th percentiles). The Kolmogorov–Smirnov test was used to determine the normality of the data. For the comparison of continuous data, Student's *T* test was used for parametric variables and Mann–Whitney *U*-test was used for non-parametric variables. Chi-square test (Fisher exact test) was used for categorical data comparison, and Kruskal–Wallis test was used for comparison between groups. To adjust for differences in baseline features and minimize bias, a probability score matching (PSM) analysis was performed using a 1:1 nearest neighbor matching ratio with a matching tolerance of 0.02. We included the following variables in PSM: age, sex, body mass index (BMI), smoking.

Kaplan–Meier method was used to compare the difference in prognosis and event-free survival of patients in different SII groups, and Log rank test was used to evaluate the significance. Multivariable Cox regression analyses were performed to identify the independent predictors of occurrence of MACE. The stepwise regression method was adopted. Variables with P values <0.1 in the univariate analysis were included in the multivariate analysis. Further subgroup analysis showed an association between SII and other cardiovascular risks.

Receiver-operating characteristic (ROC) curve analysis was used to determine the efficacy of WBC, NLR, PLR, Hs-CRP and SII in predicting MACE. A 4-knots RCS analysis was used to explore the potential association between SII and MACE risk. All analyses were performed using IBM SPSS Statistics 24.0 (IBM, Armonk, NY, USA) and R 4.4 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed p <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 3107 patients were diagnosed with CTO, of which 337 met the inclusion criteria. Three hundred thirty-five pairs of patients with or without prior CABG were obtained after PSM in this study (Figure 1). The SII values were significantly higher in the prior CABG group than in the without prior CABG group [570.10 (444.60, 814.12) vs 519.65 (446.86, 565.84), P < 0.001, respectively].

The overall patient characteristics are summarized in Table 1. Male patients comprised 76.4% of the patients in the study, and the mean age of the patients was 66 (59, 70) years. Regarding demographic characteristics, the medical history of hypertension and diabetes mellitus among groups reach statistical significance. In the laboratory measurement, individuals with prior CABG presented higher levels of WBC, neutrophil counts, platelet counts, BNP and D-dimer on admission. In the evaluation of cardiac function using echocardiography, patients with prior CABG had lower left

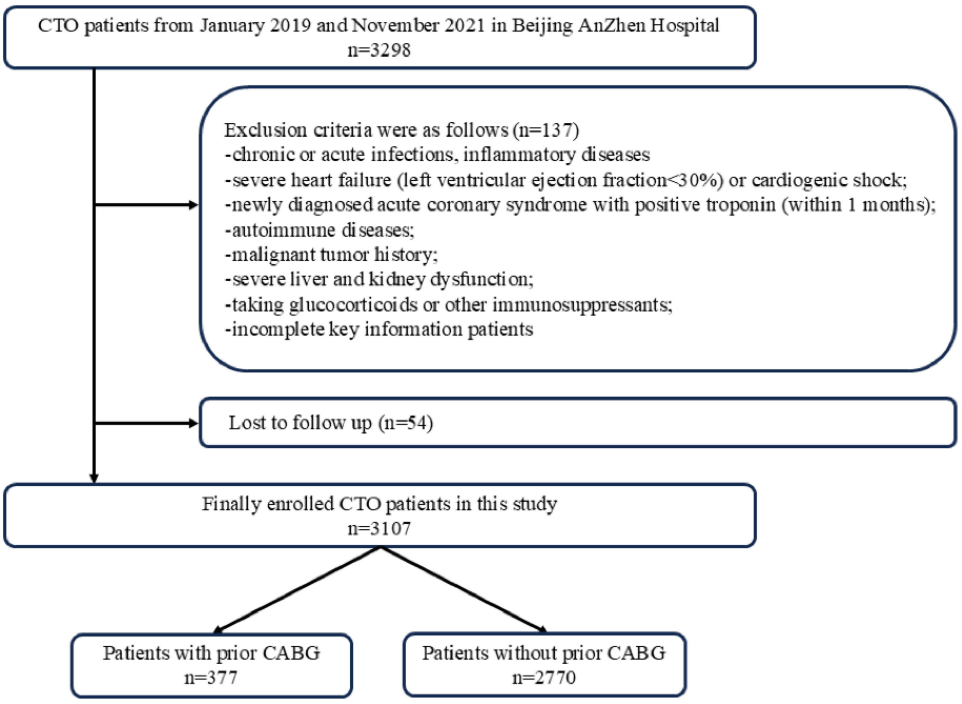

Figure 1 Population flow chart of enrolled patients.
Abbreviations: CTO, chronic total occlusion; CABG, coronary artery bypass grafting.

ventricular ejection fraction (LVEF). In terms of angiography results, prior CABG patients have higher J-CTO score and PROGRESS score compared with patients without prior CABG. The RCA-CTO PCI was predominant between two groups ($P < 0.001$). Procedurally successful CTO-PCI were performed in 81.2% patients. Patients in the prior CABG group tended to have a lower rate of PCI success rate.

According to the median value of SII level, all patients with prior CABG were divided into the higher group (N = 168) and the lower group (N = 167). There was no statistical difference in the demographic characteristics between the two groups (Table 2). The higher levels of SII were associated with WBC, lymphocyte counts, neutrophil counts, platelet counts, Hs-CRP and D-dimer on admission. However, there were no differences between the groups regarding LVEF, J-CTO score and PROGRESS score. The successful CTO-PCI was lower in higher group, albeit not significant ($P = 0.075$).

Follow-Up and Clinical Outcomes

During a median follow-up of 2.58 (2.25, 2.75) years, there were 86 (12.8%) MACE, 13 (1.9%) all-cause death, 24 (3.6%) nonfatal MI and 49 (7.3%) revascularizations in all patients (Table 3). 53 (15.8%) of the patients with prior CABG had MACE, compared with 33 (9.9%) in the patients without prior CABG, respectively ($P < 0.001$). Meanwhile, the incidence of MACE in the higher SII level group was 34 (20.2%) higher than that in the lower SII level group ($P = 0.026$) (Table 4). However, there was no significant difference in all-cause death, nonfatal MI and revascularization between the groups.

The survival Kaplan–Meier analysis showed that patients with prior CABG was significantly associated with a higher risk of MACE than patients without prior CABG in the long-term follow-up. As SII levels increased, the cumulative risk of MACE became significantly higher in the patients with prior CABG stratified by the median value of SII (Figure 2). This suggests that higher SII is associated with an increased risk of cardiovascular events.

Regression Analysis and Subgroup Analysis

Table 5 showed the univariate and multivariate Cox regression analyses of MACE for patients with prior CABG. In the univariate analysis, several potential risk factors were identified, including BMI, previous MI, hypertension, Hs-CRP, SII,

Table 1 Basic Characteristics in CTO Patients with or Without Prior CABG

	Overall (N=670)	CABG Group (N=335)	None CABG Group (N=335)	*P*-value
Demography				
Age, years	66 (59, 70)	66 (60, 70)	65 (58, 70)	0.217
Male, n, %	512 (76.4%)	259 (77.3%)	253 (75.5%)	0.585
BMI, kg/m^2	26.1±3.4	26.2±3.5	26.2±3.4	0.908
Current smoker, n, %	113 (16.9%)	48 (14.3%)	65 (19.4%)	0.079
Previous MI, n, %	148 (22.1%)	71 (21.2%)	77 (23.0%)	0.576
Previous PCI, n, %	287 (42.8%)	131 (39.1%)	156 (46.6%)	0.051
Hypertension, n, %	481 (71.8%)	253 (75.5%)	228 (68.1%)	0.032
Diabetes, n, %	322 (48.1%)	175 (52.2%)	147 (43.9%)	0.030
Previous stroke, n, %	47 (7.0%)	26 (7.8%)	21 (6.3%)	0.449
Laboratory findings				
SII, ×10^9/L	535.08 (446.53, 598.49)	570.10 (444.60, 814.12)	519.65 (446.86, 565.84)	<0.001
WBC, ×10^9/L	6.50 (5.48, 7.57)	6.73 (5.62, 7.84)	6.20 (5.20, 7.21)	<0.001
Lymphocyte, ×10^9/L	1.59 (1.14, 2.12)	1.54 (1.25, 2.00)	1.65 (0.99, 2.20)	0.913
Neutrophil, ×10^9/L	3.95 (3.21, 4.75)	4.43 (3.66, 5.36)	3.49 (2.97, 3.24)	<0.001
Monocyte, ×10^9/L	0.40 (0.32, 0.48)	0.41 (0.33, 0.50)	0.39 (0.31, 0.47)	0.060
Platelets, ×10^9/L	210 (156, 241)	225 (168, 239)	205 (152, 213)	<0.001
Hemoglobin, g/L	142 (131, 152)	143 (133, 153)	140 (130, 150)	0.056
Hs-CRP, mg/L	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (0.00, 2.00)	0.229
Creatinine, umol/L	73.8 (64.1, 85.8)	76.2 (65.5, 89.8)	72.5 (63.4, 84.1)	0.050
Triglycerides, mmol/L	1.45 (1.09, 1.99)	1.43 (1.09, 1.93)	1.46 (1.09, 2.02)	0.977
TC, mmol/L	3.62 (3.12, 4.35)	3.62 (3.19, 4.27)	3.62 (3.05, 4.41)	0.781
HDL-C, mmol/L	0.97 (0.83, 1.13)	0.96 (0.83, 1.14)	0.97 (0.83, 1.13)	0.735
LDL-C, mmol/L	1.96 (1.52, 2.53)	1.96 (1.55, 2.47)	1.95 (1.51, 2.61)	0.745
BNP, pg/mL	69 (38, 160)	84 (42, 192)	58 (33, 122)	<0.001
D-dimer, ng/mL	105 (69, 179)	116 (77, 187)	100 (64, 162)	0.033
LVEF, %	60±8.9	60±8.7	62.0±8.9	<0.001
J-CTO score	2.4±1.2	2.8±1.3	2.2±1.2	<0.001
PROGRESS score	1.4±0.9	1.6±1.1	1.2±0.9	<0.001
Treatment lesions, n (%)				<0.001
RCA	310 (46.3%)	161 (48.1%)	149 (44.5%)	
LAD	178 (26.6%)	63 (18.8%)	115 (34.3%)	
LCX	182 (27.1%)	111 (33.1%)	71 (21.2%)	
Successful CTO PCI	544 (81.2%)	257 (76.7%)	287 (85.7%)	<0.001

Abbreviations: CTO, chronic total occlusion; CABG, coronary artery bypass grafting; SII, systemic immune-inflammation index; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; WBC, white blood count; Hs-CRP, high-sensitivity C-reactive protein; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BNP, brain natriuretic peptide; LVEF, left ventricular ejection; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery.

LDL-C and LVEF (P < 0.1). However, after multivariate adjustment, only the level of SII (hazard ratio = 2.035, 95% CI, 1.103–3.753, P = 0.023) and previous MI (hazard ratio = 2.307, 95% CI, 1.253–4.248, P = 0.005) emerged as independent predictors of MACE. Figure 3 showed the effect of higher SII and risk of future cardiovascular events in different subgroups. Each subgroup included age (<65 years or ≥65 years), sex and history of MI, hypertension and diabetes. Subgroup analysis provided further evidence that this association existed independently of other identified cardiovascular risk factors. Furthermore, there was no significant interaction between SII and these subgroups.

Roc Curve and RCS Analysis

We used ROC curves to estimate the prognostic value of SII and other inflammation index (Figure 4). The area under the curve (AUC) of the SII in predicting MACE after PCI was 0.63 (95% CI 0.52–0.71, P < 0.001), a value higher than that

Table 2 Basic Characteristics in CTO Patients with CABG According to SII Score

	Higher Group (N=168)	Lower Group (N=167)	*P*-value
Demography	26.6±3.2		
Age, years	66 (61, 70)	66 (60, 70)	0.846
Male, n, %	123 (73.2%)	136 (81.4%)	0.072
BMI, kg/m^2	26.6±3.2	25.5±3.7	0.033
Current smoker, n, %	20 (16.8%)	28 (11.9%)	0.204
Previous MI, n, %	38 (22.6%)	33 (19.8%)	0.486
Previous PCI, n, %	68 (40.5%)	63 (37.7%)	0.606
Hypertension, n, %	128 (76.2%)	125 (74.9%)	0.775
Diabetes, n, %	91 (54.2%)	84 (50.3%)	0.479
Previous stroke, n, %	17 (10.1%)	9 (5.4%)	0.106
Laboratory findings			
WBC, ×10^9/L	7.18 (6.17, 8.32)	6.34 (5.28, 7.24)	<0.001
Lymphocyte, ×10^9/L	1.49 (1.13, 1.80)	1.77 (1.38, 2.04)	<0.001
Neutrophil, ×10^9/L	5.01 (4.32, 6.08)	3.88 (3.21, 4.54)	<0.001
Monocyte, ×10^9/L	0.42 (0.35, 0.50)	0.40 (0.32, 0.49)	0.247
Platelets, ×10^9/L	236 (185, 263)	211 (165, 233)	<0.001
Hemoglobin, g/L	141 (132, 152)	145 (133, 153)	0.159
Hs-CRP, mg/L	1.00 (1.00, 3.00)	1.00 (0.50, 2.00)	0.003
Creatinine, umol/L	77.1 (65.2, 92.8)	74.7 (65.5, 88.3)	0.387
Triglycerides, mmol/L	1.49 (1.15, 2.02)	1.39 (1.05, 1.87)	0.179
TC, mmol/L	3.66 (3.23, 4.20)	3.61 (3.16, 4.36)	0.855
HDL-C, mmol/L	0.96 (0.81, 1.14)	0.96 (0.84, 1.13)	0.747
LDL-C, mmol/L	1.96 (1.58, 2.39)	1.96 (1.52, 2.53)	0.842
BNP, pg/mL	91 (54, 220)	69 (39, 159)	0.099
D-dimer, ng/mL	125 (83, 187)	104 (73, 183)	0.033
LVEF, %	60±9.2	60.0±8.2	0.488
J-CTO score	2.9±1.2	2.7±1.1	0.637
PROGRESS score	1.7±1.2	1.6±1.0	0.771
Treatment lesions, n (%)			0.468
RCA	78 (46.4%)	83 (49.7%)	
LAD	36 (21.4%)	27 (16.2%)	
LCX	54 (32.1%)	57 (34.1%)	
Successful CTO PCI	122 (72.6%)	135 (80.8%)	0.075

Abbreviations: CTO, chronic total occlusion; CABG, coronary artery bypass grafting; SII, systemic immune-inflammation index; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; WBC, white blood count; Hs-CRP, high-sensitivity C-reactive protein; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BNP, brain natriuretic peptide; LVEF, left ventricular ejection; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery.

Table 3 Clinical Outcomes in CTO Patients with or Without Prior CABG

	Overall (N=670)	CABG Group (N=335)	None CABG Group (N=335)	*P*-value
MACE, n (%)	86 (12.8%)	53 (15.8%)	33 (9.9%)	0.021
All-cause death, n (%)	13 (1.9%)	9 (2.7%)	4 (1.2%)	0.161
Non-fatal MI, n (%)	24 (3.6%)	15 (4.5%)	9 (2.7%)	0.212
Revascularization, n (%)	49 (7.3%)	29 (8.7%)	20 (6.0%)	0.182

Abbreviations: CTO, chronic total occlusion; CABG, coronary artery bypass grafting; MACE, major adverse cardiovascular events; MI, myocardial infarction.

Table 4 Clinical Outcomes in CTO Patients with CABG According to SII Score

	Higher Group (N=168)	Lower Group (N=167)	*P*-value
MACE, n (%)	34 (20.2%)	19 (11.4%)	0.026
All-cause death, n (%)	7 (4.2%)	2 (1.2%)	0.179
Non-fatal MI, n (%)	10 (7.5%)	5 (3.0%)	0.191
Revascularization, n (%)	17 (10.1%)	12 (7.2%)	0.340

Abbreviations: CTO, chronic total occlusion; CABG, coronary artery bypass grafting; SII, systemic immune-inflammation index; MACE, major adverse cardiovascular events; MI, myocardial infarction.

of the NLR, PLR, Hs-CRP level and WBC (0.60, 0.62, 0.58 and 0.48, respectively). The predictive power of the SII for MACE was higher than that of the NLR, PLR, Hs-CRP level and WBC. To further visualize the relationship between the SII level and MACE risk, we performed an RCS model. The RCS curve appears to have a linear correlation. The HR > 1 for MACE became significant when SII increased over 572.84, and HR increased with the increase of SII (Figure 5).

Discussion

In this study, we found that CTO-PCI in prior CABG patients has lower success rates and higher incidence of MACE compared with patients without prior CABG. To our best knowledge, this study evaluated the correlation between plasma SII levels and patients with prior CABG, and its clinical outcome for the first time. The data reveal that SII levels were significantly higher in group with prior CABG than in group without prior CABG. A higher SII may independently predict the recurrence of adverse cardiovascular events in CTO patients with prior CABG after PCI. Moreover, SII was a better indicator for predicting MACE than the traditional inflammation index. The risk of MACE in CTO patients with prior CABG increased significantly with the increase in the SII.

The treatment of patients undergoing prior CABG may be challenging, as multiple comorbidities and graft failures often require reintervention of the native coronary artery.[20] Indeed, those patients who had prior CABG were older, had many comorbidities, extensive and complex coronary lesions, and they were more likely to have co-existing cardiovascular risk factor, which is also consistent with our findings.[21,22] Approximately half of all CABG patients who undergo coronary angiography are diagnosed with a new coronary CTO, owing to the fact that coronary bypass is associated with

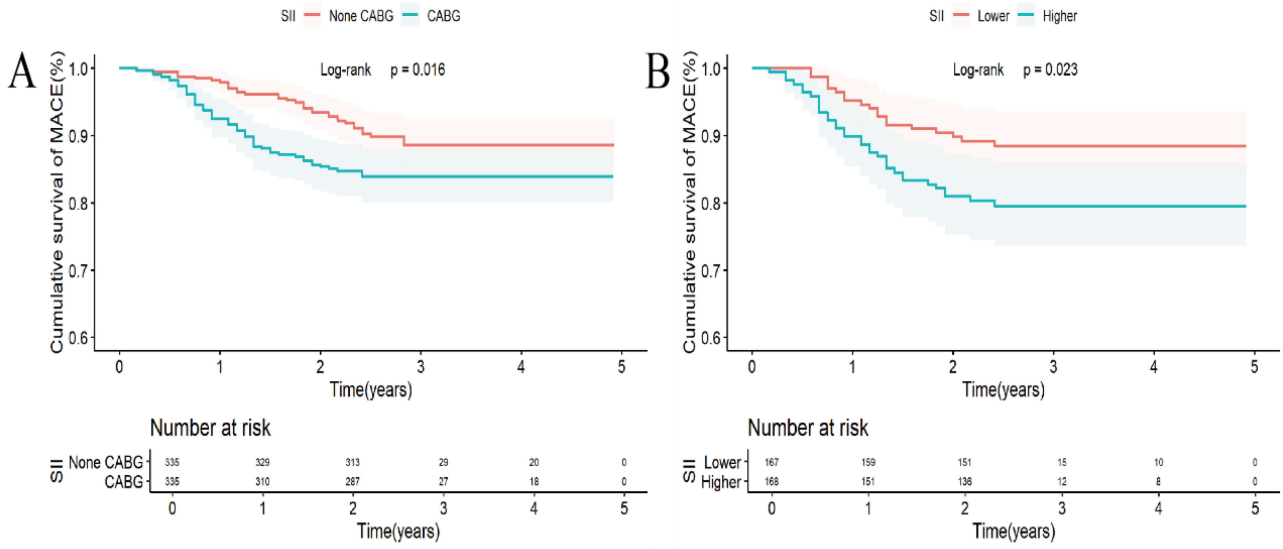

Figure 2 Kaplan-Meier survival curve for the incidence of MACE. (**A**) patients with or without prior CABG; (**B**) patients with prior CABG stratified by the median value of SII.

Abbreviations: SII, systemic immune-inflammation index; MACE, major adverse cardiovascular events; CABG, coronary artery bypass grafting.

Table 5 Cox Regression Analysis to Evaluate SII in Predicting MACE in CTO Patients with CABG

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
BMI	1.548 (1.124–2.265)	0.009		
Previous MI	2.245 (1.281–3.936)	0.005	2.307 (1.253–4.248)	0.005
Hypertension	2.659 (1.137–6.220)	<0.001		
Hs-CRP	1.082 (1.002–1.170)	0.045		
SII	1.897 (1.082–3.327)	0.025	2.035 (1.103–3.753)	0.023
LDL-C	1.229 (1.067–2.106)	<0.001		
LVEF	2.316 (1.081–4.962)	<0.001		

Abbreviations: SII, systemic immune-inflammation index; MACE, major adverse cardiovascular events; CTO, chronic total occlusion; CABG, coronary artery bypass grafting; BMI, body mass index; MI, myocardial infarction; Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection; CI, confidence interval; HR, hazard ratio.

accelerated development of atherosclerosis of native coronary arteries.[7] These patients often have recurring symptoms and events that require revascularization. Zheng et al have revealed a significant decrease in the proportion of patients without symptoms after surgery.[23]

In the present study, the most common CTO target vessel was the right coronary artery (46.3%), although in the previous CABG group, the left anterior descending artery was the target vessel less frequently (18.8% versus 34.3%), presumably because of the higher patency rate of the left intramammary artery. Similar to previous studies, we found that the success rate of CTO-PCI was lower in patients with prior CABG, indicating that advances in equipment and technology can only partially overcome the challenges associated with these patients. Correspondingly, a higher rate of follow-up MACE was also found in these patients. According to previous studies, there are pathological differences

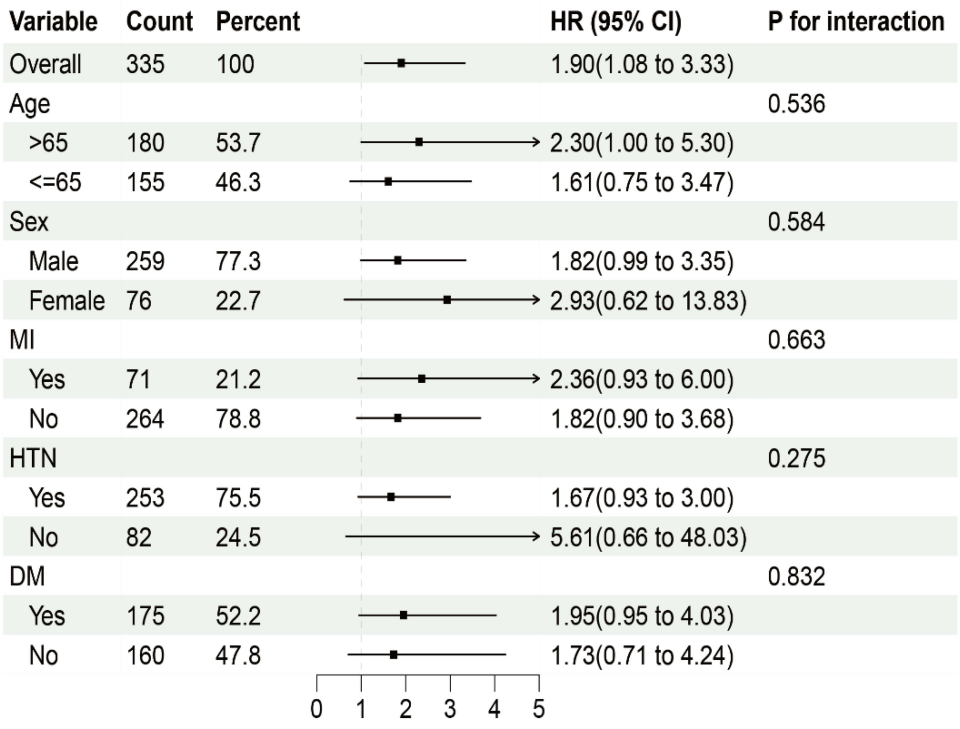

Figure 3 Subgroup analysis of the predictive value of SII for MACE in CTO patients with prior CABG.
Abbreviations: SII, systemic immune-inflammation index; MACE, major adverse cardiovascular events; CABG, coronary artery bypass grafting; HTN, Hypertension; DM, diabetes mellitus.

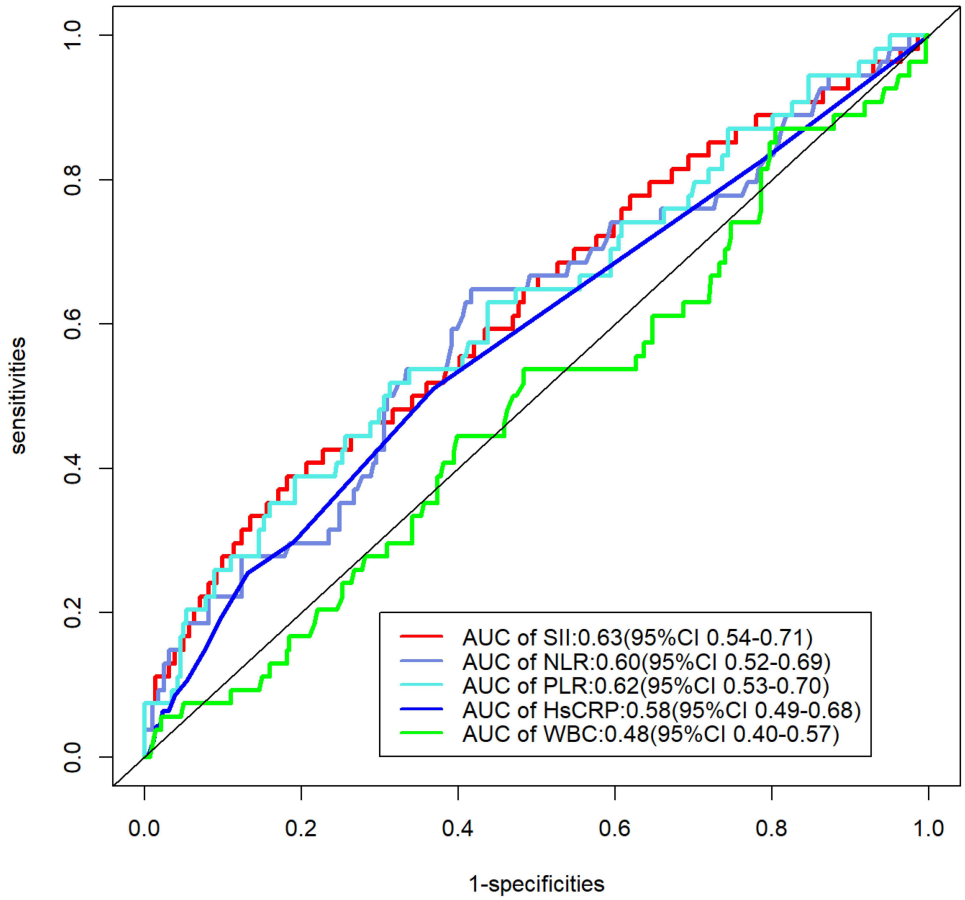

Figure 4 Receiver operating characteristic curve analysis for inflammatory index in predicting MACE.
Abbreviations: MACE, major adverse cardiovascular events; SII, systemic immune-inflammation index; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; HsCRP, high-sensitivity C-reactive protein.

between CTO patients with and without CABG. Sakakura et al reported that patients who previously received CABG showed more inflammation, fibrosis, calcification, and negative remodeling in CTO lesions.[24] So far, the main research has focused on anatomical factors of patients, with a lack of research on systemic factors of CTO patients with prior CABG.

At present, researchers have found that atherosclerosis is also a systemic chronic inflammatory vascular disease.[25,26] Leukocytes, including neutrophils, monocytes, macrophages and lymphocytes, which constitute the inflammatory system, play different roles in atherosclerosis.[27,28] In atherosclerosis, platelets not only participate in acute thrombotic vascular occlusion but also participate in chronic inflammation of early vascular wall, which may lead to instability of atherosclerosis.[29] A new inflammation marker-systemic immune inflammation index (SII), measured by neutrophils × platelet/lymphocyte calculations, can reflect the balance between host inflammation and thrombotic status simultaneously.[18] SII appears to be more stable than individual blood counts, which are susceptible to various factors such as dehydration and fluid overload.[30] A meta-analysis suggests that SII may be a potential biomarker for the development of coronary artery disease (CAD), and elevated SII is associated with an increased risk of CAD.[31] Zhao et al found that higher SII values an independent prognostic factor for long-term outcomes of adverse events after revascularization in patients with three-vessel disease.[32] A study suggests that an increase in SII index is closely related to underdeveloped collateral circulation in CTO lesions.[33] In the setting of CTO, inflammatory stimuli can lead to the activation and recruitment of leukocytes, particularly monocytes and neutrophils. These cells migrate to the site of the occlusion, influenced by chemokines and cytokines released from damaged endothelium and atherosclerotic plaques.[34] Activated platelets release pro-inflammatory mediators, such as cytokines and chemokines, which further enhance

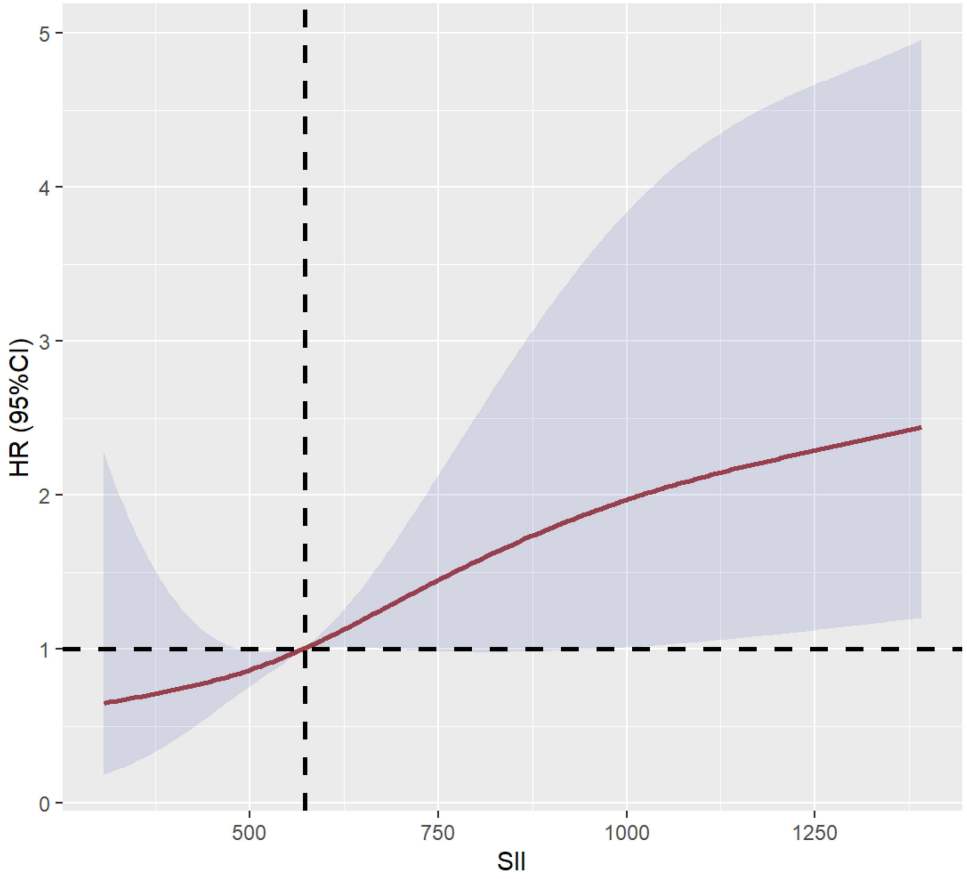

Figure 5 The restricted cubic spline of MACE and the SII in CABG group.
Abbreviations: SII, systemic immune-inflammation index; MACE, major adverse cardiovascular events; CABG, coronary artery bypass grafting; HR, hazard ratio; CI, confidence interval.

leukocyte recruitment and activation.[35] This interaction is crucial in maintaining the inflammatory microenvironment within the occluded artery. The results of a recent study suggest that high SII values indicating an increase in high inflammatory response may contribute to poor clinical outcomes in patients undergoing CABG.[36] The immune thrombotic model composed of two parts, the immune system and the hemostatic system, is believed to better reflect inflammation. However, few researchers have studied the relationship between SII index and cardiovascular risk in CTO patients with prior CABG.

In this study, the prior CABG group had higher SII and WBC values, which reflect more severe inflammation. In addition, compared to traditional inflammation indices, SII is a better indicator for predicting MACE in CTO patients with prior CABG. Myocardial dysfunction and delayed postoperative recovery may be observed due to overactivation of the inflammatory response.[37] Increased inflammation and oxidative stress have been reported to be associated with adverse outcomes of cardiovascular disease. Since these patients may exhibit altered immune responses due to previous interventions, the specificity of SII as a marker could be affected by confounding factors like comorbidities, ongoing inflammation, or other cardiovascular conditions. A high SII may correlate with more advanced disease states, but false negatives could occur in patients with milder inflammatory responses or compensatory mechanisms. Furthermore, activating platelet molecules can cause postoperative complications, such as MI and stroke.[38] Xu et al found a positive association between SII and CAD in patients with hypertension or diabetes, which may be related to endothelial dysfunction and inflammatory infiltration caused by long-term inflammation.[39,40] Indeed, group with prior CABG has a high proportion of patients with hypertension (75.5%) and diabetes (52.2%) compared with group with prior CABG in current study. Aspirin and statins have been shown to indirectly reduce thrombosis and inflammation. Therefore, these are usually used before surgery to reduce cardiovascular events.[41] Recently, Ridker et al reported that

anti-inflammatory therapy targeting interleukin-1β significantly reduced the incidence of cardiovascular events in patients with previous MI.[42]

At present, there is no consensus or guidelines for the treatment of CTO patients with prior CABG, and the prognosis of these patients is still unknown. Given the varying rates of CABG and PCI across different healthcare systems, these results can inform clinical practice in diverse settings. In regions where PCI is more frequently performed, understanding the predictive value of SII could enhance risk stratification and patient management. Our research findings have expanded our understanding of SII as a cardiovascular event tool, particularly for CTO patients with prior CABG. This suggests that SII may help identify more high-risk patients who require more aggressive treatment and follow-up strategies.

Limitation

The current study has several limitations. First, this was a single-center, retrospective study and there may be selection bias. Second, SII was only measured at admission and did not record dynamic changes after surgery and follow-up period. Finally, the medication status of the patients was not recorded in this study, and it is still unclear whether the relevant drugs have the potential to reduce anti-inflammatory risks.

Conclusion

In CTO patients with prior CABG after PCI, high SII values significantly predict a higher MACE rate in the follow-up. Based on the above results, due to SII being recognized as more stable than traditional inflammatory indicators, it can provide more reliable prognostic information for these patients.

Data Sharing Statement

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study protocol was in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Beijing An-Zhen Hospital of Capital Medical University. All patients signed a written informed consent form to participate in the study prior to any procedures.

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Disclosure

The authors declare no conflicts of interest.

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