

# The Combined Effect of Systemic Immune-Inflammation Index and Type 2 Diabetes Mellitus on the Prognosis of Patients Undergoing Percutaneous Coronary Intervention: A Large-Scale Cohort Study

Xiaohui Bian<sup>1-3,\*</sup>, Jining He<sup>1-3,\*</sup>, Rui Zhang<sup>1-3</sup>, Sheng Yuan<sup>1-3</sup>, Kefei Dou<sup>1-4</sup>

<sup>1</sup>Cardiometabolic Medicine Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; <sup>2</sup>Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; <sup>3</sup>State Key Laboratory of Cardiovascular Disease, Beijing, People's Republic of China; <sup>4</sup>National Clinical Research Center for Cardiovascular Diseases, Beijing, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Kefei Dou, Cardiometabolic Medicine Center, National Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, A 167 Beilishi Road, Xicheng District, Beijing, 100037, People's Republic of China, Tel +86-13801032912, Fax +86-10-6831-3012, Email drdoukefei@126.com

**Background:** Chronic low-grade inflammation is the common mechanism of both atherosclerosis and type 2 diabetes mellitus (T2DM), and systemic immune-inflammation index (SII) has been emerged as a novel and simple inflammatory biomarker. However, the association between SII and glycemic metabolism and their synergistic effect on the prognosis of coronary artery disease (CAD) patients remains unclear.

**Methods:** A total of 8602 patients hospitalized for percutaneous coronary intervention (PCI) were included. The primary endpoint was major adverse cardiovascular events (MACE), including all-cause death, myocardial infarction (MI), and target vessel revascularization. According to the optimal cut-off value of SII for MACEs, patients were grouped into higher levels of SII (SII-H) and lower levels of SII (SII-L) and further divided by the concomitance of T2DM into four groups: SII-H/T2DM, SII-H/Non-T2DM, SII-L/T2DM, SII-L/Non-T2DM.

**Results:** During a median 2.4-year follow-up, 522 MACEs occurred. The optimal cut-off value of SII for MACEs was 502.5. A 1-unit increase of SII (transformed by natural logarithm) was associated with a 29% increase of MACE risks in the T2DM cohort [adjusted hazard ratio (HR): 1.29, 95% confidence interval (CI): 1.03 to 1.61,  $P = 0.024$ ], while had no effect in the non-T2DM cohort (HR: 1.03, 95% CI: 0.80 to 1.34,  $P = 0.800$ ). Compared to those in SII-H/T2DM group, patients in SII-H/Non-T2DM, SII-L/T2DM, SII-L/Non-T2DM had significantly decreased risk of MACEs [adjusted HR: 0.77, 95% CI: 0.61 to 0.98,  $P = 0.036$ ; adjusted HR: 0.66, 95% CI: 0.50 to 0.87,  $P = 0.003$ ; adjusted HR: 0.58, 95% CI: 0.45 to 0.74,  $P < 0.001$ ; respectively]. Multivariable Cox regression analysis also indicated the highest risk in T2DM patients with higher levels of SII than others ( $P$  for trend  $< 0.001$ ).

**Conclusion:** In this large-scale real-world study, diabetic patients with elevated SII levels were associated with worse clinical outcomes after PCI.

**Keywords:** systemic immune-inflammation index, type 2 diabetes mellitus, coronary artery disease, percutaneous coronary intervention

## Introduction

Atherosclerosis is identified as a chronic, low-grade inflammatory condition accompanied by autoimmune responses involving both the innate and adaptive immune systems.<sup>1,2</sup> Numerous observational studies have probed the prognostic value of

inflammatory biomarkers in patients with coronary artery disease (CAD),<sup>3,4</sup> and several anti-inflammatory clinical trials have further confirmed the causal relationship between inflammation and CAD.<sup>2</sup> The growth of atherosclerotic lesion is characterized by an imbalance between inflammation and its resolving, with various types of blood cells playing distinct roles in this intricate pathological process.<sup>5</sup> A previous study has indicated that elevated neutrophil-to-lymphocyte ratio (NLR) was associated with adverse prognosis for CAD patients, especially in those with type 2 diabetes mellitus (T2DM).<sup>6</sup> Recent research has also highlighted the involvement of platelets in the recruitment and activation of leukocytes and mediate leukocyte-endothelium adhesion, which play a crucial role in the progression of atherosclerosis.<sup>7,8</sup> The uncontrolled and excessive activation of leukocytes and platelets generates a vicious circle, resulting in plaque instability and vessel occlusion.<sup>9</sup> Therefore, both leukocytes and platelets significantly contribute to the initiation and progression of CAD.

Systemic immune-inflammation index (SII), a novel index calculated as (platelet\*neutrophil)/lymphocyte, integrates the prognostic information of leukocytes and platelets into a single index, providing insights into the sophisticated interaction among host immunity, inflammation, and thrombosis. Previous studies have shown that SII was associated with the severity of coronary lesions.<sup>10,11</sup> Furthermore, SII has been identified as an independent predictor for poor clinical outcomes in patients with either stable CAD or acute coronary syndrome (ACS).<sup>12,13</sup>

Patients with T2DM tended to have a severer plaque burden and increased cardiovascular risks.<sup>14</sup> Sterile chronic inflammation, a well-recognized feature that is common to both diabetes and atherosclerosis, is considered as a possible link between T2DM and CAD. However, there is currently limited evidence regarding the prognostic value of SII in CAD patients with impaired glycemic metabolism status. Whether SII and T2DM had a synergetic effect on the prognosis remains unknown. Therefore, the present study aimed to investigate the relationship between SII and glycemic metabolism status and to further evaluate their synergetic effect on the prognosis of CAD patients undergoing percutaneous coronary intervention (PCI).

## Methods

### Study Design and Follow-Up

The design of the present study was a prospective, observational, single-center cohort study. From January 2013 to December 2013, a total of 10,724 consecutive CAD patients undergoing PCI was enrolled at Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences (Beijing, China). The exclusion criteria included: Patients with (1) missing crucial baseline data; (2) loss of follow-up; (3) no drug-eluting stent (DES) implantation; (4) unsuccessful PCI; (5) severe renal dysfunction [estimated glomerular filtration rate (eGFR) < 15 mL/(min\*1.73m<sup>2</sup>)];<sup>15</sup> (6) hematological disorders (eg, leukemia, aplastic anemia); (7) acute infection; (8) active tumor; (9) immuno-suppressant prescriptions ([Supplementary Figure S1](#)). Finally, a total of 8,602 patients were included in the present study and divided into the SII-H/T2DM (N = 1,440), SII-L/T2DM (N = 2,516), SII-H/Non-T2DM (N = 1,687) and SII-L/Non-T2DM (N = 2,959) groups, according to the optimal cut-off value of SII and whether they had T2DM or not.

The clinical status of enrolled patients was routinely followed up through telephone interviews or outpatient visits at 1, 6, and 12 months, and then annually for up to 3 years. The primary endpoint was major adverse cardiovascular events (MACEs), defined as a composite of all-cause death, myocardial infarction (MI), and target vessel revascularization (TVR). Secondary endpoints included a composite of all-cause death, MI, and individual components of MACEs. All-cause death was defined as death from any cause, whether cardiac or non-cardiac. MI was defined by clinical symptoms, electrocardiogram, and laboratory parameters based on the third universal definition of MI. TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. All events were adjudicated by 2 blinded independent specialists, and any disagreement was resolved by consensus or a third experienced cardiologist.

The study protocol underwent review and approval by the Ethics Committee of Fuwai Hospital (2016–847). The study adhered to the ethical standards outlined for medical research involving human subjects, as specified in the 1964 Declaration of Helsinki and its subsequent amendments. Relevant information, including the study's purpose, procedures, potential risks and benefits, confidentiality measures, and the rights of the participants, was provided to all participants before including them in the study. All participants in this study provided written informed consent before intervention.

## Treatment and Procedure

PCI was performed by experienced interventional cardiologists who were unaware of the study protocol, in line with recent practical guidelines. The details of equipment choice and intraoperative strategy were at the discretion of individual physicians. Before the selective PCI, all patients received aspirin (300 mg) and a loading-dose P2Y12 inhibitor (ticagrelor 180 mg or clopidogrel 300mg), unless they already received dual antiplatelet therapy; for patients presenting with acute coronary syndrome (ACS), the same dose of aspirin and ticagrelor (180 mg) or clopidogrel (300–600 mg) was given orally as soon as possible. To achieve procedural anticoagulation, unfractionated heparin (100 U/kg) was administered to all patients before PCI. After the procedure, aspirin (100 mg daily) and clopidogrel (75 mg daily) were prescribed for at least 12 months.

## Definitions

SII mentioned in the present study was calculated by the following formula:  $\frac{\text{platelet}(*10^9/L)*\text{neutrophil}(*10^9/L)}{\text{lymphocyte}(*10^9/L)}$ . T2DM was defined by fasting blood glucose (FBG)  $\geq 7.0$  mmol/L (126 mg/dL), or hemoglobin A1c (HbA1c) levels  $\geq 6.5\%$ , or 2-h blood glucose of oral glucose tolerance test (OGTT)  $\geq 11.1$  mmol/L (200 mg/dL), or known T2DM with current use of hypoglycemic drugs.<sup>16</sup> Hypertension was determined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg or previous definite diagnosis of hypertension with antihypertensive medications.<sup>17</sup> Dyslipidemia was diagnosed as fasting total cholesterol (TC)  $\geq 5.2$  mmol/L, low-density lipoprotein cholesterol (LDL-C)  $\geq 3.4$  mmol/L, high-density lipoprotein cholesterol (HDL-C)  $< 1.0$  mmol/L, triglyceride (TG)  $\geq 1.7$  mmol/L, and/or long-term use of lipid-lowering drugs.<sup>18</sup> Renal dysfunction was defined as eGFR  $< 90$  mL/(min\*1.73m<sup>2</sup>). Body mass index (BMI) was calculated as weight(kg)/height(m)<sup>2</sup>.

Coronary angiography data was interpreted and recorded by 2 independent cardiologists according to a clear and predefined criterion. Any identifying information or treatment assignment was concealed before being presented to the judges. If the 2 cardiologists disagreed, a third experienced physician was involved to reevaluate the case, and a consensus was reached to resolve the conflict. According to the coronary angiography, left main (LM) disease was defined as  $\geq 50\%$  stenosis of the LM coronary artery, and three-vessel disease was defined as  $\geq 50\%$  stenosis of all 3 main coronary arteries (ie, right coronary artery, left anterior descending artery and left circumflex artery). Chronic total occlusion (CTO) lesion was determined as thrombolysis in myocardial infarction (TIMI) flow grade of 0 in a native coronary artery for more than 3 months.<sup>19</sup> The complexity of coronary lesions was evaluated by Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score using an online calculator (<http://www.syntaxscore.com/>). Successful revascularization was determined as a residual stenosis  $< 30\%$  with TIMI flow grade 3 measured by visual estimation of post-PCI angiography.<sup>19</sup>

## Laboratory tests

All the laboratory tests mentioned in this study were performed preoperatively on the day of admission. Fasting blood samples were collected from all patients within 24 h after admission and were stored at  $-80$  °C until the test. An automatic blood cell analyzer (XT-1800i; Sysmex Corporation) was used to measure complete blood count including platelet, neutrophil, lymphocyte, and other parameters. Fasting blood glucose (FBG) was measured by the enzymatic hexokinase method. HbA1c was measured by Tosoh Automated Glycohemoglobin Analyzer (HLC-723G8, Tokyo, Japan). Other laboratory test indicators, including lipid profiles (TG, TC, LDL-C, and HDL-C), creatinine, and high-sensitivity C-reactive protein (hsCRP) were measured by standard operating procedures at the core laboratory in Fuwai Hospital. Chinese-modified Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR.<sup>20</sup>

## Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation or median (interquartile range [IQR]) and were compared by two-tailed unpaired Student's *t*-test or Mann–Whitney *U*-test as appropriate. Categorical variables were presented as frequency with percentage and were compared by Pearson  $\chi^2$  test or Fisher exact test as appropriate. Pearson correlation analysis was performed to evaluate the correlation between SII and glycemic (FBG and HbA1c) or inflammatory (hsCRP) parameters. The cumulative incidence of MACEs was depicted by Kaplan–Meier curves, and the risks of various groups were compared by Log rank test. The joint effect of T2DM and SII was analyzed by univariate

and multivariate Cox proportional hazards models. Hazard ratios (HR) and 95% confidence interval (CI) were described. Univariate Cox regression analysis was conducted to identify variables with significant associations with the outcomes ( $P < 0.1$ , [Supplementary Table S1](#)), while other variables were selected according to previous studies.<sup>6,21</sup> The included variates in multivariate Cox analysis were age, male, hypertension, dyslipidemia, prior MI, prior PCI/CABG, hsCRP, creatinine, LM/three-vessel disease, CTO, number of stents, SYNTAX score, total length of stents and average diameter of stents. An exploratory subgroup analysis was conducted to test the risk of MACEs among six different subgroups and the results were depicted by forest plot, while the choice of the subgroups was based on clinical significance and previous studies.<sup>22–24</sup> Additionally, the linear correlation between SII and the risk of MACE was examined by restricted cubic splines. A two-tailed  $P$  value  $<0.05$  was considered as statistical significance. All statistical analyses were performed using R (version 4.2.1), RStudio software (version 2022.07.1; <http://www.rstudio.org/>) and GraphPad Prism software (version 8.0.1; GraphPad Software, Inc., La Jolla, CA, United States). The mainly used R packages and their versions were “ggplot2” (3.3.6), “ezcox” (1.0.2), ‘rms’ (6.6–0), “survival” (3.3–1), and “survminer” (0.4.9).

## Results

In general, 8,602 patients who met the inclusion and exclusion criteria were ultimately included in this study. The mean age of the total population was  $58.41 \pm 10.19$  years, and 76.9% were male. During a median follow-up of 2.4 years (interquartile range: 2.2–2.6 years), 102 (1.2%) all-cause death, 90 (1.0%) MI, 393 (4.6%) TVR and 522 (6.1%) MACEs were recorded.

## Baseline Characteristics

The baseline demographic and clinical characteristics of the entire study population as well as according to the occurrence of MACE are detailed in [Table 1](#). Patients with any component of MACE tended to be older and had a higher proportion of T2DM and MI history. Besides, they also had higher levels of SII, FBG, HbA1c, and hsCRP, but lower LVEF in admission. As for angiography data, patients with MACE seemed to have more complicated lesions, which were more likely to present with LM/three-vessel disease or CTO lesions, and had higher SYNTAX scores. In addition, they tended to have more and longer stents implanted.

## Comparison of Baseline Characteristics Among Four Groups

According to the `surv_cutpoint` function of the R package `survminer` in the R programming language, the optimal cut-off point of SII for the risk of MACE was 502.5. Thus, patients were divided into four groups based on the level of SII and the presence of T2DM, and a comparison of baseline characteristic among the four groups are listed in [Table 2](#). Compared with patients in the SII-H/T2DM subset, those in the other three groups tended to be younger and had a lower prevalence of comorbidities, such as hypertension, stroke history, PAD history, and clinical presentation as ACS. In the case of laboratory test results in admission, TG, TC, LDL-C, hsCRP, and creatinine were significantly higher in the SII-H/T2DM group, while HDL-C, eGFR, and LVEF were significantly lower. Patients with higher levels of SII combined with T2DM were more likely to have LM/three-vessel disease and CTO and present with higher SYNTAX scores.

**Table 1** Baseline Characteristics for Patients Stratified by Primary Events

Variables	Overall (N=8602)	Non-MACE (N=8080)	MACE (N=522)	P value
<b>Four subgroups</b>				<0.001
SII-H/T2DM	1440 (16.7)	1311 (16.2)	129 (24.7)	
SII-H/Non-T2DM	2516 (29.2)	2350 (29.1)	166 (31.8)	
SII-L/T2DM	1687 (19.6)	1595 (19.7)	92 (17.6)	
SII-L/Non-T2DM	2959 (34.4)	2824 (35.0)	135 (25.9)	

(Continued)

Table 1 (Continued).

Variables	Overall (N=8602)	Non-MACE (N=8080)	MACE (N=522)	P value
<b>Baseline characteristics</b>				
Age, years	58.41±10.19	58.35±10.17	59.29±10.41	0.041
Male	6611 (76.9)	6197 (76.7)	414 (79.3)	0.187
BMI, kg/m <sup>2</sup>	25.90±3.19	25.90±3.19	26.00±3.14	0.463
Hypertension	5547 (64.5)	5197 (64.3)	350 (67.0)	0.224
Dyslipidemia	5741 (66.7)	5381 (66.6)	360 (69.0)	0.287
T2DM	3956 (46.0)	3661 (45.3)	295 (56.5)	<0.001
Smoking history	4899 (57.0)	4596 (56.9)	303 (58.0)	0.635
MI history	1617 (18.8)	1488 (18.4)	129 (24.7)	<0.001
PCI history	1958 (22.8)	1819 (22.5)	139 (26.6)	0.034
CABG history	337 (3.9)	310 (3.8)	27 (5.2)	0.159
Stroke history	903 (10.5)	836 (10.3)	67 (12.8)	0.085
PAD history	637 (7.4)	596 (7.4)	41 (7.9)	0.750
ACS	5070 (58.9)	4767 (59.0)	303 (58.0)	0.702
<b>Laboratory tests</b>				
Platelet, *10 <sup>9</sup> /L	207.26±55.08	207.10±54.84	209.67±58.70	0.301
Neutrophil, *10 <sup>9</sup> /L	4.25±1.53	4.23±1.51	4.55±1.76	<0.001
Lymphocyte, *10 <sup>9</sup> /L	1.95±0.64	1.95±0.64	1.99±0.64	0.192
SII	423.81 [310.25, 591.46]	422.45 [310.04, 588.03]	450.41 [319.81, 628.96]	0.033
Ln SII	6.07±0.51	6.07±0.51	6.13±0.56	0.014
FBG, mmol/L	6.26±2.22	6.23±2.18	6.68±2.71	<0.001
HbA1c, %	6.60±1.21	6.59±1.21	6.79±1.24	<0.001
TG, mmol/L	1.52 [1.14, 2.08]	1.53 [1.14, 2.08]	1.46 [1.14, 2.09]	0.526
TC, mmol/L	4.20±1.07	4.20±1.07	4.19±1.07	0.852
HDL-C, mmol/L	1.04±0.28	1.04±0.28	1.03±0.26	0.792
LDL-C, mmol/L	2.50±0.90	2.50±0.90	2.49±0.90	0.728
hsCRP, mg/L	1.57 [0.79, 3.46]	1.56 [0.78, 3.40]	1.72 [0.91, 4.15]	0.002
Creatinine, μmol/L	75.16±15.44	75.10±15.43	76.01±15.44	0.195
eGFR, mL/min/1.73m <sup>2</sup>	102.91±22.04	102.97±21.93	102.08±23.65	0.373
LVEF, %	63.12±7.12	63.19±7.07	62.09±7.83	0.001

(Continued)

**Table 1** (Continued).

Variables	Overall (N=8602)	Non-MACE (N=8080)	MACE (N=522)	P value
<b>Medications</b>				
DAPT	8407 (97.7)	7894 (97.7)	513 (98.3)	0.479
β-blocker	7739 (90.0)	7259 (89.8)	480 (92.0)	0.138
CCB	4241 (49.3)	3967 (49.1)	274 (52.5)	0.145
Statins	8258 (96.0)	7757 (96.0)	501 (96.0)	1.000
Nitrate	8417 (97.8)	7907 (97.9)	510 (97.7)	0.932
<b>Angiography data</b>				
LM/three-vessel disease	3787 (44.0)	3506 (43.4)	281 (53.8)	<0.001
CTO	1430 (16.6)	1305 (16.2)	125 (23.9)	<0.001
SYNTAX score	10.00 [6.00, 16.00]	10.00 [5.50, 16.00]	11.00 [6.00, 17.50]	0.005
Number of stents	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 3.00]	0.001
Total length of stents, mm	36.00 [23.00, 55.00]	36.00 [23.00, 55.00]	40.00 [24.00, 57.75]	0.001
Average diameter of stents, mm	3.00 [2.75, 3.50]	3.00 [2.75, 3.50]	3.00 [2.71, 3.33]	0.004

**Note:** Values are expressed as mean ± SD or median (IQR) for continuous variables and percentage for categorical variables.

**Abbreviations:** SD, standard deviation; IQR, interquartile range; MACE, major adverse cardiovascular events; SII, systematic immune-inflammation index; T2DM, type 2 diabetes mellitus; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PAD, peripheral artery disease; ACS, acute coronary syndrome; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; DAPT, dual antiplatelet therapy; CCB, calcium channel blocker; LM, left main; SYNTAX, synergy between PCI with taxus and cardiac surgery.

**Table 2** Baseline Characteristics for Patients Stratified by the Level of SII and Different Glycemic Metabolism Status

Variables	SII-H/T2DM (N=1,440)	SII-L/T2DM (N=2,516)	SII-H/Non-T2DM (N=1,687)	SII-L/Non-T2DM (N=2,959)	P value
<b>Baseline characteristics</b>					
Age, years	59.68±10.29	59.34±9.63	57.28±10.60	57.64±10.23	<0.001
Male	1070 (74.3)	1867 (74.2)	1341 (79.5)	2333 (78.8)	<0.001
BMI, kg/m <sup>2</sup>	26.18±3.19	26.31±3.12	25.43±3.24	25.68±3.16	<0.001
Hypertension	1039 (72.2)	1683 (66.9)	1091 (64.7)	1734 (58.6)	<0.001
Dyslipidemia	1004 (69.7)	1800 (71.5)	1042 (61.8)	1895 (64.0)	<0.001
Smoking history	818 (56.8)	1375 (54.7)	979 (58.0)	1727 (58.4)	0.034
MI history	271 (18.8)	526 (20.9)	281 (16.7)	539 (18.2)	0.005
PCI history	357 (24.8)	675 (26.8)	307 (18.2)	619 (20.9)	<0.001
CABG history	66 (4.6)	118 (4.7)	55 (3.3)	98 (3.3)	0.015
Stroke history	185 (12.8)	306 (12.2)	162 (9.6)	250 (8.4)	<0.001
PAD history	129 (9.0)	214 (8.5)	109 (6.5)	185 (6.3)	0.001
ACS	939 (65.2)	1331 (52.9)	1096 (65.0)	1704 (57.6)	<0.001

(Continued)

Table 2 (Continued).

Variables	SII-H/T2DM (N=1,440)	SII-L/T2DM (N=2,516)	SII-H/Non-T2DM (N=1,687)	SII-L/Non-T2DM (N=2,959)	P value
<b>Laboratory tests</b>					
Platelet, *10 <sup>9</sup> /L	239.45±61.17	189.06±44.84	236.83±56.75	190.20±43.35	<0.001
Neutrophil, *10 <sup>9</sup> /L	5.57±1.90	3.75±1.02	5.13±1.44	3.52±0.97	<0.001
Lymphocyte, *10 <sup>9</sup> /L	1.74±0.58	2.16±0.68	1.68±0.55	2.03±0.59	<0.001
SII	676.04 [572.59,863.71]	342.63 [267.90,410.63]	662.33 [569.80,835.66]	337.12 [269.07,411.40]	<0.001
Ln SII	6.62±0.38	5.77±0.32	6.58±0.31	5.78±0.31	<0.001
FBG, mmol/L	7.94±3.04	7.35±2.42	5.21±0.59	5.11±0.55	<0.001
HbA1c, %	7.41±1.29	7.48±1.32	5.88±0.33	5.87±0.34	<0.001
TG, mmol/L	1.57 [1.20,2.15]	1.59 [1.19,2.21]	1.49 [1.13,2.02]	1.45 [1.09,1.99]	<0.001
TC, mmol/L	4.27±1.10	4.19±1.10	4.19±1.02	4.18±1.05	0.053
HDL-C, mmol/L	1.01±0.27	1.02±0.27	1.05±0.29	1.06±0.28	<0.001
LDL-C, mmol/L	2.55±0.92	2.48±0.91	2.49±0.86	2.50±0.91	0.080
hsCRP, mg/L	2.46 [1.18,6.62]	1.49 [0.78,3.10]	1.93 [0.90,4.75]	1.27 [0.65,2.47]	<0.001
Creatinine, μmol/L	77.41±17.98	74.20±15.59	75.94±15.19	74.44±13.90	<0.001
eGFR, mL/min/1.73m <sup>2</sup>	99.52±23.84	103.83±23.03	102.35±21.21	104.10±20.49	<0.001
LVEF, %	61.94±7.83	63.15±6.86	63.19±7.27	63.63±6.83	<0.001
<b>Medications</b>					
DAPT	1413 (98.1)	2469 (98.1)	1649 (97.7)	2876 (97.2)	0.083
β-blocker	1324 (91.9)	2308 (91.7)	1503 (89.1)	2604 (88.0)	<0.001
CCB	737 (51.2)	1272 (50.6)	825 (48.9)	1407 (47.5)	0.061
Statins	1367 (94.9)	2400 (95.4)	1634 (96.9)	2857 (96.6)	0.006
Nitrate	1402 (97.4)	2460 (97.8)	1660 (98.4)	2895 (97.8)	0.248
<b>Angiography data</b>					
LM/three-vessel disease	730 (50.7)	1224 (48.6)	659 (39.1)	1174 (39.7)	<0.001
CTO	273 (19.0)	410 (16.3)	298 (17.7)	449 (15.2)	0.009
SYNTAX score	2.00 [1.00, 2.00]	2.00 [1.00, 3.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	<0.001
Number of stents	11.00 [6.00, 17.50]	10.00 [6.00, 17.00]	10.00 [6.00, 16.00]	9.00 [5.00, 15.00]	<0.001
Total length of stents, mm	38.00 [23.00, 57.00]	38.00 [24.00, 58.00]	35.00 [23.00, 54.00]	33.00 [23.00, 54.00]	<0.001
Average diameter of stents, mm	3.00 [2.75, 3.50]	3.00 [2.75, 3.33]	3.00 [2.75, 3.50]	3.00 [2.75, 3.50]	<0.001

**Note:** Values are expressed as mean ± SD or median (IQR) for continuous variables and number (%) for categorical variables.

**Abbreviations:** SD, standard deviation; IQR, interquartile range; MACE, major adverse cardiovascular events; SII, systematic immune-inflammation index; T2DM, type 2 diabetes mellitus; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PAD, peripheral artery disease; ACS, acute coronary syndrome; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; DAPT, dual antiplatelet therapy; CCB, calcium channel blocker; LM, left main; SYNTAX, synergy between PCI with taxus and cardiac surgery.

### Predictive Value of SII on MACE

In the whole cohort, the incidence of MACE in the SII-L and SII-H groups were 5.5% (301/5475) and 7.1% (221/3127), respectively. The Kaplan–Meier survival curve indicated that patients with T2DM or higher levels of SII had significantly increased risk for MACE compared to the other groups (log-rank  $P < 0.001$  and  $P = 0.0029$ ) (Figures 1). The multivariate Cox analysis revealed a significant association between higher risks of MACE and elevated SII (adjusted HR: 1.21, 95% CI: 1.01–1.46,  $P = 0.037$ ) (Table 3).

In the T2DM cohort, higher levels of SII were associated with increased risk of MACE, both as a continuous variable (HR: 1.36, 95% CI: 1.11–1.66 per 1-unit increase in SII,  $P = 0.003$ ) and a categorical variable (HR: 1.39, 95% CI: 1.10–1.74,  $P = 0.005$ ) in univariate analysis. This association remained statistically significant after adjustment for potential confounders in multivariate analysis (adjusted HR: 1.29, 95% CI: 1.03–1.61 per 1-unit increase in SII,  $P = 0.024$ ; adjusted HR: 1.31, 95% CI: 1.03–1.67,  $P = 0.028$ ). However, in the non-T2DM cohort, the risk of MACE did not differ significantly between groups with different levels of SII (adjusted HR: 1.11, 95% CI: 0.84–1.46,  $P = 0.476$ ) (Table 3).

### Clinical Outcomes of Different Groups Grouped by SII and Glycemic Metabolism Status

The incidence of MACE in SII-H subgroup with or without T2DM and SII-L subgroup with or without T2DM was 9.0% (129/1440), 5.5% (92/1687), 6.6% (166/2516) and 4.6% (166/2516), respectively (Figures 2a). The Kaplan–Meier survival curve indicated the highest risk of MACE in SII-H/T2DM group compared with other groups (log-rank  $P < 0.001$ ) (Figures 2b). Furthermore, clinical outcomes of the four groups were compared by univariate and multivariate Cox regression analysis (SII-H/T2DM group as reference) (Table 4). Patients in SII-L/T2DM, SII-H/Non-T2DM, and SII-L/Non-T2DM groups had significantly decreased risk of MACE (HR: 0.72, 95% CI: 0.57–0.91,  $P = 0.005$ ; HR: 0.60, 95% CI: 0.46–0.78,  $P < 0.001$ ; HR: 0.50, 95% CI: 0.39–0.63,  $P < 0.001$ ). The results remained consistent across multivariate Cox analysis (adjusted HR: 0.77, 95% CI: 0.61–0.98,  $P = 0.036$ ; adjusted HR: 0.66, 95% CI: 0.50–0.87,  $P = 0.003$ ; adjusted HR: 0.58, 95% CI: 0.45–0.74,  $P < 0.001$ ). As for secondary endpoints, it is noteworthy that patients in the SII-L/Non-T2DM group had a 39% lower risk of MI and all-cause death compared with those in the SII-H/T2DM group (adjusted HR: 0.61, 95% CI: 0.38–0.98,  $P = 0.042$ ). Moreover, multivariate Cox analysis indicated the highest risk of

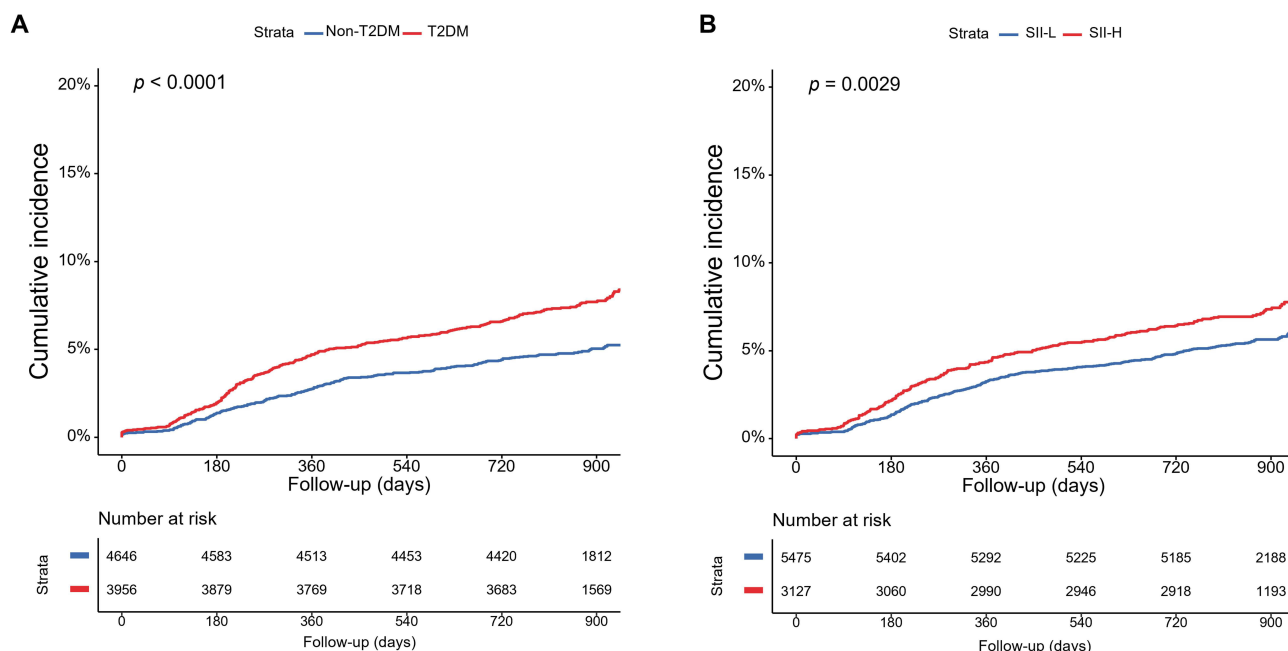


Figure 1 Kaplan–Meier curves for the cumulative incidence of MACE according to different SII levels (A), glycemic metabolism status (B).



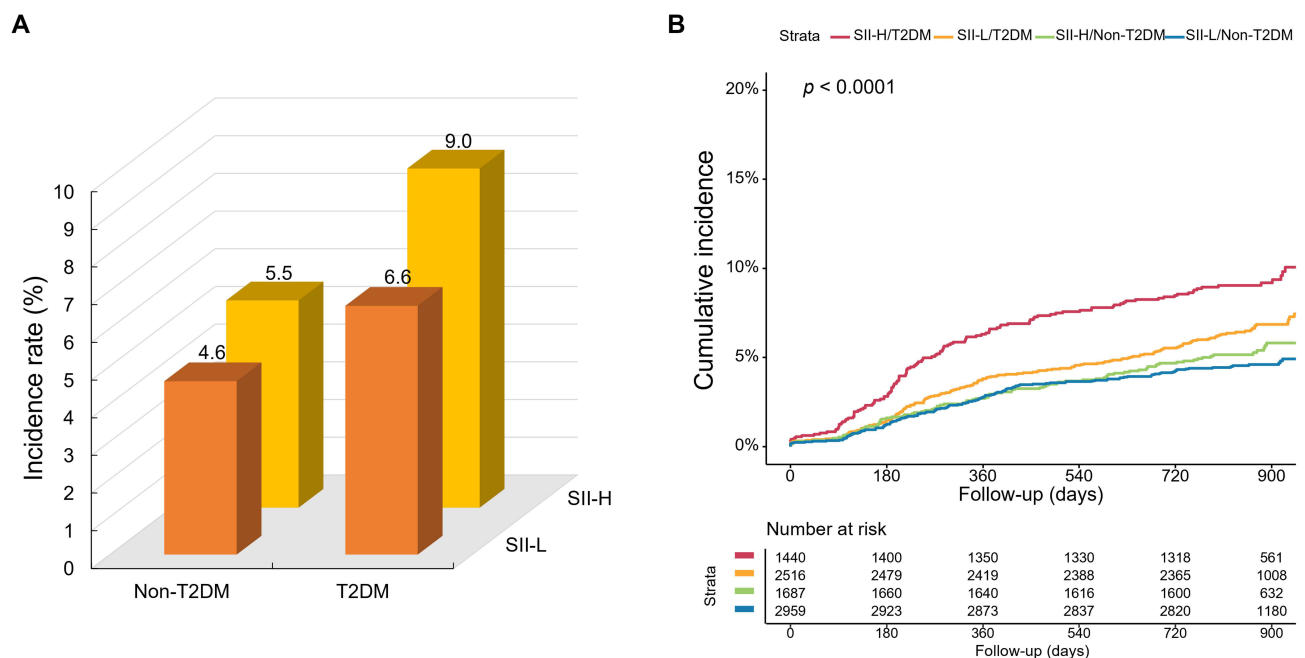
**Table 3** Relation of the SII Level and Primary Endpoint in Patients with Different Glycemic Metabolism Status

Variables	Events/Subjects	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P value	HR (95% CI)*	P value
<b>Whole cohort</b>					
SII-L	301/5475	Reference	NA	Reference	NA
SII-H	221/3127	1.30 (1.09–1.55)	0.003	1.21 (1.01–1.46)	0.037
Ln SII (per 1-unit)		1.23 (1.05–1.45)	0.013	1.12 (0.94–1.33)	0.201
<b>T2DM cohort</b>					
SII-L	166/2516	Reference	NA	Reference	NA
SII-H	129/1440	1.39 (1.10–1.74)	0.005	1.31 (1.03–1.67)	0.028
Ln SII (per 1-unit)		1.36 (1.11–1.66)	0.003	1.29 (1.03–1.61)	0.024
<b>Non-T2DM cohort</b>					
SII-L	135/2959	Reference	NA	Reference	NA
SII-H	92/1687	1.20 (0.92–1.57)	0.174	1.11 (0.84–1.46)	0.476
Ln SII (per 1-unit)		1.03 (0.80–1.34)	0.800	0.93 (0.70–1.22)	0.585

**Notes:** \*Model adjusted for age, male, hypertension, dyslipidemia, prior MI, prior PCI/CABG, hsCRP, creatinine, LM/three-vessel disease, CTO, number of stents, SYNTAX score, total length of stents and average diameter of stents.

**Abbreviations:** HR, hazard ratio; CI, confidence interval; NA, not applicable; SII, systematic immune-inflammation index; T2DM, type 2 diabetes mellitus; SYNTAX, synergy between PCI with taxus and cardiac surgery.

MACE in the SII-H/T2DM group (P for trend < 0.001) (Figure 3). Restricted spline curve analysis revealed that there was a monotonic increase in the risk of MACE with increasing SII levels in either univariable or multivariable model (P for non-linearity > 0.05 for both) (Supplementary Figure S2).



**Figure 2** Incidence rate for MACE (A) and Kaplan–Meier curves for the cumulative incidence of MACE (B) according to four groups.

**Table 4** Predictive Value of the SII Level and Different Glycemic Metabolism Status for Primary and Secondary Endpoints

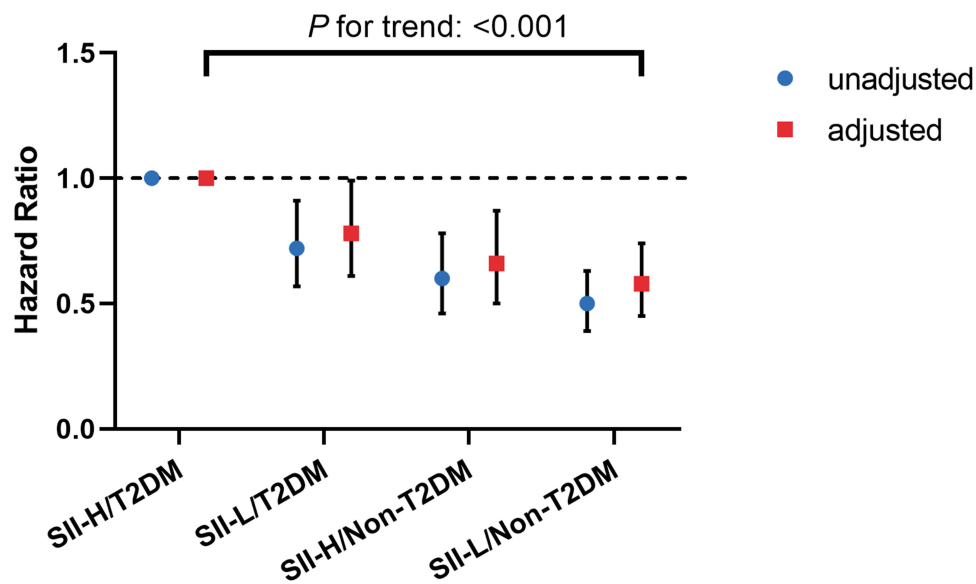
Variables	Events/Subjects	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P value	HR (95% CI)*,†	P value
<b>MACE</b>					
SII-H/T2DM	129/1440	Reference	NA	Reference	NA
SII-L/T2DM	166/2516	0.72 (0.57–0.91)	0.005	0.77 (0.61–0.98)	0.036
SII-H/Non-T2DM	92/1687	0.60 (0.46–0.78)	<0.001	0.66 (0.50–0.87)	0.003
SII-L/Non-T2DM	135/2959	0.50 (0.39–0.63)	<0.001	0.58 (0.45–0.74)	<0.001
<b>MI+All-cause mortality</b>					
SII-H/T2DM	41/1440	Reference	NA	Reference	NA
SII-L/T2DM	51/2516	0.71 (0.47–1.07)	0.097	0.84 (0.54–1.29)	0.421
SII-H/Non-T2DM	36/1687	0.75 (0.48–1.17)	0.206	0.97 (0.61–1.56)	0.906
SII-L/Non-T2DM	39/2959	0.46 (0.30–0.71)	<0.001	0.61 (0.38–0.98)	0.042
<b>All-cause mortality</b>					
SII-H/T2DM	29/1440	Reference	NA	Reference	NA
SII-L/T2DM	26/2516	0.51 (0.30–0.86)	0.012	0.66 (0.38–1.17)	0.158
SII-H/Non-T2DM	22/1687	0.65 (0.37–1.13)	0.123	0.86 (0.48–1.54)	0.602
SII-L/Non-T2DM	25/2959	0.42 (0.24–0.71)	0.001	0.64 (0.36–1.14)	0.127
<b>MI</b>					
SII-H/T2DM	357/1440	Reference	NA	Reference	NA
SII-L/T2DM	282/2516	0.46 (0.39–0.54)	<0.001	0.65 (0.55–0.76)	<0.001
SII-H/Non-T2DM	376/1687	0.95 (0.82–1.09)	0.46	0.98 (0.84–1.14)	0.775
SII-L/Non-T2DM	344/2959	0.47 (0.41–0.55)	<0.001	0.64 (0.54–0.75)	<0.001
<b>TVR</b>					
SII-H/T2DM	96/1440	Reference	NA	Reference	NA
SII-L/T2DM	126/2516	0.74 (0.56–0.96)	0.024	0.76 (0.58–1.00)	0.047
SII-H/Non-T2DM	65/1687	0.57 (0.41–0.77)	<0.001	0.58 (0.42–0.81)	0.001
SII-L/Non-T2DM	106/2959	0.52 (0.40–0.69)	<0.001	0.57 (0.43–0.76)	<0.001

**Notes:**\*Model adjusted for age, male, hypertension, dyslipidemia, prior MI, prior PCI/CABG, hsCRP, creatinine, LM/three-vessel disease, CTO, number of stents, SYNTAX score, total length of stents and average diameter of stents. †P for trend for the risk of MACE: <0.001.

**Abbreviations:** MACE, major adverse cardiovascular events; SII, systematic immune-inflammation index; T2DM, type 2 diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; hsCRP, high-sensitivity C-reactive protein; SYNTAX, synergy between PCI with taxus and cardiac surgery; NA, not applicable; HR, hazard ratio; CI, confidence interval.

## Relationship between SII and HbA1c/FBG/hsCRP

Linear correlation analysis was conducted to assess the correlation between SII and glycemic metabolism status (Supplementary Table S2). SII was positively correlated with admission FBG in the whole cohort ( $R = 0.095$ ,  $P < 0.001$ ), and the results were consistent between the T2DM cohort and non-T2DM cohort ( $R = 0.127$ ,  $P < 0.001$ );



**Figure 3** Hazard ratios (95% CI) for MACE according to four groups.

**Notes:** Adjusted for age, male, hypertension, dyslipidemia, prior MI, prior PCI/CABG, hsCRP, creatinine, LM/three-vessel disease, CTO, number of stents, SYNTAX score, total length of stents and average diameter of stents.

$R = 0.109$ ,  $P < 0.001$ ). However, no significant correlation was observed between SII and HbA1c ( $R = -0.009$ ,  $P = 0.416$ ). Furthermore, we evaluated the correlation between SII and hsCRP, which is considered a well-established inflammatory biomarker. Results showed that there was a linear positive correlation between SII and hsCRP ( $R = 0.246$ ,  $P < 0.001$ ).

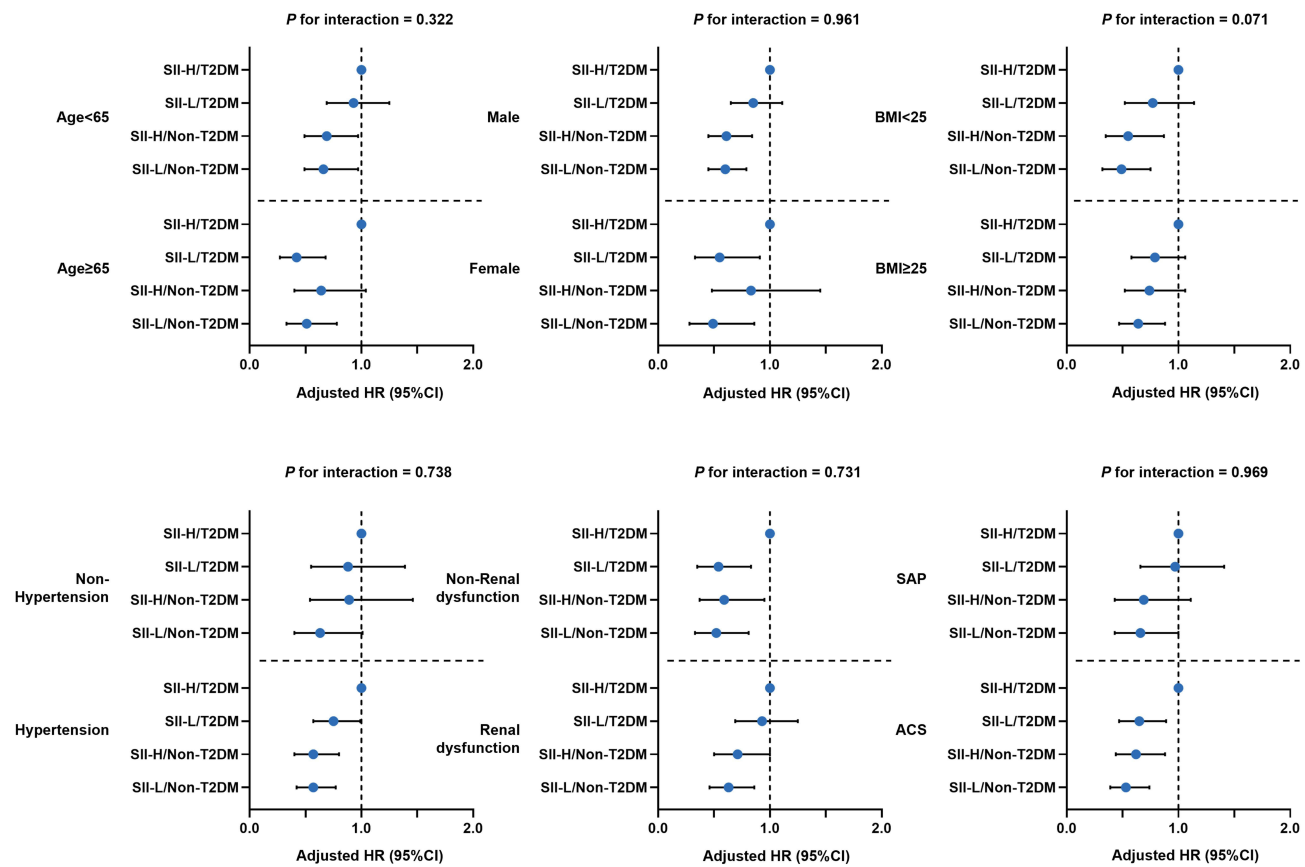
## Subgroup Analysis

Subgroup analysis indicated a consistent tendency between four groups and risks of MACE across different subgroups (age, sex, BMI, hypertension, renal dysfunction, clinical presentation), with no significant interaction effect observed (all  $P$  for interaction  $> 0.05$ ) (Figure 4; [Supplementary Tables S3](#) and [S4](#)).

## Discussion

In this large-scale, real-world, prospective observational study, we evaluated the association between SII and adverse outcomes in CAD patients with different glycemic metabolism state. The main findings of the present study are described below: (1) SII was an independent predictor for MACE in CAD patients undergoing completely coronary revascularization; (2) The prognostic value of SII could be modified by glycemic metabolism state; (3) Compared to patients in other three groups, T2DM patients with elevated SII had significantly higher risks for MACE. For the first time, we demonstrated the association between SII and T2DM in CAD patients undergoing PCI and revealed a synergetic prognostic effect of SII and T2DM on adverse cardiovascular outcomes.

In this study, SII was positively correlated to hsCRP, which is a well-established inflammatory biomarker. Compared to hsCRP, SII is derived from the examination of peripheral blood cells and is a cheaper and easily obtained biomarker. SII was first proposed by Hu et al<sup>25</sup> and used as a well-performed prognostic factor in patients with different types of carcinomas.<sup>26–28</sup> In recent years, numerous studies have been performed to evaluate the prognostic value of SII in the field of cardiology. SII was reported to be associated with the severity of lesions measured by SYNTAX scores in both ACS and stable CAD patients.<sup>10,11</sup> A study from Turkey indicated that higher levels of SII were significantly related to poor coronary collateral circulation in patients with CTO.<sup>29</sup> In a study including 3,561 three-vessel disease patients, SII was a useful predictive tool for worse clinical outcomes after adjusting for potential confounders.<sup>13</sup> As for patients with ST-segment elevation myocardial infarction, several studies suggested that SII could serve as a predictor for in-hospital malignant ventricular arrhythmias, no-reflow phenomenon, and short-term mortality after primary PCI.<sup>12,30</sup> A recent prospective study proved that SII was closely associated with all-cause death and cardiovascular death in a general



**Figure 4** Forest plot of MACE according to different subgroups.

**Notes:** Adjusted for age, male, hypertension, dyslipidemia, prior MI, prior PCI/CABG, hsCRP, creatinine, LM/three-vessel disease, CTO, number of stents, SYNTAX score, total length of stents and average diameter of stents.

population with no history of cardiovascular diseases through a 20-year follow-up.<sup>31</sup> Further, both national cross-sectional and regional cohort studies showed that SII was an independent predictor for MACE in CAD patients,<sup>32–34</sup> which was consistent with our findings.

Interestingly, we found that SII was an independent predictor in the T2DM cohort instead of the non-T2DM cohort, suggesting that the inflammatory status of the diabetic population should be paid more attention. As an integrated index derived from peripheral platelets, neutrophils, and lymphocytes, the synergetic effect of SII and T2DM on adverse cardiovascular outcomes may be attributed to the function of the above-mentioned different types of cells and their complicated interaction.

First, neutrophil extracellular traps (NETs) and the concomitant programmed cell death of neutrophils, termed NETosis, are direct evidence of links between atherosclerotic and diabetic processes through inflammatory pathways.<sup>35,36</sup> Stimulated by pathogens or sterile inflammatory stimulators (eg, cholesterol crystals, activated platelets), neutrophils release enzymes and chromatin into the extracellular space to form a net-like structure during NETosis.<sup>37</sup> T2DM patients were found to have increased levels of circulating biomarkers of NETosis.<sup>38,39</sup> The absence of NETosis in atherosclerotic *apoE*<sup>-/-</sup> mice significantly reduced plaque size and pro-inflammatory cytokine levels.<sup>40</sup> Moreover, the inhibition of NETosis in diabetic mice promoted plaque resolution after lipid lowering.<sup>41</sup>

Second, T2DM, characterized by hyperglycemia and insulin resistance, is a pro-thrombotic state with platelet dysfunction.<sup>42</sup> Hyperglycemia may induce the overexpression of P-selection and glycoating platelet surface proteins and activation of PKC, promoting platelet adhesion to impaired endothelium.<sup>43,44</sup> Abnormally increased platelet aggregation in T2DM patients may be due to insulin resistance, in which the anti-aggregation effect of insulin is impaired.<sup>45</sup>

Mounting studies have pointed out that SII may be a useful diagnostic biomarker for detecting micro- or macro-vascular complications in patients with T2DM, including diabetic macular edema, diabetic kidney disease, diabetic depression, and peripheral arterial disease.<sup>46–49</sup> However, to date, the investigation of the prognostic value of SII for cardiovascular outcomes in T2DM patients has been scant. For the first time, we illustrated a modified effect of T2DM on the prognostic value of SII in CAD patients undergoing PCI, which testified to the complicated interaction among inflammation, T2DM, and CAD from another perspective.

In the present study, we found that SII was positively correlated to FBG in both T2DM and normoglycemic patients, while had no relationship with HbA1c. However, previous studies have reported that hsCRP was positively correlated to FBG and HbA1c in patients with or without T2DM.<sup>50,51</sup> This may be since hsCRP and SII mediate the progression of diabetes through different inflammatory pathways, and we also proved that SII was a prognostic predictor for MACE independent of hsCRP. Notably, the correlation between SII and FBG should be interpreted cautiously on account of the relatively weak strength of correlation.

Our study has several limitations that need to be illustrated. First, SII and blood glucose levels were obtained only for one time before PCI, thus we cannot determine whether the dynamic changes will have an impact on the prognosis. In addition, the effect of antiplatelet drugs on SII cannot be evaluated. Second, although Fuwai hospital is a national center recruiting patients from all over the country, potential selection bias still exists on account of the single-center design. Third, due to the natural defect of observational study, there may exist unmeasured confounders leading to potential confounding bias to a certain extent, and no causal association could be established. Finally, despite a relatively large-scale sample size, this study only included the Chinese population in a single center, thus the generalization of our study results needs to be further verified.

## Conclusions

In this large-scale real-world study, the combination of elevated SII and T2DM predicted worse clinical outcomes in CAD patients undergoing PCI. Test of SII may contribute to more precise risk stratification in this specific population.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

The study process was in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Fuwai Hospital. All subjects provided informed written consent for long-term follow-up before intervention.

## Consent for Publication

The manuscript was approved by all authors for publication.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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