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Prognostic Value of Systemic Inflammation Scores in Patients with Acute Coronary Syndrome Who Underwent Percutaneous Coronary Intervention: A Prospective Cohort Study

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Background: Acute coronary syndrome (ACS) is closely associated with inflammation status. The systemic inflammation score (SIS), which is calculated using the serum albumin level and lymphocyte-to-monocyte ratio (LMR), has emerged as a valuable biomarker for predicting the clinical outcomes of several diseases. Nonetheless, the value of SIS in predicting the long-term prognostic risk in patients with ACS undergoing percutaneous coronary intervention (PCI) remains unknown. We aimed to explore the associations of SIS with major adverse cardiovascular events (MACEs), all-cause mortality, and cardiovascular death.

Methods: This prospective cohort study consecutively enrolled 1582 patients with ACS who underwent PCI at the Department of Cardiology in the Affiliated Hospital of Chengde Medical University (Chengde, China) between January 2016 and December 2018. The primary endpoint was MACEs, including all-cause mortality, rehospitalization for heart failure, revascularization, recurrence of acute myocardial infarction, and restenosis/intrastent thrombosis.

Results: The Kaplan–Meier survival analysis revealed that a high SIS was correlated with MACEs and all-cause mortality and that increasing SIS was independently associated with the risks of MACEs and all-cause mortality by Cox regression. Landmark analysis provided evidence for the time window of predictive ability, which could guide clinical applications. A clear correlation between the increasing tendency of hazard ratio in patients with ACS undergoing PCI and the risks of MACEs or all-cause mortality was noted (p for trend <0.05). The sensitivity analysis with a competing risk model showed that high SIS level was correlated with the risks of cardiac death and rehospitalization. The mediation analysis revealed that the hemoglobin level exerted a mediating effect on the relationship between SIS and MACEs.

Conclusion: The SIS exhibited a strong correlation with the risks of MACEs and all-cause mortality. Notably, the SIS was particularly effective in predicting the risk of cardiac death and likelihood of rehospitalization.

Keywords: acute coronary syndrome, prognosis, systemic inflammation score, percutaneous coronary intervention

Background

Acute coronary syndrome (ACS) is a serious concern in cardiovascular health, leading to substantial morbidity and mortality worldwide.[1] ACS has an alarming prevalence, with more than 7 million global diagnoses annually, including over 1 million hospital admissions in the United States alone.[1,2] Over the past decades, considerable research has been devoted to understanding the pathophysiology, diagnosis, and treatment of ACS,[2] resulting in substantial advances in the

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detection and diagnostic approaches for ACS.[2,3] Recent guidelines have also emphasized evolving strategies for managing ACS, adapting to new scientific evidence and external factors for cardiovascular care delivery.[3,4]

The role of inflammation in the pathogenesis and progression of atherosclerotic cardiovascular disease and ACS is an emerging area of interest. Over the years, researchers have elucidated the multifaceted roles played by systemic and localized inflammatory processes in ACS, encompassing aspects such as endothelial dysfunction, immune response modulation, plaque stability, and thrombus formation. Inflammation can destabilize atherosclerotic plaques, inducing acute coronary events.[5] Furthermore, inflammation is increasingly recognized as a contributor to the pathogenesis of ACS and an important determinant of prognosis and therapeutic response in affected patients. Understanding the inflammatory status in ACS can potentially lead to the development of more effective prognostic strategies.

Early research has identified the detrimental effects of inflammation on endothelial function, particularly via mechanisms affecting the activities of high-density lipoprotein-cholesterol (HDL-C) and endothelial nitric oxide synthase.[6] Additionally, differential cytokine profiles between patients with ACS and stable coronary artery disease (CAD) reveal specific inflammatory mediators that may serve as therapeutic targets.[7] Similarly, residual inflammation and remnant cholesterol present persistent risks despite statin therapy, necessitating comprehensive approaches that target both lipid and nonlipid inflammatory pathways.[8] Exploratory studies have also investigated novel therapeutic combinations that aim to modulate inflammation after percutaneous coronary intervention (PCI).[9]

Inflammatory biomarkers are considered valuable prognostic indicators that may help stratify patient risk and accordingly tailor therapeutic strategies. For instance, a pivotal study highlighted the crucial role of inflammation in ACS as well as the prognostic value of inflammatory biomarkers in ACS, specifically C-reactive protein (CRP) and serum amyloid A.[10] Another study reported the correlation between the use of darapladib, an inhibitor of lipoprotein-associated phospholipase A2, for patients with recent ACS and the complexity of inflammation in atherogenesis.[11] However, a trial investigating varespladib, an inhibitor of secretory phospholipase A2, highlighted the potential risks involved with certain anti-inflammatory strategies.[12] Notably, clinical trials focusing on anti-inflammatory therapies for ACS have yielded mixed results, whereas landmark studies have shown that targeted anti-inflammatory treatments can reduce cardiovascular events in certain patient populations.[13]

High-sensitivity CRP (hsCRP) is among the inflammatory biomarkers that have been extensively investigated as a predictor of outcomes in ACS.[14] The integration of biomarkers such as hsCRP into traditional risk scores such as the GRACE risk score improves the predictive accuracy for patient outcomes, suggesting that inflammatory markers offer significant incremental prognostic value.[15,16] These biomarkers facilitate nuanced risk stratification and underscore the potential for targeted inflammation reduction therapies to improve patient prognosis. Furthermore, immune cell profiles and novel inflammatory indices, such as the Systemic Immune-Inflammation Index and Systemic Inflammatory Response Index, have shown promise in predicting the severity of ACS. Higher levels of these indices are associated with greater coronary thrombus burden and more severe CAD, linking systemic inflammation to the clinical manifestations and outcomes of ACS.[17,18]

Recently, the systemic inflammation score (SIS), which can reflect inflammation status, has attracted the attention of researchers. Despite the potential of SIS to reflect inflammation levels, its relationship with major adverse cardiovascular events (MACEs), overall mortality, and cardiac death in patients with ACS who underwent PCI has been inadequately investigated. Therefore, we aimed to explore the associations of the SIS with MACEs, all-cause mortality, and cardiovascular death.

Methods

Study Population

In this prospective cohort study, we explored the associations of the SIS with MACEs, all-cause mortality, and cardiovascular death and consecutively enrolled 1582 patients with ACS who underwent PCI at the Department of Cardiology in the Affiliated Hospital of Chengde Medical University (Chengde, China) between January 2016 and December 2018.

All patients underwent coronary angiography and PCI performed by an experienced team of cardiologists. The inclusion criteria were as follows: (i) age ≥18 years; (ii) clinical types of ACS (including ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], and unstable angina) diagnosed according to the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction and 2014 AHA/ACC Guideline for the

Management of Patients with Non-ST-Elevation Acute Coronary Syndromes; and (iii) all patients with ACS, defined as stenosis of at least 50% of the luminal diameter in at least one major coronary artery branch after coronary angiography. The exclusion criteria were as follows: (i) death during hospitalization; (ii) critical structural heart disease; (iii) severe inflammatory infectious disease; (iv) connective tissue disease; (v) secondary coronary vasculitis; (vi) combination with other heart diseases that could cause angina pectoris, hypertrophic cardiomyopathy, myocarditis, and severe valvular heart disease; (vii) severe liver and kidney diseases (creatinine clearance <15 mL/min); (viii) patients with missing data exceeding 10%; and (ix) previous history of coronary artery bypass grafting.

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Chengde Medical University (approval number: CYFYLL2015006). All participants provided informed consent.

Baseline Demographics and Clinical Characteristics

The cardiovascular research team collected all data on the demographic and clinical characteristics of enrolled patients. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg at rest, or a previous diagnosis of hypertension with antihypertensive therapy.[19] Type 2 diabetes mellitus (DM) was defined as the presence of diabetes symptoms and random blood glucose level ≥11.1 mmol/L, fasting plasma glucose level ≥7.0 mmol/L, or 2-h plasma glucose level ≥11.1 mmol/L during an oral glucose tolerance test, or the absence of diabetes symptoms and at least twice the blood glucose level that met the aforementioned criteria.[20] Dyslipidemia was defined as serum total cholesterol level ≥5.18 mmol/L, HDL-C level ≤1.04 mmol/L, low-density lipoprotein-cholesterol (LDL-C) level ≥3.37 mmol/L, or triglyceride level ≥1.7 mmol/L or a previous diagnosis of dyslipidemia with lipid-lowering medication use.[21]

SIS Assessment

The lymphocyte-to-monocyte ratio (LMR) was defined as the ratio of the absolute lymphocyte count to the absolute monocyte count. The SIS was calculated based on the LMR and serum albumin level: a score of 0 point was defined as LMR >2.96 and serum albumin level >40.00 g/L, a score of 1 point was defined as LMR ≤2.96 or serum albumin level ≤40.00 g/L, and a score of 2 points was defined as LMR ≤2.96 and serum albumin level ≤40.00 g/L. The patients were divided into two groups according to their scores: the SIS low-risk group (score of 0 point) and SIS high-risk group (score of 1 or 2).[22]

Follow-up and Endpoints

Follow-up was completed by the cardiovascular physician and performed in accordance with the principles of standardization to control for bias. Follow-up data were collected via clinical visits at 1, 3, 6, and 12 months and annually thereafter through telephone interviews and medical records.

The primary endpoint was MACEs, including all-cause mortality, rehospitalization for heart failure, revascularization, recurrence of acute myocardial infarction (AMI), and restenosis/intrastent thrombosis. Rehospitalization for heart failure was defined as having grade IV heart failure (New York Heart Association class IV) that required rehospitalization. Revascularization was defined as having undergone re-PCI.

Statistical Analysis

The normality of the distribution of continuous variables was validated using the Kolmogorov–Smirnov test. Normally and non-normally distributed variables are expressed as mean ± standard deviation and median with interquartile range, respectively. Between-group variances in non-normally and normally distributed continuous variables were examined using the Mann–Whitney *U* and *t* tests, respectively. Categorical variables are presented as numbers (%) and were compared using the $\chi 2$ test. Survival analysis was conducted using the Kaplan–Meier method, and between-group comparisons were performed using the Log rank test. Univariate and multivariable Cox proportional hazards models were used to evaluate the ability of the SIS to predict the prognostic risk. The risk score was calculated based on the multivariable Cox proportional hazards model, and the risk score picture was subsequently plotted using R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria; available at http://www.R-project.org).

The correlation between the risk of rehospitalization or cardiac death and SIS level was analyzed using a competing risk model, with rehospitalization defined as a composite event that included rehospitalization for heart failure, revascularization, recurrence of AMI, and restenosis/intrastent thrombosis. A competing risk model was employed because the use of all-cause mortality as a censor event would lead to bias. In the analysis of the risk of rehospitalization, all-cause mortality was regarded as a competing event. The *p*-value by Gray's test was calculated to ascertain whether there was a difference between the low-SIS and high-SIS groups.

Furthermore, numerous subgroup analyses were conducted to determine whether the prognostic accuracy of the SIS remained consistent among patients with varied demographic characteristics or comorbidities. A mediation approach was applied to the survival data to assess the impact of the SIS (exposure) on MACEs (outcome) via age (mediator). This method involved fitting two distinct regression models: one for the mediator and the other for the outcome. The mediation effect size was derived by integrating the parameter estimates and standard errors from both models as per VanderWeele's specified formulas. The significance of the mediating effect was assessed by examining 1000 bootstrap samples. Statistical analyses and drawing were performed using SPSS software version 26 (IBM Corp., Armonk, NY, USA) and R software. All tests were two-sided, with statistical significance set at $p < 0.05$.

In this study, four different models were utilized: (i) Model 1, which was unadjusted; (ii) Model 2, which was adjusted for age ≥65 years, hypertension, DM, history of heart failure, cardiogenic shock, three-vessel disease, and left ventricular ejection fraction (LVEF); (iii) Model 3, which was adjusted for sex, age ≥65 years, dyslipidemia, hypertension, DM, history of heart failure, family history of CAD, cardiogenic shock, three-vessel disease, left ventricular end-diastolic diameter (LVEDD), and LVEF; and (iv) Model 4, which was adjusted for sex, age ≥65 years, dyslipidemia, hypertension, DM, cerebral infarction, history of heart failure, family history of CAD, cardiogenic shock, three-vessel disease, STEMI, LVEDD, creatine, and LVEF.

Results

Baseline Characteristics of Patients

A total of 24 patients (11 patients with infectious disease, 5 patients with blood system disease, 6 patients with malignant tumors, and 2 patients with a history of coronary artery bypass grafting) were excluded after applying the exclusion criteria. During the follow-up period, 111 patients lost contact. Finally, 1549 patients (women, 391 [25.2%]) with ACS completed the follow-up period and were included in the analysis (Figure 1). Among 1549 patients, 47 had left main coronary artery disease according to the results of coronary angiography. MACEs occurred in 180 (11.6%) patients with ACS; among these patients, 56 died (including 31 patients who died from heart disease), 5 developed severe heart failure requiring rehospitalization, 30 had recurrent nonfatal MI, 7 underwent stent restenosis, and 82 underwent re-PCI.

The MACE and non-MACE groups showed significant differences with respect to age ≥65 years, unstable angina, history of heart failure, cardiogenic shock, white blood cell (WBC) count, hemoglobin (Hb) level, neutrophil count, albumin level, creatine level, one-vessel disease, three-vessel disease, left atrial diameter (LAD), LVEDD >50 mm, LVEF <40%, aspirin use, ticagrelor use, statin use, and diuretic use ($p < 0.05$ for all; Table 1).

Sex; body mass index; unstable angina; STEMI; dyslipidemia; history of heart failure; cardiogenic shock; platelet, neutrophil, lymphocyte, monocyte, and WBC counts; albumin, total cholesterol, triglyceride, LDL-C, creatine, and serum uric acid levels; LAD; left ventricular end-systolic diameter; LVEF; LVEDD >50 mm; aspirin, ticagrelor, β-blocker, calcium-channel blocker, diuretic, or spironolactone use; and MACEs significantly differed among the SIS = 0, SIS = 1, and SIS = 2 groups ($p < 0.05$ for all; Table 2).

Cox Proportional Hazards Model

Patients with SIS of 2 points exhibited a poorer prognosis, we used the SIS = 0 group as the reference point in the analysis.

The relationship between the SIS level and outcomes was examined using the Cox proportional hazards model (Table 3), with MACEs and all-cause mortality being regarded as the outcome events. A higher SIS level emerged as an independent risk factor for MACEs, with hazard ratios (HRs) of 1.610 (95% confidence interval [CI]: 1.318–1.968, $p < 0.001$) for Model 1,

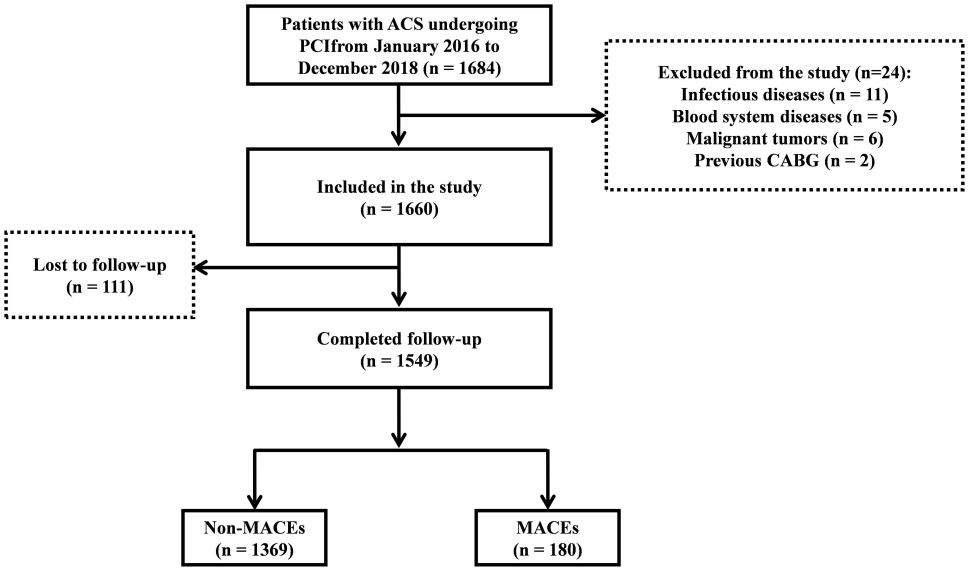

Figure 1 Flow chart of the present study.
Abbreviations: ACS, acute coronary syndrome; MACEs, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

1.422 (95% CI: 1.140–1.775, $p = 0.002$) for Model 2, 1.487 (95% CI: 1.187–1.863, $p = 0.001$) for Model 3, and 1.410 (95% CI: 1.122–1.772, $p = 0.003$) for Model 4. Subsequently, the relationship between the SIS and all-cause mortality was analyzed, demonstrating HRs of 2.007 (95% CI: 1.404–2.867, $p < 0.001$) for Model 1, 1.666 (95% CI: 1.128–2.461, $p = 0.010$) for Model 2, 1.750 (95% CI: 1.176–2.604, $p = 0.006$) for Model 3, and 1.663 (95% CI: 1.113–2.483, $p = 0.013$) for Model 4.

Table 1 Baseline Characteristics of Patients in the MACE and Non-MACE Groups

Characteristic	Overall (*N* = 1549)	NonMACE Group (n = 1369)	MACE Group (n = 180)	*p*-value
Sex				0.310
Female	391 (25.2%)	340 (24.8%)	51 (28.3%)	
Male	1158 (74.8%)	1029 (75.2%)	129 (71.7%)	
Age ≥65 years	369 (23.8%)	315 (23.0%)	54 (30.0%)	0.038
BMI	25.1 (23.0, 27.5)	25.1 (23.0, 27.5)	25.3 (23.0, 27.5)	0.376
Unstable angina	614 (39.6%)	559 (40.8%)	55 (30.6%)	0.008
STEMI	689 (44.5%)	598 (43.7%)	91 (50.6%)	0.081
NSTEMI	246 (15.9%)	212 (15.5%)	34 (18.9%)	0.240
Dyslipidemia	880 (56.8%)	772 (56.4%)	108 (60.0%)	0.358
Hypertension	911 (58.8%)	801 (58.5%)	110 (61.1%)	0.505
DM	393 (25.4%)	339 (24.8%)	54 (30.0%)	0.129
Cerebral infarction	220 (14.2%)	190 (13.9%)	30 (16.7%)	0.314
History of heart failure	155 (10.0%)	114 (8.3%)	41 (22.8%)	<0.001
Family history of CAD	217 (14.0%)	195 (14.2%)	22 (12.2%)	0.463
Cardiogenic shock	24 (1.5%)	13 (0.9%)	11 (6.1%)	<0.001
WBC count (10^9/L)	7.9 (6.4, 10.4)	7.9 (6.3, 10.3)	8.1 (6.9, 11.1)	0.024
Hb (g/L)	147 (136, 157)	148 (136, 157)	143 (133, 154)	0.002
Platelet count (10^9/L)	215 (179, 251)	215 (179, 250)	216 (179, 256)	0.617
Neutrophil count (10^9/L)	5.4 (4.0, 8.1)	5.4 (3.9, 8.0)	5.8 (4.4, 8.7)	0.013
Lymphocyte count (10^9/L)	1.67 (1.23, 2.27)	1.68 (1.24, 2.28)	1.55 (1.17, 2.19)	0.070
Monocyte count (10^9/L)	0.43 (0.32, 0.57)	0.43 (0.31, 0.57)	0.45 (0.35, 0.57)	0.096

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (*N* = 1549)	NonMACE Group (n = 1369)	MACE Group (n = 180)	*p*-value
MPV (fL)	10.40 (9.80, 11.00)	10.40 (9.80, 11.00)	10.50 (9.90, 11.00)	0.266
PDW (%)	12.00 (10.90, 13.40)	12.00 (10.90, 13.40)	12.20 (11.00, 13.30)	0.408
Albumin (g/L)	41.1 (38.6, 43.6)	41.3 (38.8, 43.7)	39.9 (37.2, 42.3)	<0.001
Total cholesterol (mmol/L)	4.33 (3.68, 5.06)	4.33 (3.69, 5.06)	4.34 (3.68, 5.07)	>0.999
Triglyceride (mmol/L)	1.60 (1.04, 2.45)	1.60 (1.05, 2.47)	1.59 (0.98, 2.32)	0.540
HDL-C (mmol/L)	1.08 (0.90, 1.26)	1.08 (0.90, 1.26)	1.05 (0.91, 1.21)	0.302
LDL-C (mmol/L)	2.30 (1.85, 2.89)	2.31 (1.85, 2.87)	2.29 (1.91, 3.05)	0.662
Creatine (μmol/L)	67 (59, 78)	67 (59, 77)	70 (61, 82)	0.010
Serum uric acid (μmol/L)	326 (265, 385)	326 (263, 384)	329 (273, 391)	0.443
One-vessel	485 (31.3%)	443 (32.4%)	42 (23.3%)	0.014
Two-vessel	494 (31.9%)	438 (32.0%)	56 (31.1%)	0.811
Three-vessel	570 (36.8%)	488 (35.6%)	82 (45.6%)	0.010
Intravascular Ultrasound	30 (1.9%)	21 (1.5%)	9 (5.0%)	0.005
Left main	47 (3.0%)	17 (1.2%)	30 (16.7%)	<0.001
Gensini score	44 (29, 66)	44 (29, 66)	39 (26, 62)	0.127
LAD (mm)	35.0 (32.0, 37.0)	35.0 (32.0, 37.0)	35.0 (33.0, 38.0)	0.022
LVEDD (mm)	50.0 (47.0, 54.0)	50.0 (47.0, 54.0)	50.0 (47.0, 54.0)	0.320
LVSDD (mm)	34.0 (32.0, 38.0)	34.0 (32.0, 38.0)	34.0 (32.0, 40.0)	0.611
LVEF (%)	58 (53, 64)	59 (53, 64)	57 (49, 62)	0.069
LVEDD >50 mm	676 (48.3%)	611 (49.3%)	65 (40.4%)	0.033
LVEF <40%	41 (2.9%)	32 (2.6%)	9 (5.6%)	0.044
Aspirin	1526 (98.5%)	1360 (99.3%)	166 (92.2%)	<0.001
Clopidogrel	1220 (78.8%)	1076 (78.6%)	144 (80.0%)	0.665
Ticagrelor	304 (19.6%)	283 (20.7%)	21 (11.7%)	0.004
β-blockers	793 (51.2%)	690 (50.4%)	103 (57.2%)	0.085
ACEI/ARB	695 (44.9%)	614 (44.9%)	81 (45.0%)	0.970
Statins	1521 (98.2%)	1355 (99.0%)	166 (92.2%)	<0.001
Calcium-channel blockers	265 (17.1%)	238 (17.4%)	27 (15.0%)	0.424
Diuretics	110 (7.1%)	89 (6.5%)	21 (11.7%)	0.011
Spironolactone	370 (23.9%)	317 (23.2%)	53 (29.4%)	0.064

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial diameter; LDL-C, low-density lipoprotein-cholesterol; LVEDD, left ventricular end-diastolic diameter; LVSDD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiovascular events; MPV, mean platelet volume; PDW, platelet distribution width; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; WBC, white blood cell.

Table 2 Baseline Characteristics of Different SIS Groups

Characteristic	Overall (*N* = 1549)	SIS = 0 (n = 722)	SIS = 1 (n = 628)	SIS = 2 (n = 199)	*p*-value
Sex					0.038
Female	391 (25.2%)	198 (27.4%)	156 (24.8%)	37 (18.6%)	
Male	1158 (74.8%)	524 (72.6%)	472 (75.2%)	162 (81.4%)	
Age ≥65 years	369 (23.8%)	146 (20.2%)	154 (24.5%)	69 (34.7%)	<0.001
BMI	25.1 (23.0, 27.5)	25.4 (23.4, 27.8)	24.9 (22.8, 27.0)	24.4 (22.6, 27.3)	<0.001
Unstable angina	614 (39.6%)	359 (49.7%)	227 (36.1%)	28 (14.1%)	<0.001
STEMI	689 (44.5%)	245 (33.9%)	306 (48.7%)	138 (69.3%)	<0.001
NSTEMI	246 (15.9%)	118 (16.3%)	95 (15.1%)	33 (16.6%)	0.796
Dyslipidemia	880 (56.8%)	460 (63.7%)	336 (53.5%)	84 (42.2%)	<0.001
Hypertension	911 (58.8%)	443 (61.4%)	357 (56.8%)	111 (55.8%)	0.158
DM	393 (25.4%)	196 (27.1%)	157 (25.0%)	40 (20.1%)	0.124

(*Continued*)

Table 2 (Continued).

Characteristic	Overall (*N* = 1549)	SIS = 0 (n = 722)	SIS = 1 (n = 628)	SIS = 2 (n = 199)	*p*-value
Cerebral infarction	220 (14.2%)	99 (13.7%)	85 (13.5%)	36 (18.1%)	0.242
History of heart failure	155 (10.0%)	44 (6.1%)	62 (9.9%)	49 (24.6%)	<0.001
Family history of CAD	217 (14.0%)	109 (15.1%)	88 (14.0%)	20 (10.1%)	0.192
Cardiogenic shock	24 (1.5%)	5 (0.7%)	14 (2.2%)	5 (2.5%)	0.025
WBC (10^9/L)	7.9 (6.4, 10.4)	7.5 (6.2, 9.4)	7.9 (6.4, 10.7)	10.3 (7.7, 12.5)	<0.001
Hb (g/L)	147 (136, 157)	150 (139, 159)	146 (135, 155)	143 (133, 154)	<0.001
Platelet count (10^9/L)	215 (179, 251)	221 (183, 259)	210 (177, 244)	207 (176, 239)	<0.001
Neutrophil count (10^9/L)	5.4 (4.0, 8.1)	4.8 (3.7, 6.5)	5.6 (4.1, 8.8)	8.3 (5.7, 10.4)	<0.001
Lymphocyte count (10^9/L)	1.67 (1.23, 2.27)	1.86 (1.47, 2.48)	1.61 (1.16, 2.14)	1.17 (0.85, 1.46)	<0.001
Monocyte count (10^9/L)	0.43 (0.32, 0.57)	0.40 (0.30, 0.51)	0.43 (0.31, 0.58)	0.62 (0.46, 0.81)	<0.001
MPV (fL)	10.40 (9.80, 11.00)	10.30 (9.80, 10.90)	10.40 (9.80, 10.90)	10.50 (9.73, 11.18)	0.417
PDW (%)	12.00 (10.90, 13.40)	12.10 (11.00, 13.40)	11.90 (10.90, 13.20)	12.25 (10.73, 13.50)	0.139
Albumin (g/L)	41.1 (38.6, 43.6)	43.1 (41.7, 44.9)	39.3 (37.5, 41.7)	37.5 (35.6, 38.8)	<0.001
Total cholesterol (mmol/L)	4.33 (3.68, 5.06)	4.49 (3.88, 5.29)	4.23 (3.58, 4.94)	4.02 (3.49, 4.69)	<0.001
Triglyceride (mmol/L)	1.60 (1.04, 2.45)	1.81 (1.25, 2.82)	1.51 (0.93, 2.25)	1.26 (0.78, 1.82)	<0.001
HDL-C (mmol/L)	1.08 (0.90, 1.26)	1.10 (0.92, 1.27)	1.05 (0.89, 1.26)	1.07 (0.87, 1.22)	0.216
LDL-C (mmol/L)	2.30 (1.85, 2.89)	2.41 (1.92, 2.99)	2.25 (1.79, 2.83)	2.22 (1.86, 2.72)	<0.001
Creatine (μmol/L)	67 (59, 78)	67 (59, 77)	67 (59, 77)	70 (60, 88)	<0.001
Serum uric acid (μmol/L)	326 (265, 385)	330 (268, 387)	317 (260, 378)	336 (274, 385)	0.049
One-vessel	485 (31.3%)	233 (32.3%)	198 (31.5%)	54 (27.1%)	0.380
Two-vessel	494 (31.9%)	226 (31.3%)	207 (33.0%)	61 (30.7%)	0.746
Three-vessel	570 (36.8%)	263 (36.4%)	223 (35.5%)	84 (42.2%)	0.223
Gensini score	44 (29, 66)	45 (30, 68)	43 (28, 65)	41 (26, 67)	0.175
LA (mm)	35.0 (32.0, 37.0)	35.0 (32.0, 37.0)	34.0 (32.0, 37.0)	35.0 (32.0, 39.0)	0.002
LVEDD (mm)	50.0 (47.0, 54.0)	50.0 (47.0, 54.0)	50.0 (47.0, 54.0)	52.0 (48.0, 55.0)	0.112
LVSDD (mm)	34.0 (32.0, 38.0)	34.0 (31.8, 38.0)	34.0 (32.0, 39.0)	37.0 (33.0, 42.0)	<0.001
LVEF (%)	58 (53, 64)	59 (55, 64)	58 (52, 64)	55 (46, 60)	<0.001
LVEDD >50 mm	676 (48.3%)	292 (45.9%)	278 (47.8%)	106 (57.9%)	0.016
LVEF <40%	41 (2.9%)	18 (2.8%)	13 (2.2%)	10 (5.5%)	0.077
Aspirin	1526 (98.5%)	715 (99.0%)	619 (98.6%)	192 (96.5%)	0.041
Clopidogrel	1220 (78.8%)	563 (78.0%)	491 (78.2%)	166 (83.4%)	0.227
Ticagrelor	304 (19.6%)	151 (20.9%)	128 (20.4%)	25 (12.6%)	0.026
β-blockers	793 (51.2%)	393 (54.4%)	313 (49.8%)	87 (43.7%)	0.019
ACEI/ARB	695 (44.9%)	327 (45.3%)	278 (44.3%)	90 (45.2%)	0.926
Statins	1521 (98.2%)	712 (98.6%)	617 (98.2%)	192 (96.5%)	0.151
Calcium-channel blockers	265 (17.1%)	154 (21.3%)	91 (14.5%)	20 (10.1%)	<0.001
Diuretics	110 (7.1%)	39 (5.4%)	38 (6.1%)	33 (16.6%)	<0.001
Spironolactone	370 (23.9%)	152 (21.1%)	146 (23.3%)	72 (36.2%)	<0.001
MACEs	180 (11.6%)	64 (8.9%)	72 (11.5%)	44 (22.1%)	<0.001
All-cause mortality	56 (3.6%)	17 (2.4%)	21 (3.3%)	18 (9.0%)	<0.001
Cardiovascular death	31 (2.0%)	7 (1.0%)	11 (1.8%)	13 (6.5%)	<0.001
Severe heart failure requiring rehospitalization	5 (0.3%)	1 (0.1%)	2 (0.3%)	2 (1.0%)	0.163
Recurrence of AMI	30 (1.9%)	10 (1.4%)	9 (1.4%)	11 (5.5%)	0.002
Restenosis/intrastent thrombosis	7 (0.5%)	4 (0.6%)	2 (0.3%)	1 (0.5%)	0.768
Re-PCI	82 (5.3%)	32 (4.4%)	38 (6.1%)	12 (6.0%)	0.367

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AMI, acute myocardial infarction; BMI, body mass index; DM, diabetes mellitus; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVSDD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiovascular events; MPV, mean platelet volume; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PDW, platelet distribution width; SIS, systemic inflammation score; STEMI, ST-segment elevation myocardial infarction; WBC, white blood cell; Hb, hemoglobin.

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Table 3 Cox Proportional Hazards Model of Predictive Factors for MACEs and All-Cause Mortality

Variables	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACEs								
SIS (increasing 1 score)	1.610 (1.318–1.968)	<0.001	1.422 (1.140–1.775)	0.002	1.487 (1.187–1.863)	0.001	1.410 (1.122–1.772)	0.003
All-cause mortality								
SIS (increasing 1 score)	2.007 (1.404–2.867)	<0.001	1.666 (1.128–2.461)	0.010	1.750 (1.176–2.604)	0.006	1.663 (1.113–2.483)	0.013

Abbreviations: CI, confidence interval; HR, hazard ratio; MACEs, major adverse cardiovascular events; SIS, systemic inflammation score.

The risk scores for patients with ACS were derived using multivariable Cox regression analysis. The risk scores are presented in Figure 2 alongside the survival status and SIS values. To better understand the distribution of SIS values and risk scores in the study population, the data were normalized using z-scores. The results indicated that a higher SIS level correlated with an elevated MACE risk.

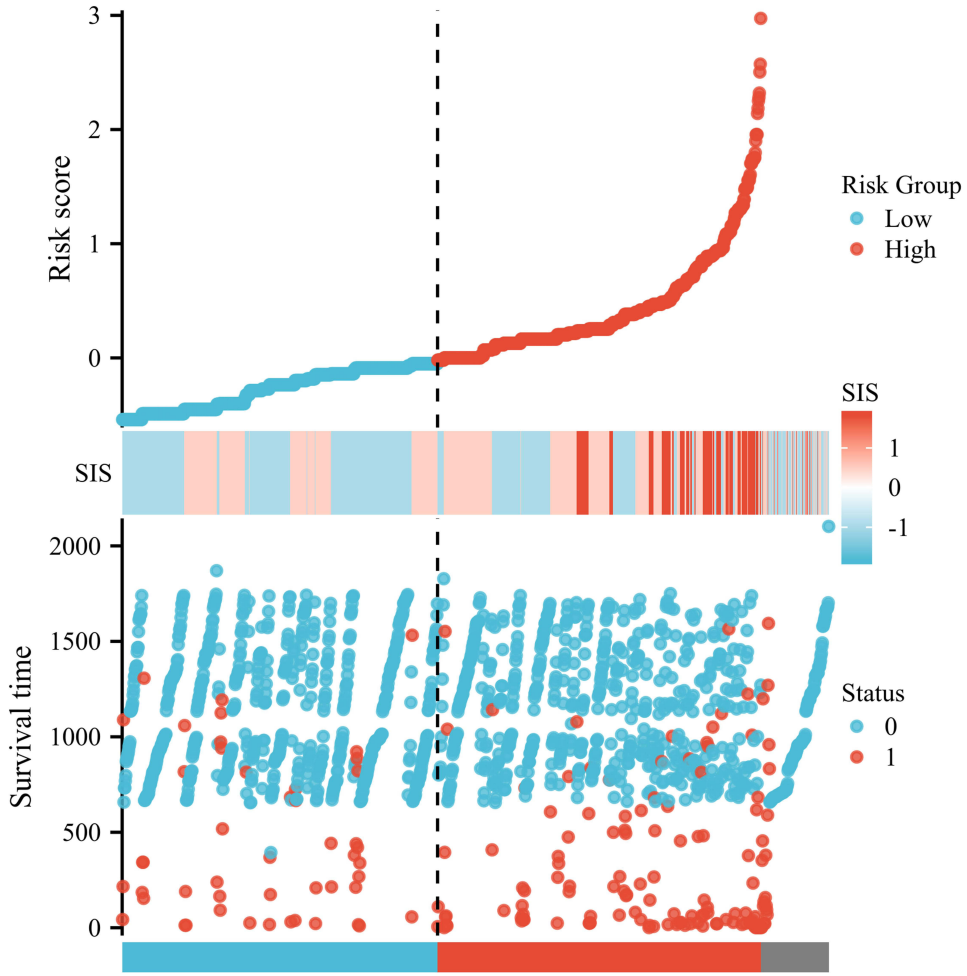

Figure 2 Distribution of the risk score, survival status, and expression profiles of SIS predicting MACEs. In the accompanying heat map, red represents higher levels, whereas light blue indicates lower levels. The risk scores are arranged in ascending order, categorizing patients into the low-risk group (blue) and high-risk group (red) according to a predetermined threshold marked by a vertical black line. Each bar in the plot represents the incidence of MACEs in individual patients: red bars indicate the occurrence of MACEs, whereas blue bars indicate the patients without recurrence during the observation time frame.
Abbreviations: MACEs, major adverse cardiovascular events; SIS, systemic inflammation score.

Kaplan–Meier Survival Curves

The Kaplan–Meier survival curves and Log rank test revealed that the cumulative survival rate of the SIS = 2 group was significantly lower than that of the SIS = 0 and SIS = 1 groups in predicting MACEs (Log rank test: $p < 0.0001$; Figure 3). Subsequently, we assigned SIS = 0 and SIS = 1 as the low-SIS group and SIS = 2 as the high-SIS group. The cumulative survival rate of the high-SIS group showed statistical significance in predicting both MACEs and all-cause mortality (Log rank test: $p < 0.05$ for all; Figure 4).

Additionally, a landmark analysis was conducted to investigate the relationship between the SIS and MACEs before and after 300 and 600 d. The results indicated a statistically significant difference before and after the 300- and 600-d periods ($p < 0.05$ for all; Figure 5A and B), suggesting that the SIS displayed similar predictable ability whether in the short or long term.

Prediction of Cardiac Death by Competing Risk Regression

Firstly, we intended to analyze the correlation of the SIS level with rehospitalization risk and all-cause mortality was considered as a competing riskevents. The comparison of the high-SIS group with the low-SIS group yielded an HR of 1.89 (95% CI: 1.22–2.92, $p = 0.004$). After adjusting for the history of heart failure and DM, with the univariate competing risk model ($p < 0.1$) being considered in the multivariable model, the HR was 1.65 (95% CI: 1.05–2.60, $p = 0.030$). The cumulative incidence function (CIF) of the high-SIS group was high, showing a statistically significant difference compared with that of the low-SIS group (Gray's test: $p = 0.004$; Figure 6A).

Next, the relationship between the SIS and cardiac death was also analyzed, with death except for cardiovascular death being used as a competing event. The comparison of the high-SIS group with the low-SIS group yielded an HR of 5.04 (95% CI: 2.47–10.28, $p < 0.001$). After adjusting for age ≥65 years, history of heart failure, LVEF <40%, and

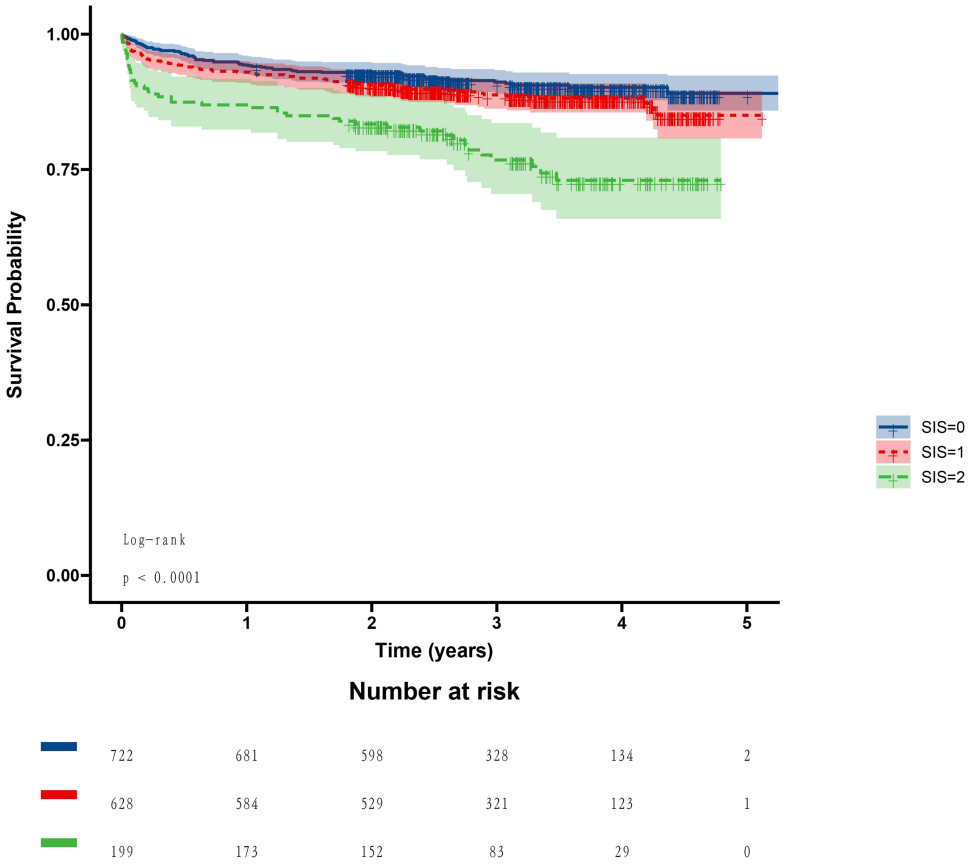

Figure 3 Cumulative incidence of MACEs stratified by the SIS.
Abbreviations: MACEs, major adverse cardiovascular events; SIS, systemic inflammation score.

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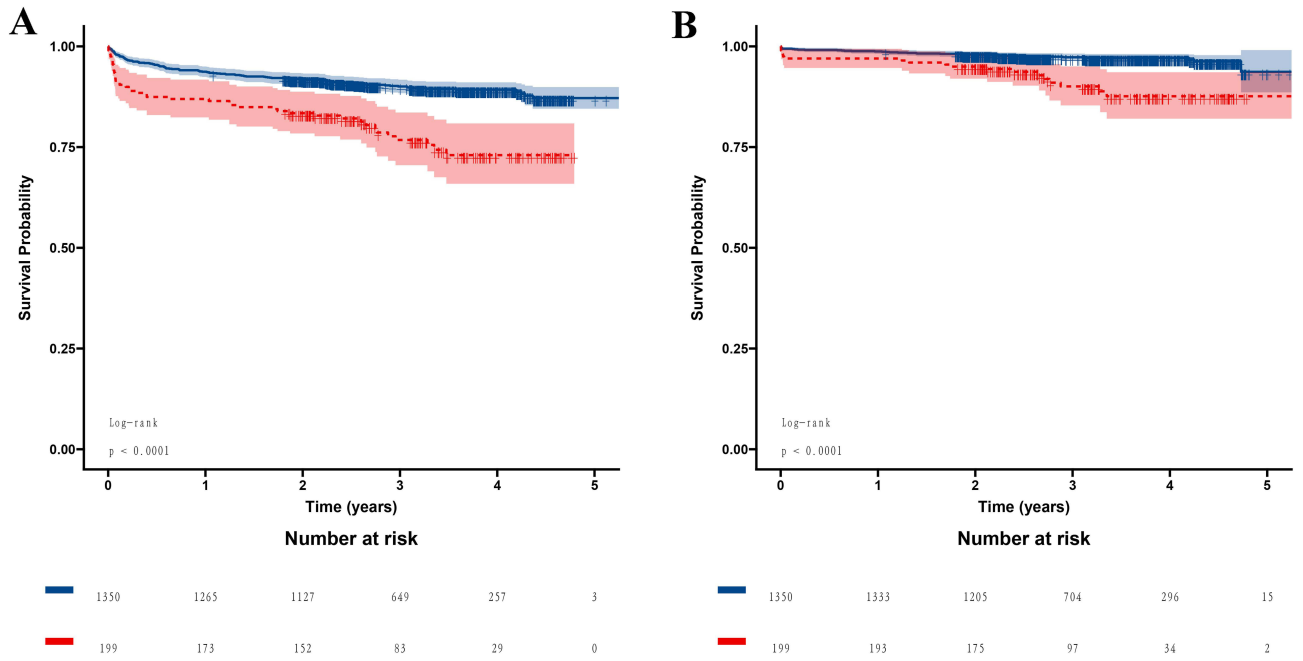

Figure 4 Cumulative incidence of MACEs (**A**) and all-cause mortality (**B**) at follow-up stratified by SIS. The blue line represents the low-SIS group, whereas the red line represents the high-SIS group.
Abbreviations: MACEs, major adverse cardiovascular events; SIS, systemic inflammation score.

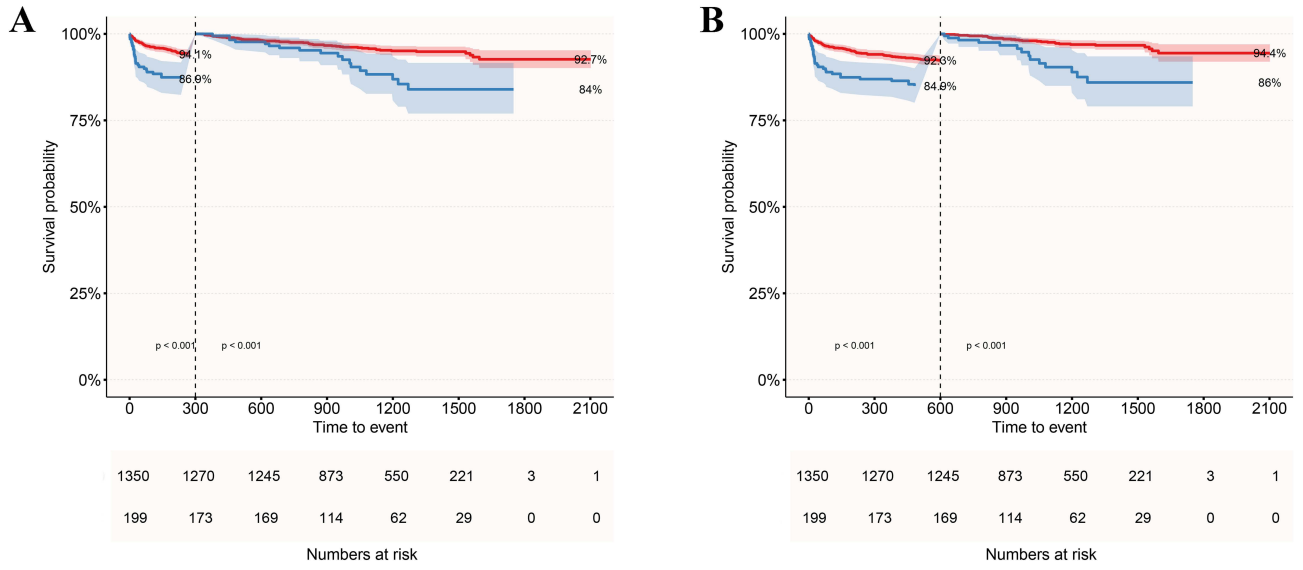

Figure 5 Landmark Kaplan–Meier curves for cumulative survival. (**A**) Landmark analysis discriminating MACEs that occurred before and subsequent to the 300-d follow-up period. (**B**) Landmark analysis discriminating MACEs that occurred before and subsequent to the 600-d follow-up period. The red line represents the low-SIS group, whereas the blue line represents the high-SIS group.
Abbreviations: MACEs, major adverse cardiovascular events; SIS, systemic inflammation score.

cerebral infarction, with the univariate competing risk model ($p < 0.1$) being considered in the multivariable model, the HR was 3.66 (95% CI: 1.65–8.13, $p = 0.001$). The CIF of the high-SIS group was high and exhibited a statistically significant difference compared with that of the low-SIS group (Gray's test: $p < 0.001$; Figure 6B).

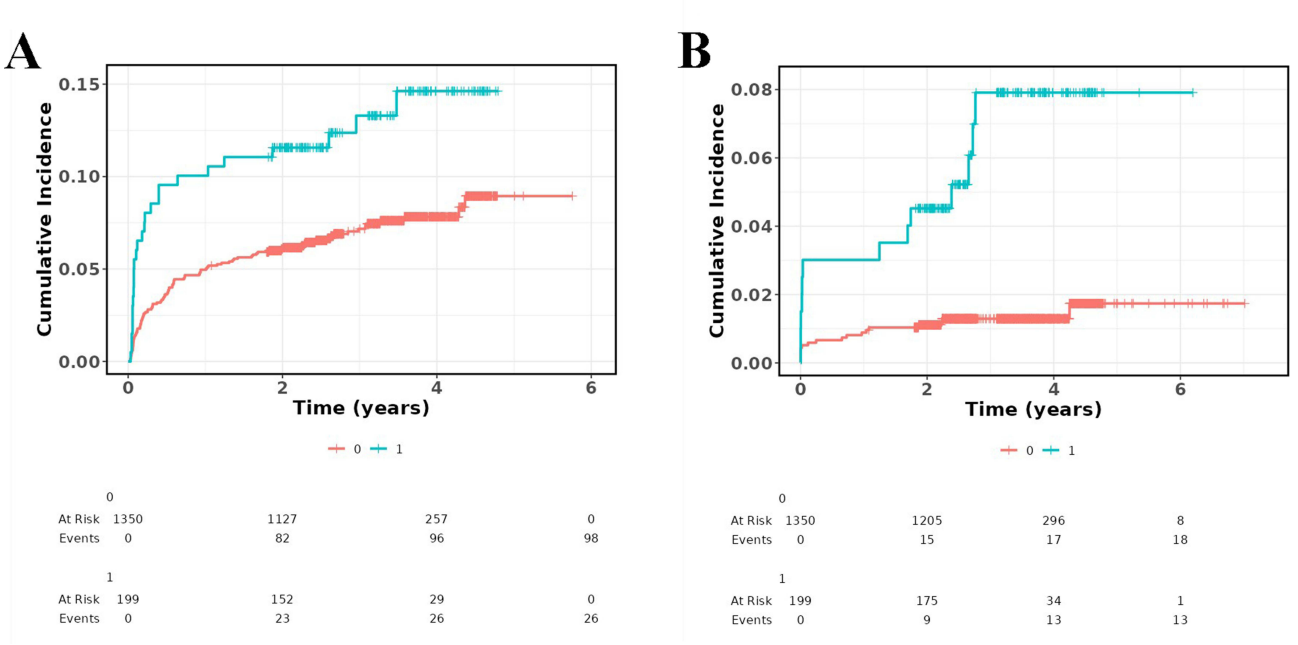

Figure 6 Cumulative incidence function (CIF) of high- and low-SIS groups. The competing risk model to obtain the CIF for the prediction of rehospitalization risk (**A**) and cardiovascular death (**B**). The red line represents the low-SIS group, whereas the green line represents the high-SIS group (Gray's test: $p < 0.05$ for all).
Abbreviation: SIS, systemic inflammation score.

Predictive Value of the SIS in Various Subgroups

Figure 7 presents the relationship of the SIS with MACEs (Figure 7A) and all-cause mortality (Figure 7B), categorized by factors such as sex, age, STEMI, dyslipidemia, hypertension, DM, family history of CAD, three-vessel disease, LVEF <40%, and LVEDD >50 mm. The SIS was deemed to be a good predictor of MACEs and overall mortality across various

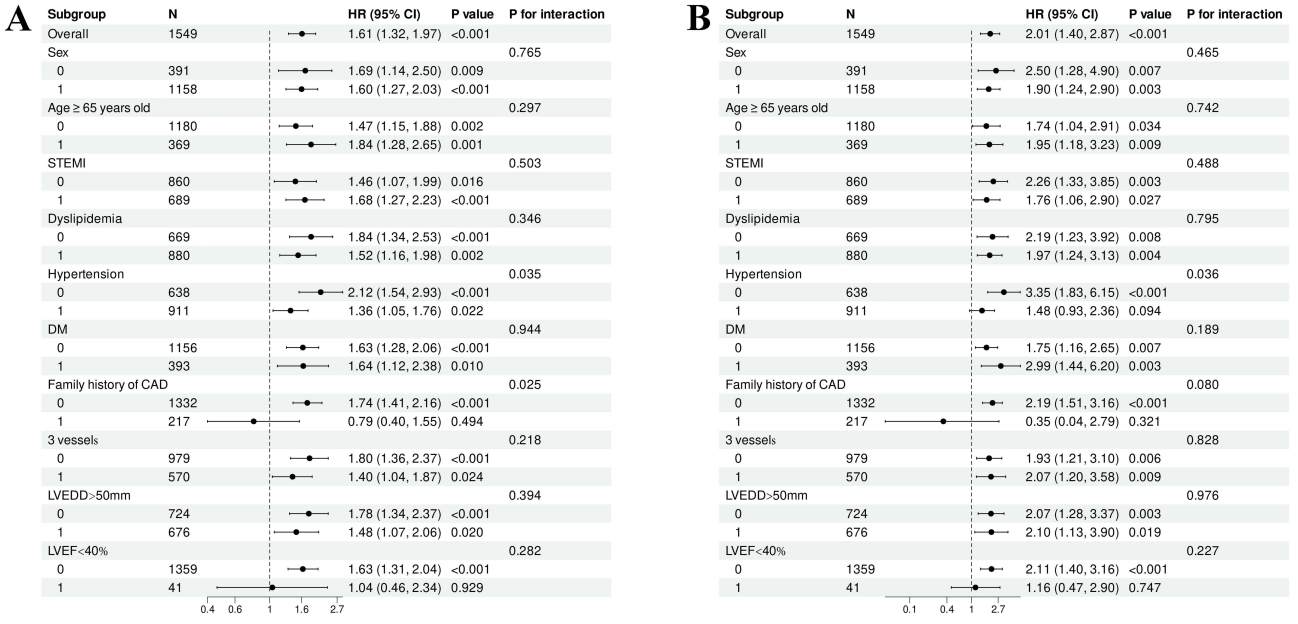

Figure 7 Forest plot showing the association of SIS with MACE (**A**) and all-cause mortality (**B**) risks. The associations are stratified by various subgroups of patients with ACS undergoing PCI.
Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; DM, diabetes mellitus; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiovascular events; PCI, percutaneous coronary intervention; SIS, systemic inflammation score; STEMI, ST-segment elevation myocardial infarction.

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Table 4 Cox Proportional Hazards Models According to SIS Subgroups

SIS	Unadjusted		Adjusted	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACEs				
SIS = 0	1 (Reference)	–	1 (Reference)	–
SIS = 1	1.294 (0.924–1.812)	0.134	1.092 (0.759–1.571)	0.634
SIS = 2	2.702 (1.841–3.967)	<0.001	1.092 (0.759–1.571)	<0.001
p for trend	–	<0.001	–	0.001
All-cause mortality				
SIS = 0	1 (Reference)	–	1 (Reference)	–
SIS = 1	1.402 (0.740–2.659)	0.300	1.260 (0.633–2.508)	0.511
SIS = 2	3.991 (2.057–7.747)	<0.001	2.853 (1.346–6.044)	0.006
p for trend	–	<0.001	–	0.014

Notes: Adjusted for age ≥65 years, sex, STEMI, family history of CAD, cardiogenic shock, history of heart failure, three-vessels disease, LVEDD, and LVEF.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiovascular events; SIS, systemic inflammation score; STEMI, ST-segment elevation myocardial infarction.

subgroups. This significance remained robust even after adjusting for numerous factors, with all interaction *p*-values exceeding 0.05.

Variation in the SIS and Poor Prognosis by p for Trend

Changes in HR among various SIS subgroups (SIS = 0, SIS = 1, and SIS = 2) were analyzed using *p* for trend. The HR values of the SIS = 1 and SIS = 2 groups increased with *p* for trend <0.001 (adjusted *p* for trend = 0.001; Table 4) compared to those of the SIS = 0 group. Similar results were obtained with *p* for trend <0.001 when all-cause mortality was set as the outcome (adjusted *p* for trend = 0.014).

Mediation Analysis of the SIS for MACEs in Patients with ACS

The mediation analysis revealed that Hb level exerted a significant partial mediating effect on the relationship between the SIS and MACEs incidence across multiple adjusted models. In particular, the mediation proportions of Hb level were 5.36%, 4.17%, and 7.42% in the three models of the observational association between the SIS and MACEs risk (Figure 8A–C).

Discussion

Our prospective cohort study investigated the relationship between the SIS and various outcomes, including MACEs and all-cause mortality, in patients with ACS. The key findings of the current study were that the SIS was a valuable predictor of the risks of rehospitalization and cardiac death in patients with ACS and that a high SIS was an independent risk factor for both MACEs and all-cause mortality, with age acting as a mediating factor. To the best of our knowledge, this is the first study to analyze the SIS in relation to the prognostic risks of patients with ACS undergoing PCI.

Systemic inflammation plays a crucial role in the development and progression of various diseases, including cancers and cardiovascular conditions. The activation of inflammatory cells and release of pro-inflammatory mediators in systemic inflammation have wide-ranging effects on multiple organ systems. In recent years, several inflammation-related biomarkers (eg, neutrophil-to-lymphocyte ratio, LMR, C-reactive protein) and composite scores (eg, Glasgow prognostic score, SIS, prognostic nutritional index) have been developed to quantify the degree of systemic inflammation and assess its effects on patient outcomes.[23–25] The SIS, which is typically calculated using the serum albumin level and LMR, has been recognized as an innovative and convenient score with better prognostic ability and has emerged as a valuable biomarker for predicting the clinical outcomes of several diseases. Additionally, cumulative research on the relationship between systemic inflammation and prognosis has led to the application of SIS in numerous clinical settings.

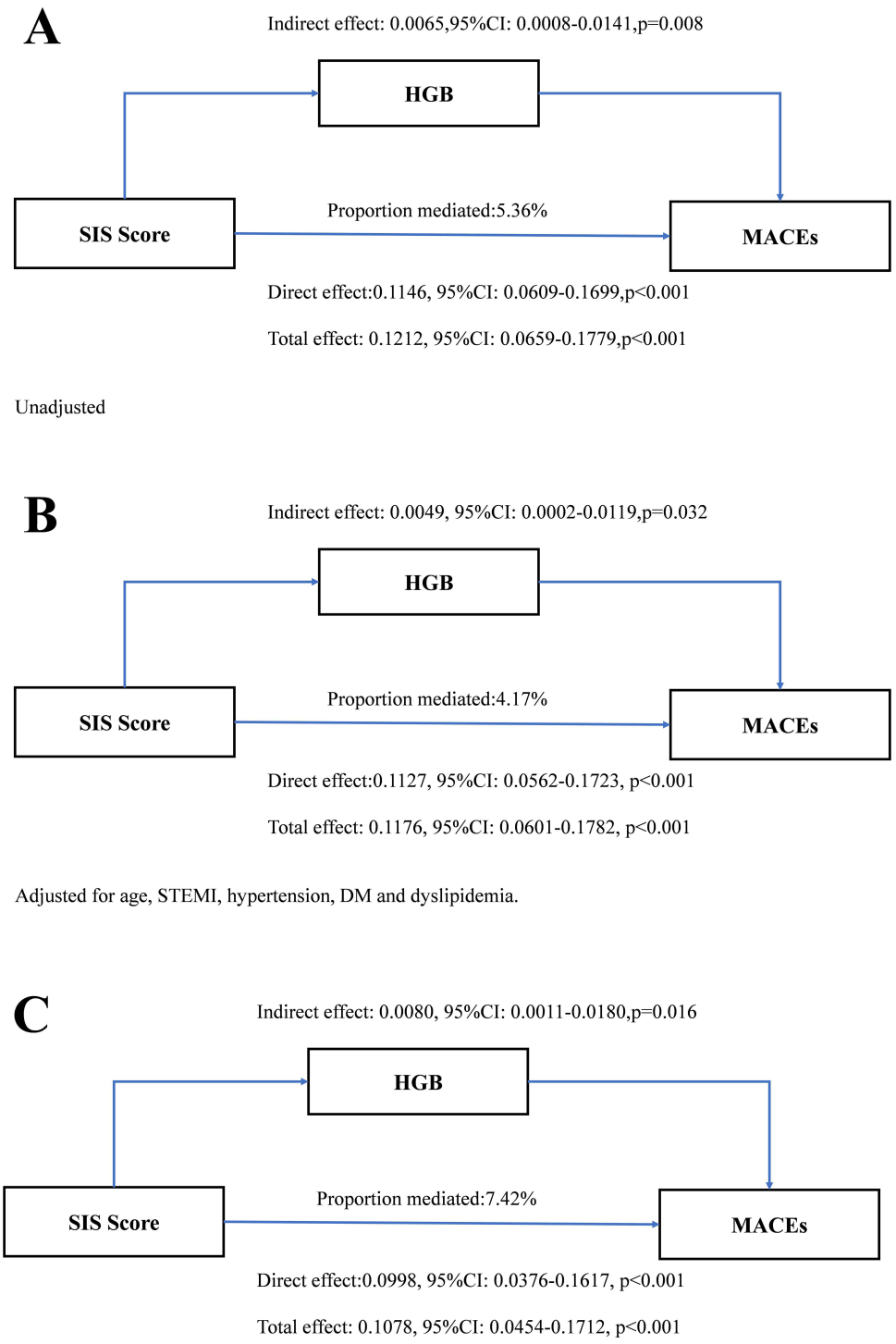

Figure 8 Decomposition of the total association between SIS and MACE risk in ACS patients undergoing PCI. (**A**) Unadjusted (**B**) Adjusted for age, STEMI, hypertension, DM and dyslipidemia. (**C**) Adjusted for age, STEMI, hypertension, DM, dyslipidemia, 3 vessels, LVEDD > 50mm, LVEF < 40%, sex, history of HF, cerebral infraction and family history of CAD. The decomposition of the total association shows direct and indirect associations mediated by baseline Hb level in different adjusted models, respectively. **Abbreviation**: SIS, systemic inflammation score.

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Elevated levels of inflammatory markers such as albumin and LMR indicate an increased risk of adverse events and poorer prognosis; the SIS encapsulates these inflammatory processes and provides a prognostic indicator.

Atherosclerosis is a complex and multifaceted cardiovascular disease characterized by the accumulation of lipids and immune cells within the arterial walls, resulting in plaque formation and vascular obstruction. This disease is the leading cause of ACS and has been increasingly recognized as an inflammatory condition involving various components of the immune system, notably lymphocytes and monocyte, as key players in its pathogenesis. Previous studies using experimental models have demonstrated how chemokines facilitate the recruitment of lymphocytes to areas of atherosclerotic development, implicating the crucial role of adaptive immunity in this disease process.[26] The adaptive immune response in atherosclerosis involves T- and B-lymphocytes, which regulate various immune pathways that influence the stability of atherosclerotic plaques.[27] Recent findings have suggested that B- and T-lymphocyte attenuator plays a novel role in immune regulation in atherosclerosis. This shift promotes plaque stability by increasing the collagen content within lesions.[28] The involvement of lymphocytes in atherosclerosis is also reflected in systemic inflammatory ratios such as the platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio, which serve as potential biomarkers for disease activity and prognosis. A higher platelet-to-lymphocyte ratio has been reported to be associated with the coronary slow-flow phenomenon, suggesting its role as an independent predictor of certain cardiovascular conditions.[29] Similarly, variations in the neutrophil-to-lymphocyte ratio correlate with racial differences in the incidence of atherosclerotic events, revealing a complex interplay between systemic inflammation and disease expression.[30] Taken together, lymphocytes represent a critical link between the immune system and pathogenesis of atherosclerosis.

Monocytes and their descendant macrophages play a pivotal role in the development and progression of atherosclerosis. The influx of monocytes into the vessel wall in atherosclerosis contributes to vascular inflammation.[31] The primary source of circulating monocytes is the bone marrow, and this systemic interaction extends to how monocytes behave in atherosclerotic plaques, where they may differentiate into foam cells after ingesting lipids.[32,33] Recent studies have expanded our understanding of epigenetic factors related to monocytes in atherosclerosis, further highlighting the involvement of complex molecular mechanisms.[34] Monocytes also exhibit dual roles in cardiovascular diseases, acting as effectors of immune homeostasis and contributors to pathological conditions. They are involved not only in injury repair but also in immune defense.[35]

The LMR has emerged as a novel inflammatory marker with substantial prognostic implications in patients with ACS. The importance of the LMR in this context roots from its potential to reflect systemic inflammatory status, which is intrinsically linked to the pathophysiology of cardiovascular diseases. Oylumlu et al reported that both the monocyte-to-HDL-C ratio and LMR are significant predictors of in-hospital and long-term mortality in patients with ACS.[36] A systematic review and meta-analysis conducted by Quan et al further reinforced this finding by highlighting the association of lower LMR with increased short- and long-term mortality and MACEs in patients with ACS.[37] Karauzum et al explored the ability of LMR to predict contrast-induced nephropathy in patients undergoing PCI and reported the association between lower LMR values and the development of contrast-induced nephropathy, suggesting another dimension to the clinical utility of LMR in the management of ACS.[38] Additionally, another previous study showed that a lower LMR at admission independently correlated with long-term MACEs and all-cause mortality after discharge in patients with STEMI.[39]

Over the years, the role of albumin in the prognosis of various cardiovascular and oncological conditions has received considerable attention. Albumin, a major plasma protein, is implicated in numerous physiological processes, such as the maintenance of colloidal osmotic pressure and transportation of substances, and serves as a biomarker for nutritional and inflammatory status. The role of albumin also extends to oncology, implying its versatility as part of a multifaceted marker in gauging a host's state in malignant conditions.[40] This diverse functional profile makes albumin a valuable indicator in clinical prognostication. The fibrinogen-to-albumin ratio has been extensively evaluated as a prognostic marker for conditions such as acute decompensated heart failure and general heart failure. An elevated fibrinogen-to-albumin ratio is independently associated with poor prognostic outcomes, including higher MACE risk in patients with acute decompensated heart failure and DM, implying its potential utility in risk stratification and therapeutic decision-making.[41,42] In the context of AMI, the lactate-to-albumin ratio has also been identified as a relevant prognostic marker. In particular, a higher lactate-to-albumin ratio has been reported to be independently associated with an increased

mortality risk at 14, 28, and 90 d after AMI, underscoring its potential as an early indicator of adverse outcomes in critically ill patients with AMI.[43,44] This ratio reflects not only the metabolic derangements associated with lactate elevation caused by hypoperfusion and anaerobic glycolysis in myocardial ischemia but also the nutritional and systemic status indicated by albumin levels.

We speculate that the predictive ability of the SIS is related to the LMR and albumin. Serum albumin level, a component of the SIS, is linked to an increased mortality risk in patients with cardiovascular diseases. The SIS offers several potential advantages, particularly its simplicity and cost-effectiveness. Furthermore, the SIS relies on routine blood tests commonly performed in clinical practice and is therefore widely available. Compared to individual biomarkers, the SIS enables a more comprehensive assessment of inflammatory and nutritional status, with improved prognostic accuracy. Overall, the SIS, which combines both inflammatory and nutritional parameters, may provide valuable prognostic information in cardiovascular disease and may serve as a valuable tool for evaluating the prognosis of patients with ACS.

Current prognostic scoring tools for patients with acute coronary syndrome (ACS), such as the GRACE and TIMI scores, integrate clinical characteristics including gender, creatinine levels, and cardiac function to evaluate short-term prognosis. Our study identified that SIS, derived from albumin levels and the LMR, is also associated with ACS patient prognosis. The SIS serves to assess a patient's inflammatory status. Unlike traditional scoring systems, the SIS specifically measures the inflammatory state at the time of onset. However, traditional inflammation scoring systems do not provide a comprehensive evaluation of a patient's inflammatory status. Therefore, combining these approaches to develop more meaningful prognostic tools is a promising avenue that warrants further exploration. This study has some limitations, particularly its limited sample size and single-center design. Notably, given that this study is an observational study, the exact mechanism underlying the relationship between the SIS and MACEs requires further exploration.

Conclusions

The SIS is a novel inflammatory and nutrition index that shows a strong correlation with the risks of MACEs and all-cause mortality in patients with ACS who underwent PCI. Notably, the SIS is particularly effective in predicting the risks of cardiac death and likelihood of rehospitalization.

Abbreviations

ACS, Acute coronary syndrome; AMI, Acute myocardial infarction; CAD, Coronary artery disease; CIF, Cumulative incidence function; CRP, C-reactive protein; DM, Diabetes mellitus; HDL-C, High-density lipoprotein-cholesterol; hsCRP, High-sensitivity C-reactive protein; LDL-C, Low-density lipoprotein-cholesterol; LMR, Lymphocyte-to-monocyte ratio; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; MACEs, Major adverse cardiovascular events; NSTEMI, Non-ST-segment elevation myocardial infarction; PCI, Percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Chengde Medical University (approval number: CYFYLL2015006). All participants provided informed consent.

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Disclosure

The authors declare that they have no competing interests.

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