Clinical Interventions in Aging

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ORIGINAL RESEARCH

The Systemic Immune-Inflammation Index and High-Sensitivity C-Reactive Protein to High-Density Lipoprotein Cholesterol Ratio Predict Moderate and Severe Coronary Artery Stenosis in Older Patients with Coronary Heart Disease

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Objective: Coronary heart disease (CHD) stems from functional and organic coronary artery stenosis (CAS). This study explored associations of the systemic immune-inflammation index (SII) and high-sensitivity C-reactive protein to high-density lipoprotein cholesterol ratio (hsCRP/HDL-C) with CAS severity in older patients with CHD.

Methods: This retrospective analysis recruited 786 older patients with CHD, with their clinical data and laboratory parameters collected. Patients were allocated into training and validation sets (7:3, randomization) or into mild, moderate, and severe stenosis groups according to Gensini scores (GS). Correlations of SII and hsCRP/HDL-C with GS, influencing factors for moderate-to-severe CAS, and their diagnostic value in older patients with CHD or complicated with hypertension and/or diabetes were assessed using Spearman's, univariate/multivariate logistic regression, and receiver operating characteristic curve analyses, respectively.

Results: Elevated SII and hsCRP/HDL-C were observed in patients with moderate-to-severe stenosis, which demonstrated certain correlations with GS, and were independent risk factors (IRFs) for moderate-to-severe CAS in older patients with CHD in both sets. The comparable regression coefficients between the two sets suggested good model consistency and no significant multicollinearity. The area under the curve of the combination of SII and hsCRP/HDL-C for predicting CAS severity was outperforming either marker alone. Hypertension significantly affected the discriminating performance of SII. SII remained stable in the hypertensive population, but its efficacy decreased evidently in the non-hypertensive population.

Conclusion: SII and hsCRP/HDL-C are IRFs for moderate-to-severe CAS in older patients with CHD, and their combination yields good predictive performance. Regression coefficients were well consistent between the two datasets.

Keywords: elderly coronary heart disease, coronary artery stenosis, systemic immune-inflammation index, high-sensitivity c-reactive protein to high-density lipoprotein cholesterol ratio, correlation

Introduction

Coronary heart disease (CHD), a chronic and complex condition marked by high morbidity and mortality, primarily results from atherosclerotic lesions in the coronary arteries, which can progress to stroke and myocardial infarction.[1] Cardiovascular incidents such as heart failure, myocardial infarction, stroke, and cerebral thrombosis are common causes of morbidity and mortality among CHD patients.[2] In mainland China, the economic burden imposed by CHD, particularly the direct costs, is more substantial compared to developed nations.[3] Although remarkable progress has

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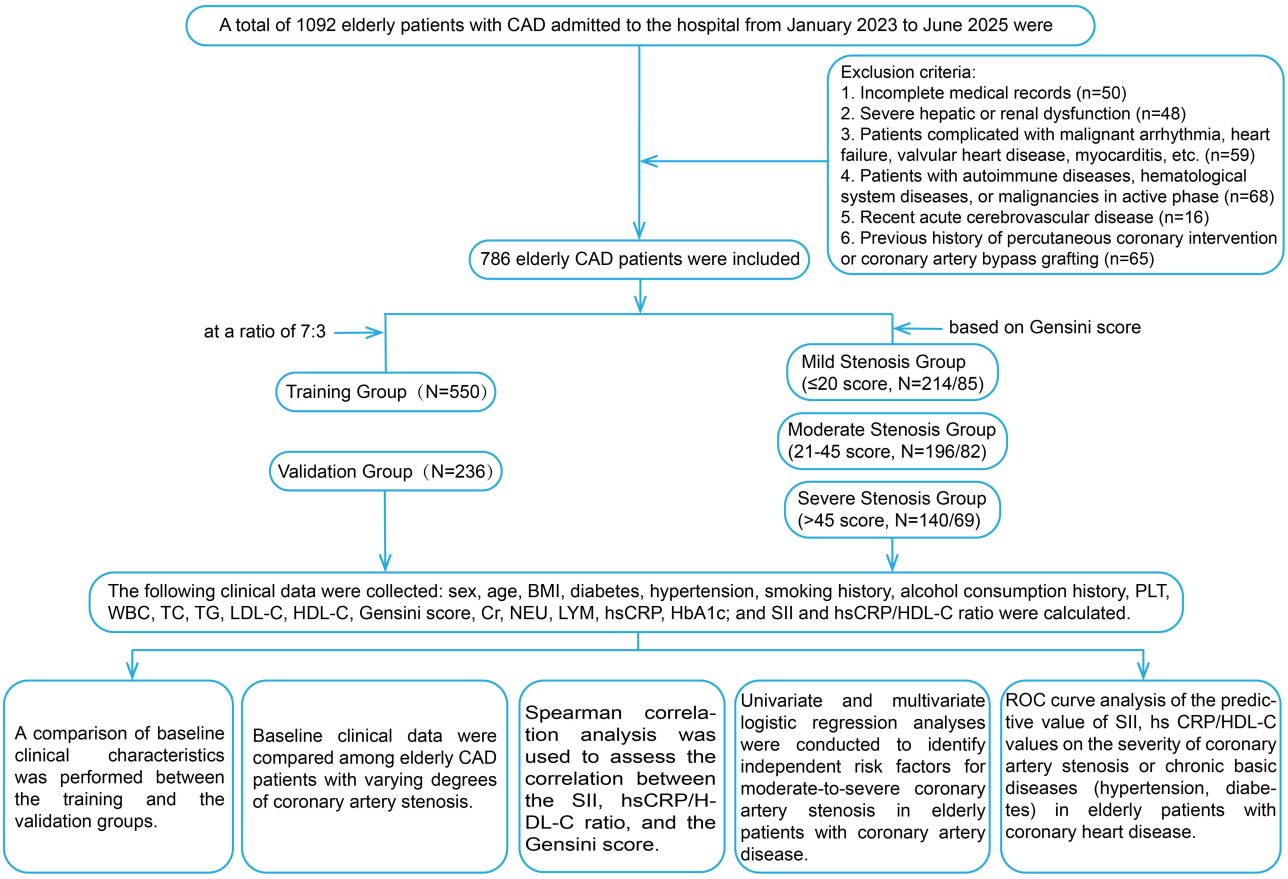
Graphical Abstract



SII and hs CRP/HDL-C values are independent risk factors for moderate to severe coronary artery stenosis in elderly patients with coronary heart disease, and the regression coefficients of the training and validation sets are in good agreement. The predictive performance of SII combined with hs CRP/HDL-C values for moderate to severe coronary artery stenosis in elderly patients with coronary heart disease is significantly better than that of a single indicator.

been made in CHD management, predicting adverse coronary events remains difficult.[4] Moreover, elderly patients often exhibit variations in drug response and metabolism due to age-related physiological decline and comorbidities; therefore, they are prone to adverse drug complications and reactions.[5] Thus, early and precise identification of older CHD patients at high risk of severe coronary artery stenosis (CAS) is clinically essential for optimizing therapeutic approaches and enhancing outcomes.

Preoperative coronary angiography (CAG) is a well-established standard for evaluating significant CAS.[6,7] Despite being relatively safe, CAG remains an invasive procedure and has potential risks, particularly in patients with CHD and other comorbidities.[8] Additionally, current imaging techniques have limitations. CAG images often suffer from low resolution, poor contrast, and considerable noise or artifacts, which complicate the segmentation of blood vessels.[9] These challenges are especially relevant in elderly patients, who frequently present with complications such as renal insufficiency, coagulation disorders, or general intolerance to CAG.[10] Such factors underscore the need for more suitable alternative diagnostic approaches.

The systemic immune-inflammation index (SII), a recently developed inflammatory biomarker, is calculated from peripheral neutrophil count (NEUT), lymphocyte count (LYM), and platelet count (PLT).[11,12] As one of the innovative inflammatory indicators compared to traditional peripheral blood cell markers, it can predict the occurrence and

prognosis of CHD.[13] A myriad of evidence indicates that SII can rapidly and accurately identify CHD in young adults with chest pain,[14,15] predict CAS severity in CHD patients,[16] and serve as an independent risk factor (IRF) for coronary atherosclerotic heart disease and CAS severity.[17,18] Owing to its clinical accessibility and low cost, SII represents a convenient and cost-effective tool for CHD detection.[15] Emerging evidence has validated that the SII serves as a powerful prognostic biomarker in patients diagnosed with acute coronary syndrome.[19] Furthermore, inflammation and lipid metabolism have been shown to be closely interrelated.[20] For instance, the ratio of monocyte or white blood cell count to high-density lipoprotein cholesterol (HDL-C) has been identified as a predictor of long-term adverse outcomes in patients following percutaneous coronary intervention.[21,22] Further supporting this link, the high-sensitivity C-reactive protein to HDL-C ratio (hsCRP/HDL-C) has been identified as a significant risk factor for cardiovascular disease in US adults.[23] However, the relevance of the SII and hsCRP/HDL-C ratio to CAS severity in older patients with CHD remains unexplored. The objective of this study was to systematically evaluate correlations of both SII and the hsCRP/HDL-C ratio with CAS severity in older individuals with CHD. This study is expected to offer clinicians a simple, low-cost method to more accurately identify high-risk older CHD patients for intensified intervention and improved clinical management.

Materials and Methods

Participants

A total of 1,092 patients with suspected CHD from the Department of Cardiology of Yongchuan Hospital of Chongqing Medical University between January 2023 and June 2025 were retrospectively selected. Based on the inclusion and exclusion criteria, 786 older patients with CHD were ultimately enrolled as the study subjects. Following a ratio of 7:3,[24] all participants were randomly assigned to the training set (n = 550) and the validation set (n = 236). The training set data were utilized to identify influencing factors for the severity of CAS in older CHD patients and to establish a predictive model. The validation set data were employed to assess the validity of the model. Subsequently, based on their Gensini scores (GS), older patients with CHD within both the training and validation sets were further classified into the mild stenosis group (≤ 20 points, n = 214/85), the moderate stenosis group (21–45 points, n = 196/82), and the severe stenosis group (> 45 points, n = 140/69). This study complied with the *Declaration of Helsinki* and was approved by the Ethics Committee of Yongchuan Hospital of Chongqing Medical University (No. 2025EC0249).

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) aged ≥ 60 years and < 80 years; (2) diagnosed with CHD by CAG.

Exclusion criteria were as follows: (1) incomplete clinical data; (2) severe hepatic or renal dysfunction; (3) complication of malignant arrhythmia, heart failure, valvular heart disease, or myocarditis; (4) autoimmune diseases, hematological system diseases, or active malignancy; (5) recent acute cerebrovascular disease; (6) a history of percutaneous coronary intervention or coronary artery bypass grafting surgery.

Diagnostic Criteria for CHD

Diagnostic criteria for CHD included clinical manifestations of myocardial ischemia (chest pain or chest tightness, etc.) and a degree of stenosis ≥ 50% in any of the following four major branches: the left main coronary artery, left anterior descending artery, left circumflex artery, or right coronary artery, as revealed by percutaneous CAG results.

Assessment of CAS Severity Using GS

Based on the angiographic results, each coronary artery segment was evaluated for the location and degree of stenosis. GS was calculated as the sum of the baseline score for the most severe stenosis at each lesion multiplied by the corresponding coefficient (Table 1). According to GS, a score ≤ 20 was defined as mild stenosis, a score between 21 and 45 (inclusive) as moderate stenosis, and a score > 45 as severe stenosis.

Table 1 Weighting Coefficients of Different Coronary Artery Lesion Sites

CAS Severity	Score	Lesion Site	Coefficient
1–25%	1	Left main coronary artery	5
26–50%	2	Proximal left anterior descending artery, proximal circumflex artery	2.5
51–75%	4	Mid left anterior descending artery	1.5
76–90%	8	Distal left anterior descending artery	1
91–99%	16	Distal circumflex artery, posterior descending artery	1
100%	32	First diagonal branch	1
		Right coronary artery	1
		Remaining small branches	0.5

Collection of Medical Record Data

General clinical data were gathered for all patients, including age, sex, body mass index (BMI), diabetes, hypertension, smoking history, and drinking history. A smoking history was defined as smoking one or more cigarettes per day for a minimum of six months prior to hospitalization.[25] A drinking history was defined as an average weekly intake of at least 100 grams of alcohol for over one year prior to hospitalization.[26]

Additional laboratory parameters were acquired at the time of admission, including PLT, white blood cell count (WBC), total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C), HDL-C, creatinine (Cr), GS, hsCRP, NEUT, LYM, and glycosylated hemoglobin A1c (HbA1c). SII = PLT × NEUT/LYMPH. hsCRP/HDL-C was calculated as below: hsCRP/HDL-C = hsCRP (mg/L)/ [HDL-C (mmol/L) * 386.65].[27]

Statistical Analysis

Data analysis and graph generation were conducted utilizing SPSS 27.0 (IBM, Armonk, NY, USA) and GraphPad Prism 9.5 (GraphPad, San Diego, CA, USA) software. Data normality was assessed using the Kolmogorov–Smirnov test. Normally distributed measurement data were presented as mean ± standard deviation (SD) and were compared between groups using the independent sample *t*-test. Non-normally distributed measurement data were expressed as the median (minimum, maximum). Inter-group comparisons were conducted utilizing the Mann–Whitney *U*-test. Categorical variables were depicted as counts and percentages. The Spearman correlation analysis was employed to evaluate correlations of SII and hsCRP/HDL-C with GS in CHD patients.

Additionally, the variables with $p < 0.05$ in the univariate analysis were incorporated into the multivariate logistic regression analysis to identify IRFs for severe CAS or coronary occlusion. The Enter method was employed for variable inclusion. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated. Multicollinearity was assessed by examining the variance inflation factor (VIF); a VIF < 5 indicates no significant multicollinearity among the explanatory variables, whereas a VIF ≥ 5 suggests the presence of multicollinearity. Interaction terms were constructed, and stratified regression analysis was performed. The Chow test was used to compare differences in regression coefficients between the two groups. The predictive value of SII and hsCRP/HDL-C, both individually and in combination, was evaluated using the receiver operating characteristic (ROC) curve analysis. Comparisons of multiple areas under ROC curves (AUCs) were carried out using MedCalc 20.0.15 software (MedCalc Software, Ostend, Belgium). $p < 0.05$ was considered statistically significant.

Results

Comparisons of Clinical Baseline Data Between Training and Validation Sets in Older Patients with CHD

The two sets showed no statistically significant differences in terms of age, sex, BMI, diabetes, hypertension, smoking history, drinking history, PLT, WBC, TC, TG, LDL-C, HDL-C, GS, Cr, NEUT, LYM, hsCRP, HbA1c, SII, and hsCRP/HDL-C (all $p > 0.05$) (Table 2).

Table 2 Comparisons of Clinical Baseline Data of Older Patients with CHD Between Training and Validation Sets

Clinical Indicators	Training Set (n = 550)	Validation Set (n = 236)	*p* value
Age (years)	69 (60, 80)	69 (61, 80)	0.553
Sex (male/female, cases)	305/245	125/111	0.532
BMI (kg/m^2)	24.93 (20.70, 28.92)	24.89 (221.16, 28.78)	0.975
Diabetes (n, %)	287 (52.18%)	109 (45.99%)	0.120
Hypertension (n, %)	298 (54.18%)	127 (53.81%)	0.938
Smoking history (n, %)	268 (48.73%)	101 (42.80%)	0.139
Drinking history (n, %)	240 (43.64%)	102 (43.22%)	0.937
PLT ($\times 10^9$/L)	188.8 (154.7, 268.3)	194.5 (127.3, 397.8)	0.148
WBC ($\times 10^9$/L)	6.36 (4.48, 8.71)	6.35 (4.54, 8.03)	0.335
TC (mmol/L)	3.87 (3.18, 5.09)	3.85 (3.04, 4.75)	0.980
TG (mmol/L)	1.240 (0.42, 2.28)	1.25 (0.46, 2.48)	0.055
LDL-C (mmol/L)	2.44 (1.38, 4.10)	2.36 (1.60, 3.26)	0.304
HDL-C (mmol/L)	1.04 (0.53, 1.52)	1.06 (0.39, 1.68)	0.574
GS	28 (8, 121)	28 (8, 120)	0.120
Cr (μmol/L)	66.46 (46.46, 86.45)	67.23 (47.10, 86.26)	0.051
NEUT ($\times 10^9$/L)	4.19 (2.94, 5.50)	4.22 (3.20, 6.11)	0.064
LYM ($\times 10^9$/L)	1.77 (0.98, 2.99)	1.79 (1.34, 2.51)	0.124
hsCRP (mg/dL)	11.05 (6.33, 41.40)	11.55 (7.19, 31.66)	0.054
HbA1c (%)	6.97 (5.62, 8.65)	6.97 (5.16, 8.56)	0.629
SII ($\times 10^9$/L)	454.2 (328.2–737.2)	442.8 (281.0, 753.7)	0.534
hsCRP/HDL-C ($\times 10^{-2}$)	2.79 (1.36, 11.64)	2.86 (1.39, 10.03)	0.075

Notes: Non-normally distributed data were presented as median (minimum, maximum) and were analyzed using the Mann–Whitney *U*-test. Categorical variables were compared using the Fisher's exact test. $p < 0.05$ was considered statistically significant.

Abbreviations: BMI, body mass index; PLT, platelet count; WBC, white blood cell count; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; NEUT, neutrophils; LYM, lymphocytes; hsCRP, high-sensitivity C-reactive protein; HbA1c, glycated hemoglobin; SII, systemic immune-inflammation index.

Comparisons of Clinical Baseline Data Among Older Patients with CHD with Varying Degrees of CAS

Patients in the training and validation sets were subsequently stratified by GS into mild stenosis, moderate stenosis, and severe stenosis groups. Patients in the training set exhibited significant differences in BMI, hypertension, PLT, TG, LDL-C, HDL-C, GS, Cr, NEUT, LYM, hsCRP, and HbA1c (all $p < 0.05$), whereas no statistically significant differences were observed for age, sex, diabetes, smoking history, drinking history, WBC, and TC (all $p > 0.05$). In the validation set, significant differences were observed for BMI, hypertension, PLT, TG, LDL-C, HDL-C, GS, Cr, NEUT, hsCRP, and HbA1c (all $p < 0.05$), while no statistically significant differences were found for age, sex, diabetes, smoking history, drinking history, WBC, TC, and LYM (all $p > 0.05$) (Table 3).

Associations of SII and hsCRP/HDL-C with CAS Severity in Older Patients with CHD

A comparative analysis among groups revealed that SII and hsCRP/HDL-C values were elevated in patients in the moderate or severe stenosis group relative to those in the mild stenosis group (all $p < 0.05$) (Table 4).

Correlation Analyses of SII and hsCRP/HDL-C with GS in Older Patients with CHD

The Spearman correlation analysis was performed to assess the correlations of SII and hsCRP/HDL-C with GS. In the training set, positive correlations were observed between SII and GS ($r = 0.6874$, $p < 0.01$), as well as between hsCRP/

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Table 3 Comparisons of Clinical Baseline Data Among Patients with Different Degrees of CAS in Training and Validation Sets

Clinical Indicators	Training Set			Validation Set		
	Mild Stenosis Group (n = 214)	Moderate Stenosis Group (n = 196)	Severe Stenosis Group (n = 140)	Mild Stenosis Group (n = 85)	Moderate Stenosis Group (n = 82)	Severe Stenosis Group (n = 69)
Age (years)	69 (61,80)	69.5 (64,80)	69 (60,80)	70 (61,80)	69 (62,80)	69 (61,80)
Sex (Male/Female, cases)	120/94	105/91	80/60	45/40	43/39	37/32
BMI (kg/m^2)	24.64 (20.70,28.50)	24.95 (22.39, 28.92)[a]	25.38 (23.05, 28.81)[ab]	24.60 (21.16, 28.70)	24.82 (22.54, 28.78)	25.03 (23.09, 28.65)[a]
Diabetes (n, %)	10	102	76	39	36	34
Hypertension (n, %)	98	110	90	55	37	35
Smoking history (n, %)	104	96	68	38	33	30
Drinking history (n, %)	90	92	58	36	35	31
PLT (×10^9/L)	185.3 (154.7,232.3)	188.6 (163.6,268.3)[a]	194.8 (162.6,244.4)[ab]	171.6 (132.9,230.6)	195.9 (155.0,261.4)[a]	212.3 (127.3, 233.5)[ab]
WBC (×10^9/L)	6.31 (4.89,7.90)	6.36 (4.97,8.71)	6.42 (4.84, 7.91)	6.37 (4.54, 8.01)	6.30 (5.55, 7.62)	6.70 (4.91, 8.03)
TC (mmol/L)	3.89 (3.33, 4.75)	3.88 (3.27, 5.09)	3.86 (3.18, 4.61)	3.86 (3.04, 4.75)	3.84 (3.39, 4.63)	3.91 (3.28, 4.75)
TG (mmol/L)	1.23 (0.52, 2.06)	1.16 (0.42, 2.05)	1.36 (0.70, 2.28)[ab]	1.04 (0.79, 1.44)	1.40 (0.93, 2.06)[a]	1.63 (0.98, 2.48)[ab]
LDL-C (mmol/L)	2.37 (1.38, 3.32)	2.47 (1.67, 4.10)[a]	2.47 (1.84, 3.38)[a]	2.33 (1.76, 3.26)	2.32 (1.60, 3.18)[a]	2.49 (1.95, 3.19)[a]
HDL-C (mmol/L)	1.06 (0.53, 1.52)	1.08 (0.56, 1.50)[b]	0.96 (0.77, 1.44)[ab]	1.10 (0.68, 1.68)	1.13 (0.39, 1.50)[b]	0.91 (0.48, 1.50)[ab]
GS	16 (8, 20)	31 (22, 45)[a]	81 (46, 121)[ab]	14 (8, 20)	29 (21, 45)[a]	66 (45, 120)[ab]
Cr (μmol/L)	66.38 (46.46, 86.45)	61.46 (52.44, 83.16)[a]	74.29 (62.07, 85.98)[ab]	66.37 (47.10, 80.26)	66.20 (61.90, 73.83)	70.95 (63.37, 86.25)[ab]
NEUT (×10^9/L)	3.92 (2.94, 5.30)	4.21 (3.04, 5.34)[a]	4.62 (3.67, 5.50)[ab]	4.25 (3.20, 5.22)	3.99 (3.43, 4.86)[a]	4.82 (3.76, 6.11)[ab]
LYM (×10^9/L)	1.74 (1.16, 2.53)	1.75 (0.98, 2.99)	1.81 (1.23, 2.81)[ab]	1.80 (1.34, 2.31)	1.82 (1.47, 2.51)	1.76 (1.49, 2.36)[a]
hsCRP (mg/dL)	9.41 (6.33, 20.33)	12.33 (7.63, 30.22)[a]	13.17 (8.06, 41.40)[ab]	10.99 (7.21, 22.88)	11.94 (7.19, 31.66)[a]	11.93 (7.69, 27.61)[a]
HbA1c (%)	6.93 (5.62, 8.11)	7.03 (5.96, 8.65)[a]	6.94 (6.13, 8.20)	6.80 (5.16, 8.56)	6.99 (5.84, 8.16)[a]	7.05 (5.33, 8.25)

Notes: Non-normally distributed data were expressed as median (minimum, maximum), and the Kruskal–Wallis test was used for multi-group comparisons. Categorical variables were compared using the Fisher's exact test. $p < 0.05$ was considered statistically significant, where a denoted $p < 0.05$ compared with the Mild stenosis group, and b denoted $p < 0.05$ compared with the Moderate stenosis group.

Abbreviations: BMI, body mass index; PLT, platelet count; WBC, white blood cell count; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; NEUT, neutrophils; LYM, lymphocytes; hsCRP, high-sensitivity C-reactive protein; HbA1c, glycated hemoglobin.

Table 4 Comparisons of SII and hsCRP/HDL-C Among Patients with Different Degrees of CAS

		SII	hsCRP/HDL-C (× 10^{-2})
Training set	Mild stenosis group (n = 214)	415.0 (328.2, 536.0)	2.27 (1.36, 6.55)
	Moderate stenosis group (n = 196)	456.7 (405.8, 658.4)	2.95 (1.38, 10.10)
	Severe stenosis group (n = 140)	485.5 (370.3, 737.2)	3.33 (1.84, 11.64)
	*p*a	0.001	0.001
	*p*b	0.001	0.001
Validation set	Mild stenosis group (n = 85)	382.9 (207.6, 602.1)	2.60 (1.39, 5.06)
	Moderate stenosis group (n = 82)	430.0 (281.0, 482.0)	2.85 (1.74, 9.29)
	Severe stenosis group (n = 69)	552.3 (399.9, 753.7)	3.36 (2.15, 10.03)
	*p*a	0.001	0.001
	*p*b	0.001	0.002

Notes: Non-normally distributed data were reported as median (minimum, maximum), and the Kruskal–Wallis test was employed for multi-group comparisons. *p*a, compared with the Mild stenosis group; *p*b, compared with the Moderate stenosis group.

Abbreviations: SII, systemic immune inflammation index; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

HDL-C and GS (r = 0.4524, $p < 0.01$). In the validation set, both SII (r = 0.6404, $p< 0.01$) and hsCRP/HDL-C (r = 0.3534, $p < 0.01$) showed positive correlations with GS (Table 5). Overall, the severity of CAS progressively increased in older patients with CHD as SII and hsCRP/HDL-C levels elevated.

Table 5 Correlation Analysis of SII and hsCRP/HDL-C with GS in Older Patients with CHD

	GS			
	Training Set		Validation Set	
	r	*p*	*r*	*p*
SII	0.6874	< 0.01	0.6404	< 0.01
hsCRP/HDL-C	0.4524	< 0.01	0.3534	< 0.01

Note:. $p < 0.05$ was considered statistically significant.
Abbreviations: GS, Gensini score; SII, systemic immune inflammation index; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

SII and hsCRP/HDL-C Were IRFs for Moderate and Severe CAS in Older Patients with CHD

CAS severity (mild stenosis group = 0, moderate and severe stenosis group = 1) was used as the dependent variable, and potential influencing factors for moderate-to-severe CAS in older patients with CHD (age, sex, BMI, diabetes, hypertension, smoking history, drinking history, PLT, WBC, TC, TG, LDL-C, HDL-C, Cr, NEUT, LYM, hsCRP, HbA1c, SII, hsCRP/HDL-C) were first subjected to the univariate logistic regression analysis. The results showed that age, BMI, hypertension, PLT, WBC, HDL-C, Cr, NEU, hsCRP, HbA1c, SII and hsCRP/HDL-C were potential risk factors for moderate-to-severe CAS in elderly CHD patients. The VIF was further used to evaluate multicollinearity, and variables with a VIF ≥ 5 were excluded to ensure model stability.

Furthermore, the variables with $p < 0.05$ and VIF < 5 in the univariate analysis were then included as independent variables for the multivariate logistic regression analysis. After adjusting for NEUT ($p = 0.001$, OR = 4.563) in the training set, elevated SII ($p = 0.001$, OR = 1.055) and hsCRP/HDL-C ($p = 0.001$, OR = 2.785) were IRFs for the development of moderate and severe CAS in older patients with CHD (Table 6).

Further, increased SII ($p = 0.001$, OR = 1.017) and hsCRP/HDL-C ($p = 0.043$, OR = 3.034) in the validation set were identified as IRFs for moderate-to-severe CAS in older patients with CHD. Furthermore, interaction terms were constructed for a stratified regression analysis on the training set ($R^2 = 0.387$) and the validation set ($R^2 = 0.367$). The Chow test was adopted to compare the regression coefficients of common variables in these two sets, including BMI, PLT, Cr, NEU, HbA1c, SII, and hsCRP/HDL-C. All interaction terms showed $p > 0.05$, indicating good model consistency and absence of substantial multicollinearity (Table 6).

ROC Curve Analysis of Predictive Value of SII and hsCRP/HDL-C for CAS Severity in Older Patients with CHD

The ROC curve analysis was conducted to evaluate the predictive value of SII and hsCRP/HDL-C for CAS severity. In the training set, the AUC of SII for predicting CAS severity in older patients with CHD was 0.865 (444.02 cut-off value, 83.33% sensitivity, 92.99% specificity), that of hsCRP/HDL-C was 0.766 (2.31 cut-off value, 88.99% sensitivity, 52.80% specificity) (Figure 1A and B). In the validation set, the AUC of SII for predicting CAS severity was 0.846 (cut-off value = 450.31, sensitivity = 64.24%, specificity = 90.59%), that of hsCRP/HDL-C was 0.711 (cut-off value = 2.71, sensitivity = 73.51%, specificity = 63.53%) (Figure 1D and E). The findings suggested that both SII and hsCRP/HDL-C demonstrated certain predictive value for the development of severe stenosis or occlusion in older patients with CHD.

To further improve predictive efficacy, a diagnostic model based on SII combined with hsCRP/HDL-C was established. In the training set, the combined model yielded an AUC of 0.913 at a cut-off value of 0.56, with a sensitivity of 90.77%, and a specificity of 87.38% (Figure 1C). In the validation set, the AUC was 0.869 at the same cut-off value of 0.56, with a sensitivity of 82.78%, and a specificity of 76.47% (Figure 1F). The combined model yielded notably higher diagnostic value than either marker alone ($p < 0.05$) (Table 7), suggesting superior predictive performance of the combined ROC model. Additionally, no statistically significant difference was observed in the AUC

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Table 6 Logistic Regression Analysis of Factors Influencing the Development of Moderate-to-Severe CAS in Ageing CHD Patients

Influencing Factors	Training Set									Validation Set									Chow Test
	Univariate Logistic Regression Analysis			VIF	R^2	Multivariate Logistic Regression Analysis				Univariate Logistic Regression Analysis			VIF	R^2	Multivariate Logistic Regression Analysis				*p*
	p	OR	95% CI			*β*	*p*	OR	95% CI	*p*	OR	95% CI			*β*	*p*	OR	95% CI	
Age (years)	0.005	1.072	1.021–1.126	1.149	0.387	−0.012	0.787	0.988	0.907–1.077	0.329	0.959	0.881–1.043	–	0.367	–	–	–	–	–
Sex (Male/Female, cases)	0.815	0.960	0.680–1.355	–		–	–	–	–	0.995	1.002	0.588–1.706	–		–	–	–	–	–
BMI (kg/m^2)	0.000	1.588	1.348–1.871	4.469		0.123	0.740	1.131	0.547–2.338	0.049	1.284	1.001–1.647	1.081		0.131	0.332	1.140	0.875–1.486	0.871
Diabetes (n, %)	0.640	1.085	0.770–1.529	–		–	–	–	–	0.944	1.019	0.598–1.737	–		–	–	–	–	–
Hypertension (n, %)	0.002	1.741	1.231–2.460	1.025		0.319	0.213	1.376	0.833–2.272	0.244	0.722	0.417–1.250	–		–	–	–	–	–
Smoking history (n, %)	0.961	1.008	0.716–1.421	–		–	–	–	–	0.657	0.885	0.518–1.514	–		–	–	–	–	–
Drinking history (n, %)	0.551	1.111	0.786–1.571	–		–	–	–	–	0.840	1.057	0.618–1.808	–		–	–	–	–	–
PLT (×10^9/L)	0.001	1.036	1.022–1.050	3.653		−0.011	0.702	0.989	0.936–1.045	0.001	1.051	1.035–1.067	2.795		0.022	0.051	1.022	1.000–1.045	0.133
WBC (×10^9/L)	0.026	1.413	1.042–1.916	1.309		−0.232	0.391	0.793	0.466–1.348	0.174	1.305	0.889–1.916	–		–	–	–	–	–
TC (mmol/L)	0.687	0.889	0.501–1.576	–		–	–	–	–	0.971	0.984	0.408–2.371	–		–	–	–	–	–
TG (mmol/L)	0.060	1.733	0.977–3.076	–		–	–	–	–	0.063	1.132	1.026–1.216	–		–	–	–	–	–
LDL-C (mmol/L)	0.058	2.254	0.967–3.516	-		-	-	-	-	0.086	1.984	0.907–4.337	-		-	-	-	-	-
HDL-C (mmol/L)	0.059	0.411	0.163–1.036	-		-	-	-	-	0.003	0.142	0.039–0.519	2.784		3.159	0.092	23.536	0.595–931.619	-
Cr (μmol/L)	0.011	1.029	1.006–1.052	1.764		−0.025	0.300	0.975	0.930–1.022	0.001	1.145	1.071–1.224	1.440		0.004	0.649	0.517	0.694–1.440	0.297
NEUT (×10^9/L)	0.001	5.703	3.808–8.541	2.110		1.518	0.001	4.563	1.898–10.967	0.001	3.380	2.011–5.680	2.597		0.018	0.277	0.782	0.385–2.597	0.063
LYM (×10^9/L)	0.200	1.466	0.817–2.633	-		-	-	-	-	0.059	0.292	0.081–1.048	-			-	-	-	-
hsCRP (mg/dL)	0.001	1.516	1.388–1.656	5.024		-	-	-	-	0.001	1.139	1.056–1.230	2.887		−0.089	0.511	0.915	0.701–1.193	-
HbA1c (%)	0.002	1.915	1.279–2.868	1.970		0.050	0.909	1.051	0.446–2.478	0.041	1.510	1.017–2.242	1.051		0.382	0.138	1.466	0.884–2.429	0.652
SII (×10^9/L)	0.001	1.028	1.021–1.035	1.387		0.054	0.001	1.055	1.043–1.068	0.001	1.020	1.014–1.026	4.441		0.017	0.001	1.017	1.008–1.026	0.370
hsCRP/HDL-C (×10^{-2})	0.001	3.098	2.373–4.044	4.908		1.024	0.001	2.785	2.063–3.760	0.001	3.038	1.939–4.759	3.878		1.110	0.043	3.034	1.034–8.902	0.121

Abbreviations: BMI, body mass index; PLT, platelet count; WBC, white blood cell count; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; NEUT, neutrophils; LYM, lymphocytes; hsCRP, high-sensitivity C-reactive protein; HbA1c, glycated hemoglobin; SII, systemic immune inflammation index.

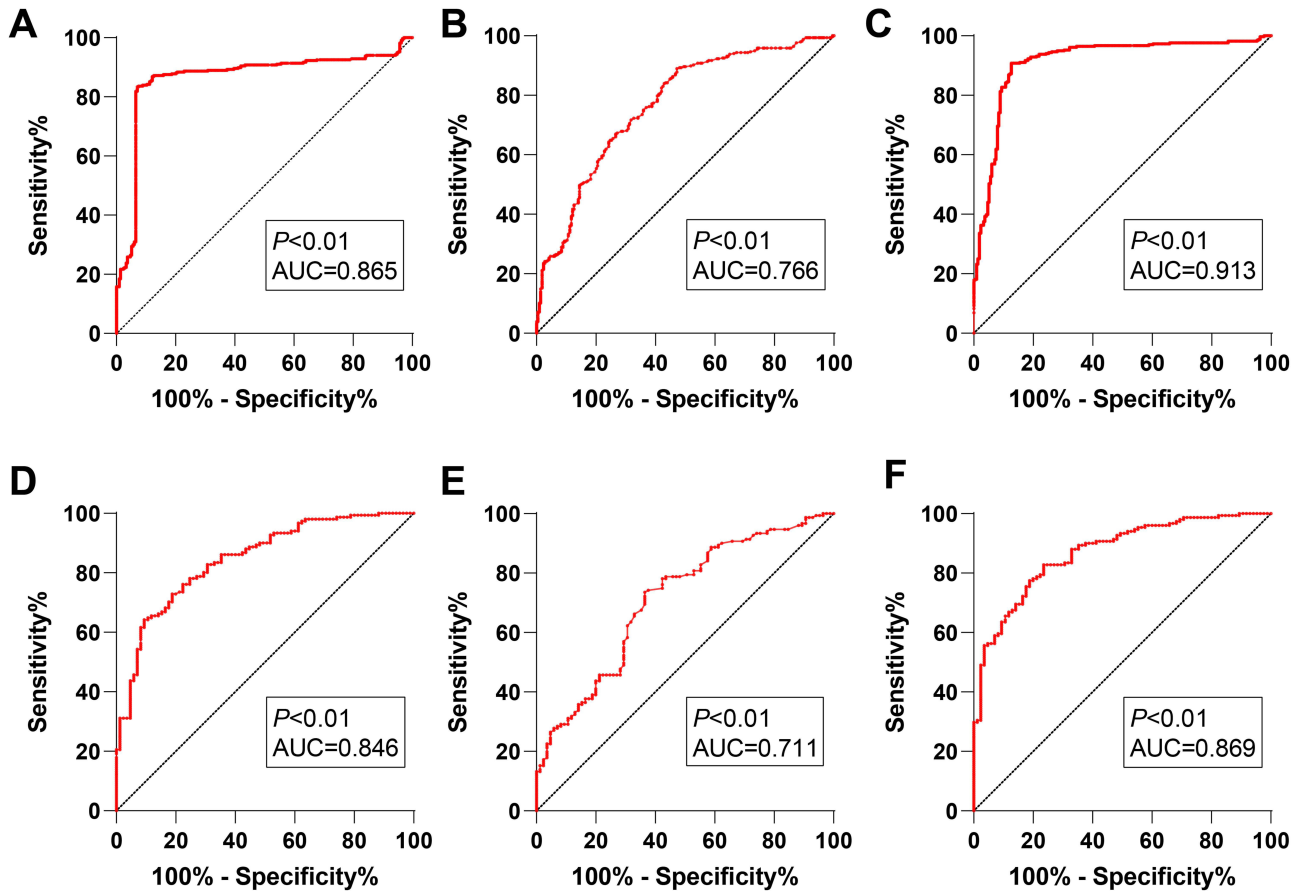

Figure 1 ROC curve analysis of SII, hsCRP/HDL-C, and their combination for predicting CAS severity in older patients with CHD. The ROC curve analysis was used to evaluate the predictive value of SII (**A** and **D**), hsCRP/HDL-C (**B** and **E**), and their combination (**C** and **F**) for CAS severity in older patients with CHD in the training set and the validation set.

of the combined detection of SII and hsCRP/HDL-C between the training set (AUC = 0.913) and the validation set (AUC = 0.869) ($p = 0.109$).

ROC Curve Analysis of the Predictive Value of SII and hsCRP/HDL-C Values for CAS Severity in Older Patients with CHD Complicated by Underlying Chronic Diseases

Subgroup ROC analyses of SII and hsCRP/HDL-C in the training and validation sets were performed based on hypertension and diabetes status (Figure 2). The DeLong test was utilized to compare the AUC values among different subgroups. In the validation set, the AUC of SII reached 0.903 in the hypertensive group, which decreased to 0.759 in the non-hypertensive group, showing a significant intergroup difference ($p = 0.011$) (Table 8). These findings indicated that the discriminating performance of SII was weakened in inflammatory conditions in the absence of hypertension, and hypertension could affect its discriminating ability. Thus, the cut-off value should be adjusted according to hypertensive status in clinical practice.

Notably, diabetes exerted no significant stratified effect on the diagnostic performance of the two indicators ($p > 0.05$) (Table 8), which was not completely consistent with general clinical expectations. Diabetes is commonly recognized as a strong pro-inflammatory state that may amplify the signals of inflammatory biomarkers. However, our data suggested that diabetes might alter the baseline inflammatory levels in both cases and controls, thereby narrowing the discriminatory capacity of the model.

Among elderly CHD patients with or without hypertension and diabetes, no notable differences were found in the AUC values of hsCRP/HDL-C in the training and validation sets ($p > 0.05$). Although the results were comparable

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Table 7 DeLong Test-Based Comparisons of AUC Values

Item	Training Set				Validation Set			
	AUC	95% CI	Sensitivity	Specificity	AUC	95% CI	Sensitivity	Specificity
SII	0.865	0.834–0.892	83.33%	92.99%	0.846	0.794–0.890	64.24%	90.59%
hsCRP/HDL-C	0.766	0.730–0.802	88.99%	52.80%	0.711	0.649–0.768	73.51%	63.53%
Combination	0.913	0.887–0.935	90.77%	87.38%	0.869	0.820–0.910	82.78%	76.47%
SII~Combination	$p < 0.001$				$p = 0.047$			
hsCRP/HDL-C~Combination	$p < 0.001$				$p < 0.001$			

Note: Comparisons of multiple AUCs were performed using the Delong test in MEDCALC software.
Abbreviations: AUC, area under curve; SII, systemic immune inflammation index; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

between the two sets, the predictive values remained at a moderate level, suggesting acceptable subgroup stability but limited clinical applicability. For SII, favorable internal consistency was observed in the hypertensive subgroup (training set AUC: 0.839 vs. validation set AUC: 0.903). By contrast, a notable decline was seen in the non-hypertensive group (0.892 vs. 0.759, $p = 0.017$), indicating poor stability of SII in this subgroup. For the screening of non-hypertensive populations, insufficient sensitivity (declining from 86.09% to 60.00%) may increase the risk of missed diagnosis (Table 8).

Discussion

Monocytes/HDL-C ratio can serve as an independent predictor for CHD and long-term adverse cardiovascular events in elderly patients, and it is positively related to the degree of coronary artery lesions.[28] Moreover, an observational study has proposed that SII is an independent predictor for functionally significant CAS in patients with chronic coronary syndrome.[29] This study further demonstrates that both SII and hsCRP/HDL-C are independently associated with CAS severity (assessed by the GS) in older patients with CHD. Their combination exhibits favorable predictive performance for CAS severity in older patients with CHD. These findings, including group differences, correlation with severity, independent predictive value, and strong predictive performance, were consistently confirmed in both training and validation sets, which supported the reliability of our results.

SII, which integrates NEUT, LYM, and PLT, provides more comprehensive information on systemic inflammation than many other biomarkers.[16,30,31] SII is closely associated with cardiovascular-cause and all-cause mortality in a long-term (20-year) follow-up cohort investigation on 42,875 US adults.[32] A strong association exists between SII levels and coronary plaque burden severity as observed by CAG, particularly in patients suffering from CHD.[19] Prior studies have also documented an independent association between SII and cardiovascular events after percutaneous coronary intervention[30] and a similar link between SII and GS in patients with non-alcoholic fatty liver disease and CHD comorbidity.[18] Notably, a study conducted by H Kitano et al has revealed that SII is positively interrelated with CAS severity and has an excellent predictive value in determining the occurrence of CHD and severe CAS.[16] Evidence also indicates that elevated SII levels and elevated plaque thickness are associated with atherosclerotic plaque vulnerability in patients with CAS and may signal aggravated CAS.[33] In our investigation, SII was elevated in CHD patients with moderate-to-severe CAS. Our study data consistently revealed a positive correlation between SII and CAS severity (assessed by GS) in older patients with CHD. As SII levels increased, CAS severity progressively worsened in older patients with CHD. Intriguingly, our study emphasized that, based on the logistics regression analyses, SII served as an IRF for moderate-to-severe CAS in older patients with CHD. This may be similar to the finding that SII is a key risk factor for coronary artery lesions at admission in either unadjusted or confounder-adjusted models.[34] SII remained stable in the hypertensive population, but its efficacy decreased evidently in the non-hypertensive population. Although hypertension may limit the predictive performance of SII, diabetes did not induce such a stratified effect, which is slightly different from the clinical expectation. The reason may be explained by the fact that diabetes affects baseline inflammation in both cases and controls, narrowing its discriminatory capacity.

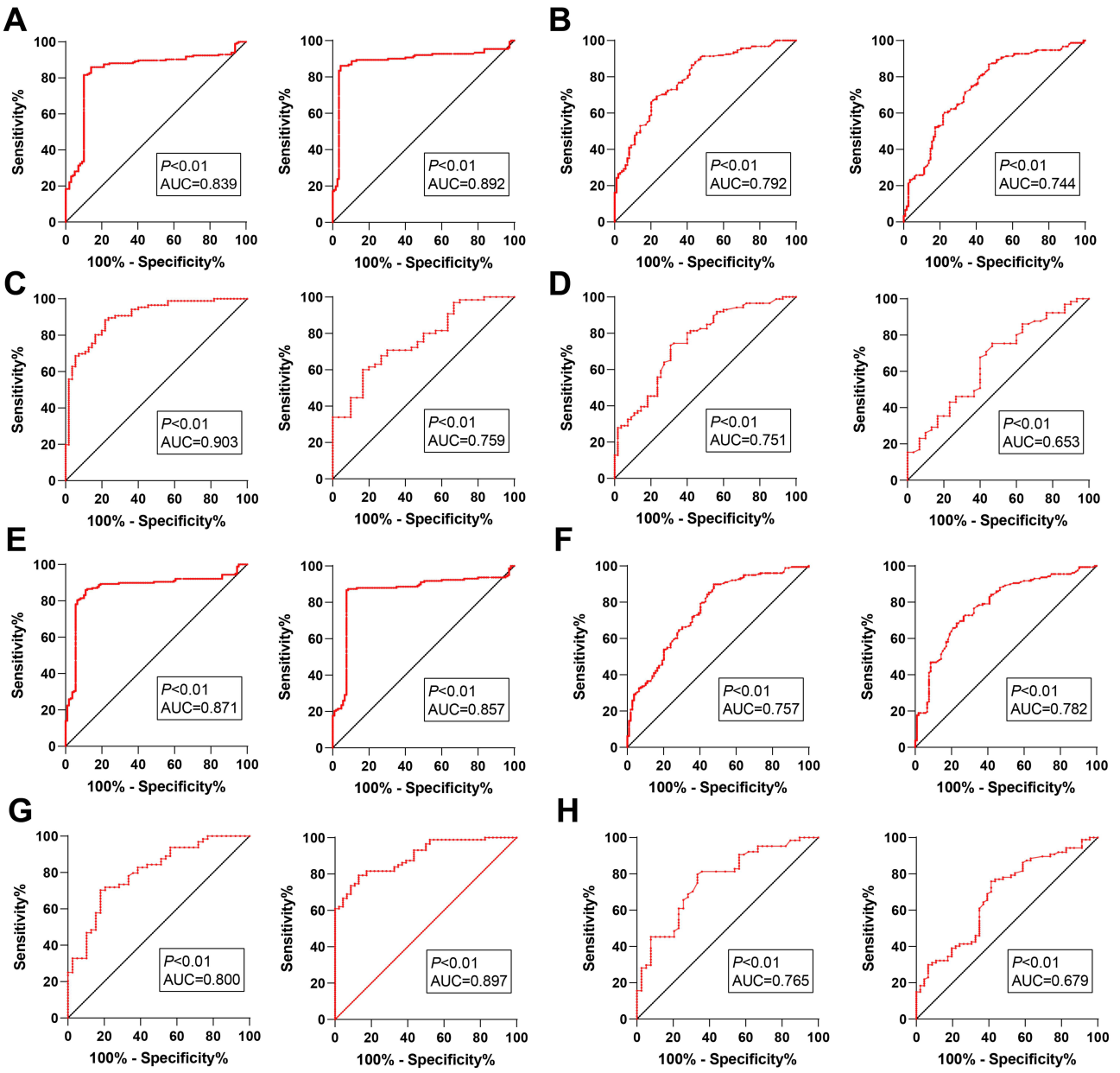

Figure 2 ROC curve analysis of SII and hsCRP/HDL-C values for predicting CAS severity in older patients with CHD complicated by underlying chronic diseases. ROC analysis of SII (**A** and **C**) and hsCRP/HDL-C (**B** and **D**) for predicting CAS severity in CHD population complicated with hypertension in the training and validation sets; ROC analysis of SII (**E** and **G**) and hsCRP/HDL-C (**F** and **H**) for predicting CAS severity in CHD population complicated with diabetes in the training and validation sets.

Owing to the limited diagnostic performance of a single marker, previous studies have paid attention to the combined effects of lipid and inflammatory indicators. hsCRP is a validated inflammatory marker associated with cardiovascular events.[35–37] Unlike most lipids, HDL-C can facilitate reverse cholesterol transport and regulate inflammation, exhibiting an adverse correlation with cardiovascular event risk.[38] hsCRP/HDL-C also provides enhanced value for predicting cardiovascular risk.[39] Observably, our study found that hsCRP/HDL-C was elevated in older patients with CHD with moderate-to-severe stenosis. The epidemiological meta-analysis has shown that hsCRP levels > 3.0 mg/dL increase CAD risk 1.6-fold and correlate with greater lesion count and CHD severity,[40] while each 1 mg/dL increment in HDL-C reduces cardiovascular risk by 2–3%.[41,42] Furthermore, high-risk hsCRP is independently linked with CAS progression.[43] Bilhorn et al have suggested that elevated hsCRP (> 3 mg/L) negates the protective association of HDL-C with CHD.[44] Moreover, hsCRP/HDL-C has been reported to be positively interrelated with GS and is an

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Table 8 DeLong Test-Based Comparisons of AUC Values Between Different Subgroups

		Training Set				Validation Set				*p*
		AUC	**Cutoff value**	**Sensitivity**	**Specificity**	**AUC**	**Cutoff value**	**Sensitivity**	**Specificity**	
SII	Hypertension	0.839	431.13	85.95	85.86	0.903	406.01	88.37	78.18	0.086
	Non-hypertension	0.892	443.64	86.09	95.65	0.759	450.27	60.00	83.33	0.017
	p	0.137				0.011				
	Diabetes	0.871	431.13	85.96	88.99	0.800	454.78	70.31	82.05	0.677
	Non-diabetes	0.857	443.64	56.71	92.38	0.897	406.01	79.31	86.96	0.634
	p	0.246				0.186				
hsCRP/HDL-C	Hypertension	0.792	2.74	69.19	76.77	0.751	2.71	73.26	69.09	0.415
	Non-hypertension	0.744	2.31	86.75	53.04	0.653	2.63	75.38	53.33	0.182
	p	0.654				0.322				
	Diabetes	0.757	2.30	89.89	52.29	0.765	2.71	79.69	66.67	0.887
	Non-diabetes	0.782	2.76	68.35	77.14	0.679	2.66	75.86	58.70	0.071
	p	0.545				0.210				

Note: Comparisons of multiple AUCs were performed using the Delong test in MEDCALC software.
Abbreviations: AUC, area under curve; SII, systemic immune inflammation index; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

independent predictor of CAD.[45] A recent study has proposed hsCRP/HDL-C as a risk factor for cardiometabolic multimorbidity in the middle-aged and elderly population.[46] Consistent with this finding, our study also identified hsCRP/HDL-C elevation to be an IRF for moderate-to-severe CAS in older patients with CHD. While each marker alone demonstrated a good predictive ability (AUCs of 0.865 and 0.846 for SII and 0.766 and 0.711 for hsCRP/HDL-C), their combination yielded significantly higher AUCs of 0.913 and 0.869 in the training and validation sets, respectively. This indicates a superior predictive performance of this combination for CAS severity in older patients with CHD.

However, several limitations of this study should be acknowledged. First, the single-center retrospective design may reduce the generalizability of the results. Given the retrospective design, there is a lack of complete data on medication types, dosages, treatment courses, and compliance. Second, not all potential confounders were fully included in this research. In this study, patients aged over 80 years were excluded because the super-aged population usually has multiple comorbidities and medications that may interfere with inflammatory and immune biomarkers.[47] In addition, hypertension influences the diagnostic performance and subgroup stability of SII. Owing to the effects of age, underlying diseases, and treatment history; thus, a unified cut-off value is not suitable for populations with different pathological states. The detection results should be interpreted based on individualized patient characteristics, and if necessary, combining with other clinical indicators and imaging examinations. It is worth noting that acute infection and other stress states, such as chronic obstructive pulmonary disease, can trigger systemic inflammatory responses and elevate neutrophils, hsCRP, and SII levels, causing bias in the evaluation of CAS.[48–51] Metabolic disorders such as insulin resistance and obesity can reduce HDL-C levels, further interfering with inflammatory biomarkers.[52,53] Although patients with obvious inflammatory confounders were excluded, and chronic comorbidities were adjusted during the analysis, whether other chronic inflammation and metabolic disorders (chronic obstructive pulmonary disease, chronic kidney disease, obesity) may still affect these two indicators is undefined. Also, the absence of stratified correction for drug-related confounders might cause bias. Furthermore, smoking status was only defined in this study as a binary variable without quantitative data on smoking intensity and duration, and detailed medications, such as statins, were not finely controlled,[54] restricting accurate assessment as well.

Conclusion

Taken together, our study highlighted that elevated SII and hsCRP/HDL-C were IRFs for moderate-to-severe CAS and had predictive value for assessing CAS severity in older patients with CHD. A pivotal finding of our study was the

superior predictive performance of their combination over either marker alone. Furthermore, the statistical rigor of our multivariate regression analysis is underscored by the absence of significant multicollinearity. Despite certain limitations in this study, our findings lay a foundation for in-depth research on risk stratification tools. The combined detection of SII and hsCRP/HDL-C is expected to become an effective, auxiliary risk stratification method for optimizing the clinical management of older patients with CHD. In future studies, we will adopt multi-center, prospective designs, expand the sample size, and combine individualized characteristics to better interpret test results. Additionally, we would like to conduct subgroup analyses based on different diseases to clarify the effect size of different interfering factors and dynamically monitor the association between these indicators and the progression of CAS in the following studies.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study complied with the *Declaration of Helsinki* and was approved by the Ethics Committee of Yongchuan Hospital of Chongqing Medical University (No. 2025EC0249). The requirement for informed consent was waived due to the retrospective nature of the study and the use of de-identified data.

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 report there are no competing interests to declare.

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