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ORIGINAL RESEARCH

Predictive Potential of CRTP5 and SII for Coronary Artery Severity and Myocardial Fibrosis in Patients with NSTE-ACS: An Exploratory Biomarker Study

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Purpose: Findings from this research aim to enhance clinical assessments of coronary artery disease severity and myocardial fibrosis (MF).

Methods: A total of 523 eligible non-ST-segment elevation acute coronary syndromes (NSTE-ACS) patients were included. Clinical data were collected and analyzed. Multifactorial logistic regression analysis was applied to identify factors influencing coronary artery lesions in patients with NSTE-ACS. Diagnostic accuracy for Complement C1q tumor necrosis factor-related protein 5 (CTRP5) and systemic immune-inflammation index (SII) in assessing coronary artery lesions and MF was analyzed via receiver operating characteristic (ROC) curve analysis.

Results: The levels of CTRP5 and SII were significantly different between the unstable angina pectoris (UAP) and ST-segment elevation myocardial infarction (NSTEMI) groups (all P<0.05). Significant differences in CTRP5, SII, PCI, and PCIII were noted across the Single-, Two-, and Three-vessel lesion groups (all P<0.05). Multifactorial logistic regression analysis revealed that CTRP5 (odds ratio [OR], 1.621; 95% confidence interval [CI], 1.103–1.984; P<0.001) and SII (OR, 1.473; 95% CI, 1.178–1.840; P<0.001) were independent risk factors for three-vessel lesions. The ROC curve analysis demonstrated that CTRP5 and SII effectively predicted three-vessel lesions, with area under curve (AUC) values of 0.823 [cut-off value13.99; 95% confidence interval (CI), 0.779–0.866, P<0.001] and 0.796 [cut-off value, 837.5; 95% CI, 0.747–0.845, P<0.001], respectively. The ROC curve analysis evaluated the ability of CTRP5 and SII to predict MF; AUC values were 0.809 (cut-off value, 11.95; 95% CI, 0.724–0.895, P<0.001) and 0.713 (cut-off value, 624.2; 95% CI, 0.611–0.815, P<0.001), respectively.

Conclusion: CTRP5 and SII demonstrate strong potential as early diagnostic markers for assessing the severity of coronary artery disease and MF in patients with NSTE-ACS.

Keywords: complement C1q tumor necrosis factor-related protein 5, systemic immune-inflammation index, myocardial fibrosis, non-ST-segment elevation acute coronary syndromes

Introduction

Acute Coronary Syndrome (ACS), the most severe form of coronary heart disease, is an essential contributor to cardiovascular mortality and poses a significant threat to public health. While the incidence of ST-segment elevation myocardial infarction (STEMI) in China has declined in recent years, the prevalence of non-ST-segment elevation acute coronary syndromes (NSTE-ACS) has risen significantly, now accounting for over 70% of ACS diagnoses.[1] Patients with ACS, particularly those with non-STEMI, frequently present with diffuse and multifocal coronary artery lesions, making

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revascularization procedures more complex and increasing the likelihood of early cardiac insufficiency.[2,3] Coronary artery stenosis or occlusion leads to ischemia and necrosis of cardiomyocytes in affected regions, triggering an inflammatory response and reparative fibrosis. Myocardial fibrosis (MF), a critical pathological process, underpins adverse cardiac remodeling and subsequent cardiac dysfunction.[4]

Atherosclerosis, an inflammatory condition driven by lipid deposition, involves inflammation and immunity at every stage, from development to complications.[5,6] Recently, the systemic immune-inflammation index (SII), a novel composite marker, has gained attention due to its ability to balance local immunity and systemic inflammatory responses.[7] SII is associated with the prognosis of tumors, coronary heart disease, and autoimmune diseases such as leukemia.[7] The SII is valued for its simplicity, cost-effectiveness, and reliability. Complement C1q tumor necrosis factor-related protein (CTRP), a glycoprotein secreted by adipocytes and structurally related to lipocalins, has emerged as a molecule of interest.[8] Evidence suggests that CTRPs play a regulatory role in inflammatory and metabolic disorders.[9,10] While members of the CTRP exhibit dual rules in promoting or inhibiting atherosclerosis and MF,[11] limited research exists on CTRP5's association with coronary artery disease severity and MF. This study focused on the correlation between CTRP5, SII, and the extent of coronary artery disease and MF in patients with NSTE-ACS. Findings from this research aim to enhance clinical assessments of coronary artery disease severity and MF.

Materials and Methods

Study Design and Patients

This retrospective cohort study received approval from our hospital's ethics committee. A total of 350 patients admitted to the Department of Cardiovascular Medicine of the People's Hospital of Henan University of Traditional Chinese Medicine and the Seventh People's Hospital of Zhengzhou between January 2022 and January 2024, with confirmed NSTE-ACS diagnoses via coronary angiography were selected.

Inclusion criteria: 1. Patients meeting the European Society of Cardiology (ESC)'s diagnostic criteria for NSTE-ACS;[12] 2. First-time diagnosis of NSTE-ACS; 3. Those aged between 18 and 75 years; 4. Coronary angiography revealing ≥50% stenosis in at least one major coronary artery; 5. Voluntary participation with signed informed consent. Exclusion criteria: 1. History of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); 2. Severe cardiac insufficiency [left ventricular ejection fraction (LVEF) <35%]; 3. Significant hepatic or renal dysfunction (ghrelin levels exceeding three times the upper normal limit or glomerular filtration rate <30 mL/min/1.73m2); 4. Presence of acute or chronic infectious diseases; 5. Presence of thyroid disorders, hematologic diseases, malignancies, or connective tissue disorders; 6. Known allergy to contrast agents; 7. Mental health disorders impairing patient compliance.

The 350 patients with NSTE-ACS were categorized into subgroups based on clinical and diagnostic criteria. These included:

Clinical Presentation

Patients were classified into the unstable angina pectoris (UAP) group (n=207) or the NSTEMI group (n=143).

Coronary Lesion Severity

Based on coronary angiography findings, patients were assigned to the Single-vessel lesion group (n=95), Two-vessel lesion group (n=125), or Three-vessel lesion group (n=130).

Synergy Between PCI with TAXUS and Cardiac Surgery II (SYNTAX II Score)

Patients were categorized into Low-risk (0–22 points, n=146), Intermediate-risk (23–32 points, n=138), or High-risk groups (≥33 points, n=66).

MF Assessment

Based on the cardiovascular magnetic resonance imaging (CMR) with late gadolinium enhancement (LGE) performed one month after enrollment, patients were stratified into the LGE-positive (n=57) or LGE-negative (n=43) groups.

Procollagen Levels

Patients were grouped by median procollagenI levels (PCI: 136.5 μg/L) into low-PCI (≤136.5 μg/L, n=179) and high-PCI groups (>136.5 μg/L, n=171). Similarly, based on the median procollagenIII (PCIII: 92.4 μg/L), they were categorized as low-PCIII (≤ 92.4 μg/L, n=180) or high-PCIII (>92.4 μg/L, n=170) groups.

Moreover, a control group of 350 patients with non-obstructive coronary (coronary stenosis <50%) lesions identified through coronary angiography during the same period was included. Controls were matched with patients with NSTE-ACS based on age (± 2 years) and sex.

Data Collection

Baseline data for participants included demographic and clinical characteristics such as sex, age, body mass index (BMI), smoking status, diabetes, and hypertension.

Biochemical Assessments

Blood samples were collected from the median cubital vein upon admission. High-sensitivity cardiac troponin I (hs-cTnI) levels was measured using latex immunoturbidimetric assays. A fully automated blood cell analyzer (DxH 500, Beckman Coulter, Inc., California, USA) was employed to determine neutrophil count (NC), lymphocyte count (LC), and platelet (PLT) counts; N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were quantified via enzyme-linked immunosorbent assay (ELISA).

On the second morning after admission, after 12 h of fasting, blood samples were drawn to measure total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) using latex immunoturbidimetric methods. Fasting blood glucose (FBG) levels were assessed with the glucose oxidase method; glycated hemoglobin A1c (HbA1c) was determined using high-performance liquid chromatography. Uric acid (UA) was measured via the uricase method, serum creatinine (Scr) via sarcosine oxidase.

On the next day after hospitalization and the early morning of the seventh day after hospitalization, 5 mL of blood was drawn from the median cubital vein of each patient on an empty stomach. The blood was allowed to stand for 30 min at room temperature. Subsequently, it was centrifuged at 3000 r/min for 10 min at 40°C (radius, 10 cm) (Thermo Heraeus Fresco 21, Thermo Fisher Scientific, Massachusetts, USA). The resulting supernatant was collected as serum and stored at –80°C for further analysis. To maintain the stability of CTRP5 in serum samples, repeated freezing and thawing were avoided. The concentrations of CTRP5, PCI, and PCIII in serum were measured on a fully automated enzyme labeling instrument (Model 680, Bio-Rad, California, USA) using the corresponding ELISA kits (CTRP5: Jiangsu Boshen Biotechnology Co., Ltd., Nanjing, China; PCI and PCIII: Elabscience Biotechnology Co., Ltd., Wuhan, China) according to the manufacturer's instructions. The intra-group variability was <10% for CTRP5 and <15% for PCI and PCIII, whereas the inter-group variability was <15% for all three proteins.

Coronary Angiography

All patients underwent coronary angiography, performed by a qualified interventional cardiologist through the transradial artery. The location of lesions, number of affected branches, degree of stenosis, and lesion length were recorded. Stenosis >50% of the luminal diameter was considered significant. Stenosis in the obtuse marginal branch was included in the circumflex artery count, while stenosis in diagonal branches was counted under the anterior descending artery. The total number of affected branches was calculated for each patient. Isolated left main coronary artery stenosis was classified under the two-vessel lesion group, while left main coronary artery stenosis combined with either left or right coronary arteries was classified under the three-vessel lesion group. The SYNTAX II scores were calculated using the online tool at[13] https://www.syntaxscore.org.

Doppler Echocardiography

All participants underwent echocardiographic assessment (Philips EPIQ 7G, Philips Medical Systems Nederland B.V., Amsterdam, the Netherlands) in the left lateral decubitus position during calm breathing. Measurements of three consecutive cardiac cycles in the parasternal long-axis view were averaged. The measured parameters include left atrial dimension (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular posterior wall thickness at diastole (LVPWd), interventricular septal thickness at diastole (IVSd), and LVEF. Doppler echocardiograms were performed by ultrasonographers with over 5 years of experience.

Cardiovascular magnetic resonance imaging (CMR; MAGNETOM Spectra 3.0T MR, SIEMENSAGFWB, Munich, Germany) was performed after one postoperative month with cardiac gating and end-expiratory breath-hold protocols. The imaging included the following sequences:

(1) True fast imaging with steady-state precession (True-FISP) Cine Imaging: True-FISP sequences were used for left ventricular (LV) short-axis cine imaging with a field of view (FOV) of 280 mm × 280 mm, a matrix of 256×192, repetition time (TR) of 6.8 ms, echo time (TE) of 1.4 ms, flip angle of 45°, and a layer thickness 6 mm with no interlayer spacing. Standard two-chamber and four-chamber cine images were captured under identical settings, with slight variations in matrix (256×160), layer thickness (8 mm), and interlayer spacing (2 mm).
(2) Dual-inversion recovery imaging: Short-axis, two-chamber, and four-chamber images were acquired using dual-inversion recovery sequences. Parameters included FOV 280 mm × 280 mm, matrix 256 × 192, TE 80 ms, TR 1400 ms, echo chain length of 24, layer thickness 8 mm, and interlayer spacing of 2 mm.
(3) Myocardial perfusion imaging: For perfusion imaging, a gadopentetic acid (Gd-DTPA) contrast agent (0.05 mmol/kg) was administered via the median cubital vein using a high-pressure syringe at a rate of 4 mL/s, following by a 15 mL saline flush at the same rate. Continuous short-axis scans, covering the LV base to apex, commenced simultaneously with contrast injection. Imaging utilized a fast gradient echo sequence with a matrix of 128 × 128, heart-rate adjusted TR, TE of 1.4 ms, flip angle of 25°, echo chain length of 4, and a layer thickness of 10 mm with no interlayer spacing.
(4) Delayed Enhancement Imaging: Following myocardial perfusion imaging, a second injection of Gd-DTPA contrast (0.1 mmol/kg) was administered at 2 mL/s. After a 10-min delay, a phase-sensitive inversion recovery (PSIR) sequence was performed to evaluate LGE. Images were acquired with left ventricular short-axis views, and standard two-chamber and four-chamber cardiac views, employing a matrix size of 224×192, inversion time of 250 ms, TR adjusted to heart rate, TE of 1.4 ms, one excitation, a flip angle of 25°, slice thickness of 8 mm, and 2-mm slice spacing. Two expert imaging specialists independently evaluated the LGE-CMR images. Myocardial LGE was classified as positive when the signal exceeded six standard deviations above the mean threshold for normal myocardium in a healthy population.

The BMI was calculated as weight (kg)/height (m^2). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication.[14] Diabetes mellitus was defined as FBG level ≥7.0 mmol/L, random glucose ≥11.0 mmol/L, or an abnormal 2 h glucose tolerance test.[15] Smoking history referred to smoking at least one cigarette per day for over 6 months. The SII was calculated as NC (×109/L)/LC (×109/L) × PLT (×109/L).[16]

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) statistical software (version 25.0, International Business Machines Corporation, New York, USA) and GraphPad Prism software (version 6.0, GraphPad Prism software, San Diego, California). Normally distributed continuous variables were expressed as mean ± standard deviation (SD), and group comparisons were conducted using independent samples *t*-tests for two groups or one-way analysis of variance (ANOVA) with SNK-q tests for multiple groups. Non-normally distributed data were expressed as M (P25, P75), with comparisons between two groups performed using the Mann–Whitney *U*-test and the Kruskal–Wallis H-test for multiple groups. Categorical data were expressed as n (%), and comparisons were performed using the $\chi 2$ test. Multifactorial logistic regression analysis was applied to identify factors influencing coronary artery lesions in patients with NSTE-ACS. Diagnostic accuracy for CTRP5 and SII in assessing coronary artery lesions and MF was analyzed via receiver operating characteristic curve (ROC) analysis. Statistical significance was set at $P < 0.05$.

Results

General Data Comparison Between Groups

Substantial differences ($P < 0.05$) were observed between the groups in FBG, NC, hs-cTnI, NT-proBNP, CTRP5, SII, PCI, and PCIII. However, no considerable differences were observed in age, sex, hypertension, diabetes, BMI, TC, TG, LDL-C, HbA1c, UA, Scr, LC, PLT, LAD, LVEDD, LVPWd, IVSd, and LVEF (all $P > 0.05$, Table 1).

Table 1 General Data Comparison Between Groups

Variable	Control Group (n=350)	NSTE-ACS Group (n=350)	P-value
Age (year)	59.34±9.86	60.45±9.22	0.122
Male, n (%)	202 (57.7)	202 (57.7)	1.000
Hypertension, n (%)	197 (56.3)	213 (60.9)	0.220
Diabetes, n (%)	145 (41.4)	169 (47.4)	0.110
BMI (kg/m2)	26.23±2.85	26.31±3.02	0.686
TC (mmol/L)	4.62±1.09	4.73±1.11	0.188
TG (mmol/L)	1.50 (1.10, 2.41)	1.69 (1.10, 2.47)	0.246
LDL-C (mmol/L)	2.59±0.91	2.67±0.81	0.217
FBG (mmol/L)	6.0 (5.3, 5.9)	6.5 (5.7, 7.2)	<0.001
HbA1c (%)	7.1 (6.3, 7.8)	7.2 (6.4, 7.9)	0.289
UA (μmom/L)	325.46±52.45	331.14±54.67	0.161
Scr (umom/L)	69.45±12.41	70.34±13.64	0.367
NC ($\times 10^9$/L)	4.53 (3.64, 6.08)	5.36 (4.44, 7.11)	<0.001
LC ($\times 10^9$/L)	1.62 (1.15, 1.87)	1.67 (1.01, 2.13)	0.267
PLT ($\times 10^9$/L)	251.56±54.45	249.34±51.45	0.579
hs-cTnI (mg/mL)	0.04 (0.03, 0.34)	2.89 (0.04, 5.37)	<0.001
NT-proBNP (ng/L)	87.00 (54.00–127.00)	264.00 (159.00–737.80)	<0.001
LAD (mm)	31.34±1.34	31.50±1.39	0.121
LVEDD (mm)	48.21±2.45	48.53±4.66	0.269
LVPWd (mm)	8.65±0.97	8.74±1.03	0.214
IVSd (mm)	8.91±0.74	8.98±1.09	0.332
LVEF (%)	56.50±6.45	55.65±7.68	0.112
CTRP5 (ng/mL)	8.36±2.57	13.45±4.13	<0.001
SII	478.57 (390.92, 561.40)	668.43 (497.87, 902.42)	<0.001
PCI (ug/L)	112.45±16.45	136.55±21.75	<0.001
PCIII (ug/L)	84.46±18.56	92.45±24.68	<0.001

Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; UA, uric acid; Scr, serum creatinine; NC, neutrophil count; LC, lymphocyte count; PLT, platelet; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic diameter; LVPWd, left ventricular posterior wall thickness at diastole; IVSd, interventricular septal thickness at diastole; LVEF, left ventricular ejection fraction; CTRP5, Complement C1q tumor necrosis factor-related protein 5; SII, systemic immune-inflammation index; PCI, procollagenI; PCIII, procollagenIII.

Comparison of CTRP5, SII, PCI, and PCIII Between UAP and NSTEMI Groups

The levels of CTRP5 and SII were significantly different between the UAP and NSTEMI groups ($P < 0.05$ for both). However, no statistically significant differences were observed between these groups for PCI and PCIII (all $P > 0.05$, Table 2).

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Table 2 Comparison of CTRP5, SII, PCI, and PCIII Between UA and NSTEMI Groups

Variable	UA Group (n=207)	NSTEMI Group (n=143)	P-value
CTRP5 (ng/mL)	10.35±4.32	13.53±5.41	<0.001
SII	558.05 (374.19, 747.73)	773.41 (597.78, 912.76)	<0.001
PCI (ug/L)	134.42±21.34	138.46±27.75	0.128
PCIII (ug/L)	91.34±21.45	95.05±28.98	0.174

Abbreviations: CTRP5, Complement C1q tumor necrosis factor-related protein 5; SII, systemic immune-inflammation index; PCI, procollagenI; PCIII, procollagenIII.

Comparison of CTRP5, SII, PCI, and PCIII Among Single-, Two-, and Three-Vessel Lesion Groups

Significant differences in CTRP5, SII, PCI, and PCIII were noted across the Single-, Two-, and Three-vessel lesion groups (all $P < 0.05$). Pairwise comparisons revealed that the Three-vessel lesion group had higher CTRP5, SII, PCI, and PCIII levels than the Single- and Two-vessel lesion groups (all $P < 0.05$). However, no significant differences were found between the Single- and Two-vessel lesion groups for PCI and PCIII ($P > 0.05$, Table 3).

Comparison of CTRP5, SII, PCI, and PCIII Among Low-, Intermediate-, and High-Risk Groups

Substantial differences were identified in CTRP5, SII, PCI, and PCIII (all $P < 0.05$) across the Low-, Intermediate-, and High-risk groups. Pairwise analysis showed that the High-risk group exhibited higher levels of CTRP5, SII, PCI, and PCIII compared to the Intermediate- and Low-risk groups (all $P < 0.05$). Conversely, no significant differences were observed between the Low- and Intermediate-risk groups for PCI and PCIII (all $P > 0.05$, Table 4).

Comparison of CTRP5 and SII Between Low- and High-PCI Groups

CTRP5 and SII levels were considerably higher in the high-PCI group compared to the low-PCI group (all $P < 0.05$, Table 5).

Comparison of CTRP5 and SII Between Low- and High-PCIII Groups

The high-PCIII group exhibited significantly elevated levels of CTRP5 and SII compared to the low-PCIII group (all $P < 0.05$, Table 6).

Table 3 Comparison of CTRP5, SII, PCI, and PCIII Among Single-, Two-, and Three-Vessel Lesion Groups

Variable	Single–Vessel Lesion Group (n=95)	Two–Vessel Lesion Group (n=125)	Three–Vessel Lesion Group (n=130)	P-value
CTRP5 (ng/mL)	9.78±2.86	13.13±3.92[a]	16.52±3.33[a,b]	<0.001
SII	587.89 (447.53, 706.62)	776.46 (666.35, 860.75)[a]	889.98 (711.84, 1035.14)[a,b]	<0.001
PCI (ug/L)	129.45±18.31	135.66±20.67	141.55±29.71[a,b]	0.001
PCIII (ug/L)	82.34±19.71	91.53±23.33	98.34±29.33[a,b]	0.002

Notes: [a]Compare with Single–vessel lesion group (P<0.05); [b]Compare with Two–vessel lesion group (P<0.05).
Abbreviations: CTRP5, Complement C1q tumor necrosis factor-related protein 5; SII, systemic immune-inflammation index; PCI, procollagenI; PCIII, procollagenIII.

Table 4 Comparison of CTRP5, SII, PCI, and PCIII Among Low-, Intermediate-, and High-Risk Groups

Variable	Low-Risk Group (n=146)	Intermediate-Risk Group (n=138)	High-Risk Group (n=66)	P-value
CTRP5 (ng/mL)	10.13±3.16	13.54±3.89[a]	17.12±3.15[a,b]	<0.001
SII	595.18 (452.17, 680.72)	719.06 (547.03, 849.30)[a]	836.58 (689.46, 1115.96)[a,b]	<0.001
PCI (ug/L)	131.64±18.43	136.67±19.34	143.78±33.21[a,b]	0.001
PCIII (ug/L)	88.55±19.45	91.67±24.66	100.56±32.55[a,b]	0.004

Notes: [a]Compare with Low-risk group (P<0.05); [b]Compare withIntermediate-risk group (P<0.05).
Abbreviations: CTRP5, Complement C1q tumor necrosis factor-related protein 5; SII, systemic immune-inflammation index; PCI, procollagenI; PCIII, procollagenIII.

Table 5 Comparison of CTRP5 and SII Between Low- and High-PCI Groups

Variable	CTRP5 (ng/mL)	SII
Low-PCI group (n=179)	12.45±4.45	571.44 (471.45, 866.68)
High-PCIgroup (n=171)	13.67±5.64	847.92 (569.05, 938.61)
P-value	0.025	<0.001

Abbreviations: CTRP5, Complement C1q tumor necrosis factor-related protein 5; SII, systemic immune-inflammation index; PCI, procollagenI.

Table 6 Comparison of CTRP5 and SII Between Low- and High-PCIII Groups

Variable	CTRP5 (ng/mL)	SII
Low-PCIII group (n=180)	12.56±4.56	560.55 (468.40, 894.11)
High-PCIII group (n=170)	13.77±5.32	853.90 (516.77, 948.68)
P-value	0.023	<0.001

Abbreviations: CTRP5, Complement C1q tumor necrosis factor-related protein 5; SII, systemic immune-inflammation index; PCIII, procollagenIII.

Comparison of CTRP5 and SII Between LGE-Negative and LGE-Positive Groups

CTRP5 and SII levels were substantially higher in the LGE-positive group than in the LGE-negative group (all $P < 0.05$, Table 7).

Table 7 Comparison of CTRP5 and SII Between LGE-Negative and LGE-Positive Groups

Variable	CTRP5 (ng/mL)	SII
LGE-negative group (n=43)	9.48±3.96	623.78 (462.67, 845.54)
LGE-positive group (n=57)	14.45±3.97	962.22 (659.86, 1017.80)
P-value	<0.001	<0.001

Abbreviations: CTRP5, Complement C1q tumor necrosis factor-related protein 5; SII, systemic immune-inflammation index.

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Logistic Regression Analysis of Risk Factors for Three-Vessel Lesion

A multifactorial logistic regression analysis was performed with the three-vessel lesion as the dependent variable (categorical: 0=no, 1=yes). Independent variables included those with P < 0.10 in univariate analysis and deemed clinically significant (such as FBG, NC, hs-cTnI, NT-proBNP, CTRP5, and SII). The results identified CTRP5 and SII as independent risk factors for three-vessel lesions (Figure 1).

Diagnostic Value of CTRP5 and SII for Three-Vessel Lesions

The ROC curve analysis demonstrated that CTRP5 and SII effectively predicted three-vessel lesions, with area under curve (AUC) values of 0.823 [95% confidence interval (CI), 0.779–0.866, P<0.001] and 0.796 [95% CI, 0.747–0.845, P<0.001], respectively. The optimal threshold for CTRP5 was 13.99 ng/mL, yielding a sensitivity and specificity of 84.62% and 70.45%, respectively. For SII, the optimal cut-off was 837.5, with a sensitivity and specificity of 66.92% and 80.00%, respectively. The AUC value of CTRP5 + SII for diagnosing three-vessel lesions was 0.913 (95% CI, 0.860–0.965), and its sensitivity and specificity were 89.73% and 76.67%, respectively (Figure 2).

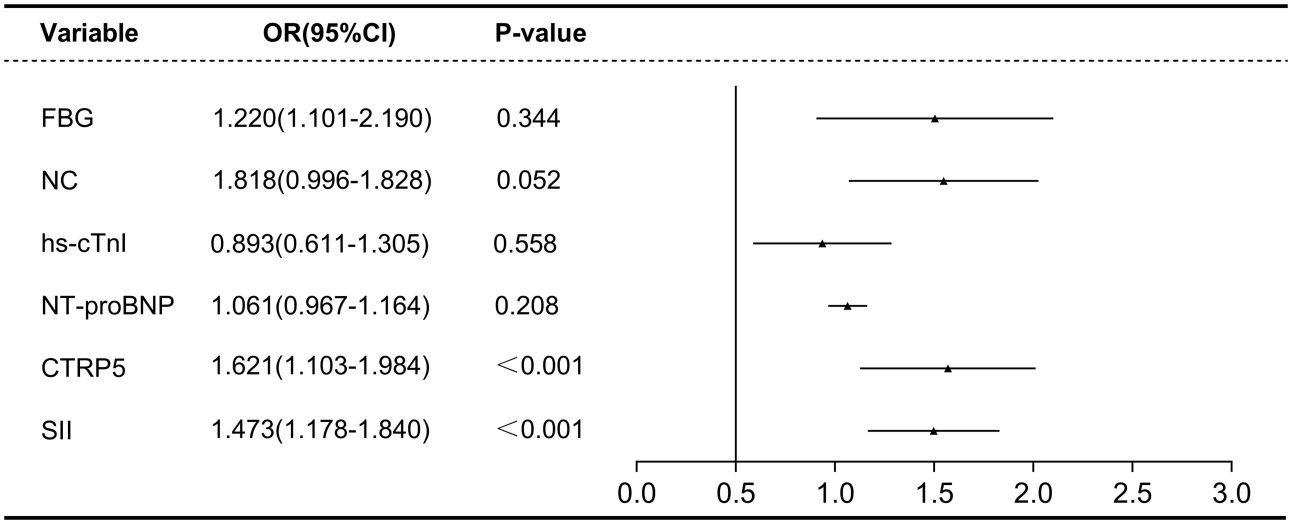

Figure 1 Multivariate logistic regression analysis.

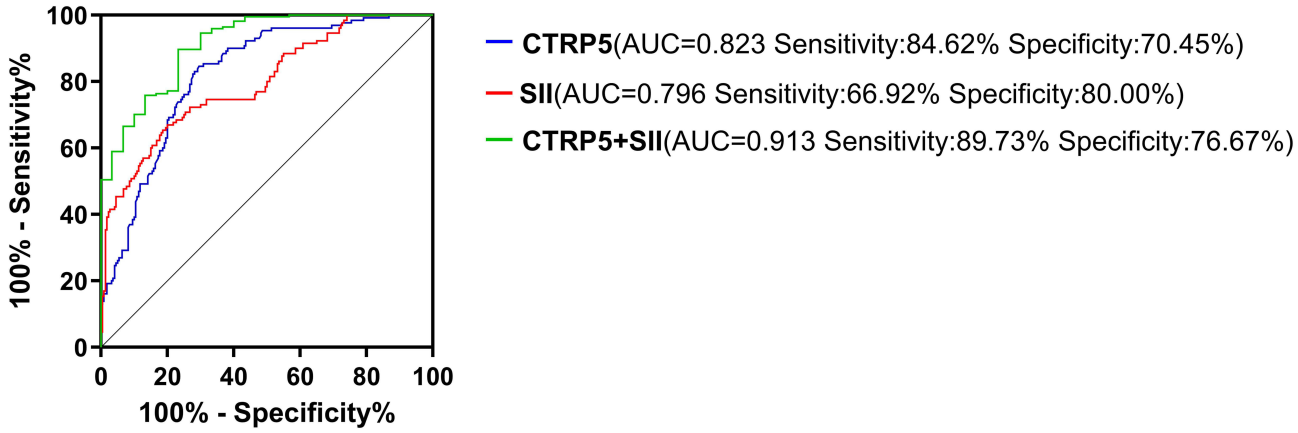

Figure 2 Diagnostic value of CTRP5 and SII for three-vessel lesions.

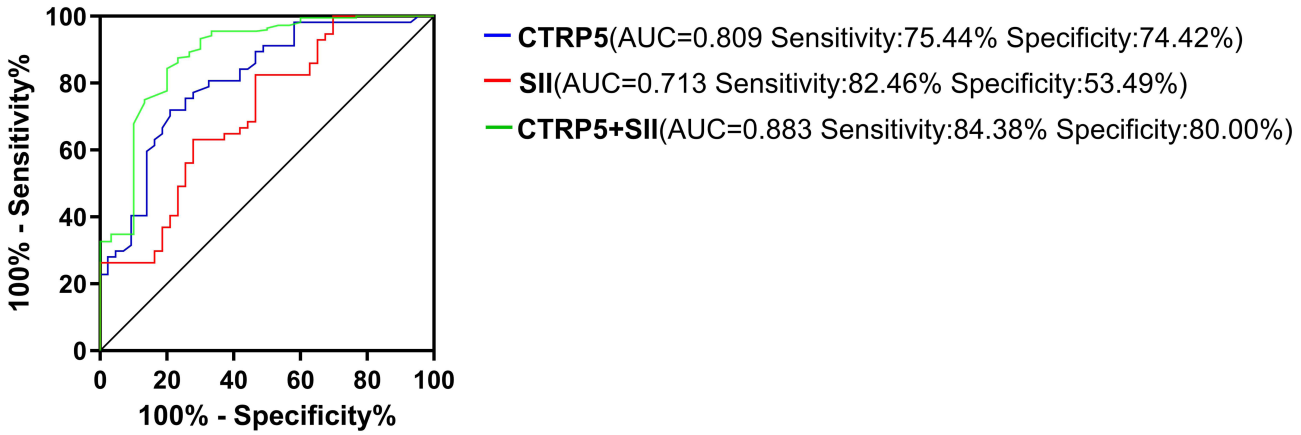

Figure 3 Diagnostic value of CTRP5 and SII for MF.

Diagnostic Value of CTRP5 and SII for MF

The ROC curve analysis evaluated the ability of CTRP5 and SII to predict MF; AUC values were 0.809 (95% CI, 0.724–0.895, P<0.001) and 0.713 (95% CI, 0.611–0.815, P<0.001), respectively. The optimal cut-off value for CTRP5 was 11.95 ng/mL, with a sensitivity and specificity of 75.44% and 74.42%, respectively. For SII, the best threshold was 624.2, with a sensitivity and specificity of 82.46% and 53.49%, respectively. The AUC value of CTRP5 + SII for diagnosing MF was 0.883 (95% CI, 0.811–0.956), and its sensitivity and specificity were 84.38% and 80.00%, respectively (Figure 3).

Discussion

Acute coronary syndromes (ACS) are predominantly caused by atherosclerosis, where chronic inflammation accelerates disease progression.[17] Inflammatory cell infiltration occurs in ischemic myocardial segments during coronary artery stenosis or occlusion, resulting in local MF. Inflammation plays a dual role in myocardial infarction;[18] it facilitates tissue healing when controlled but leads to myocardial damage and fibrosis when excessive, ultimately impairing cardiac function.[19,20] Non-invasive and cost-effective serologic markers for assessing coronary artery disease and MF could significantly enhance early risk stratification and facilitate timely interventions in patients with ACS, bypassing the need for invasive coronary angiography, histological examination, or CMR. Therefore, identifying inflammation-related biomarkers and therapeutic targets remains critical, especially in managing NSTEMI.

Adipokines have complex roles in regulating the onset and progression of atherosclerosis;[21] their associations with coronary and peripheral atherosclerosis severity and poor prognosis are well-documented.[22,23] As a member of the adipokine superfamily, CTRP5 shares functional similarities with lipocalins. It is implicated in glucose metabolism and fatty acid oxidation through its regulatory effects on activated protein kinases, which are potential biomarkers of mitochondrial dysfunction.[24] The CTRP5 is pivotal in regulating glycolipid metabolism, inflammatory responses, vascular endothelial function, and apoptosis.[25] Dysregulation of these physiological processes forms the basis for the occurrence and development of atherosclerosis and coronary artery disease, ultimately contributing to myocardial injury. CTRP5 has emerged as a novel pro-atherosclerotic cytokine, with key mechanisms that include[26–28] regulating the phenotypic switching of monocytes and macrophages, enhancing LDL-C transport and oxidation via upregulation of 12/15-lipoxygenase expression, promoting vascular smooth muscle cell growth, migration, and inflammation through activation of pathways such as transforming growth factor β (TGF-β), Notch1, and Hedgehog signaling. Elevated CTRP5 expression has been detected in human coronary endarterectomy specimens compared to non-atherosclerotic arteries. Immunofluorescence studies further localized CTRP5 primarily to macrophages and smooth muscle cells within the endothelium and neointima.[29] Inflammatory and immune responses are integral to the pathophysiology of atherosclerosis.[30] The SII levels have been significantly associated with the severity of coronary lesions and adverse cardiovascular events in patients with ACS.[31] This study detected higher levels of CTRP5 and SII in patients with NSTE-ACS compared to the control group, suggesting a correlation between these markers and NSTE-ACS. This association may be explained by their

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roles in the progression of atherosclerotic plaques in patients with NSTE-ACS. Further subgroup analysis revealed that CTRP5 and SII levels were substantially higher in patients with NSTEMI than those with UAP, suggesting a more pronounced inflammatory response in NSTEMI. These findings indicate that CTRP5 and SII levels may reflect disease severity and provide valuable insights for assessing the condition of patients with NSTE-ACS.

Among CTRP family members, their influence on coronary artery disease progression varies; CTRP1 levels are positively correlated with the Gensini score, while CTRP2, CTRP13, and CTRP15 levels show negative correlations.[27,32] Conversely, CTRP1 and CTRP15 are more closely linked to the severity of coronary artery lesions.[27] This study found that CTRP5 levels increased with the number of coronary lesion branches and the SYNTAX II score, indicating that CTRP5 may be a marker for coronary lesion severity. Furthermore, considerable differences were observed in FBG, NC, hs-cTnI, NT-proBNP, CTRP5, and SII levels. However, multifactorial logistic regression analysis revealed that FBG, NC, hs-cTnI, and NT-proBNP had limited predictive value for three-vessel lesions. Moreover, CTRP5 and SII emerged as significant predictors. The optimal diagnostic cut-off for CTRP5 was 13.99 ng/mL, with a sensitivity and specificity of 84.62% and 70.45%, respectively. For SII, the best cut-off was 837.5, yielding a sensitivity and specificity of 66.92% and 80.00%, respectively. These findings underscore the diagnostic value of CTRP5 and SII in evaluating the severity of coronary artery lesions.

Serum levels of PCI and PCIII rose 3 days after acute myocardial infarction, peaked between 5 and 14 days, and then gradually returned to baseline levels.[33] The CTRP protein family members have been implicated in promoting and inhibiting MF.[34,35] This study revealed that serum PCI and PCIII concentrations in the NSTE-ACS group were significantly higher than in the control group. However, no substantial difference was observed in these biomarkers between the UAP and NSTEMI groups, potentially due to the multifactorial nature of MF and the lack of dynamic monitoring of the parameters. Elevated CTRP5 levels in patients with high PCI and PCIII levels suggest a potential link between CTRP5 and MF in ACS. Furthermore, patients in the LGE-positive group exhibited higher CTRP5 levels at admission, reinforcing its possible role as a serological marker for assessing MF in NSTE-ACS. Inflammation is critical in coronary atherosclerosis and MF progression.[36] Various inflammatory cytokines influence ventricular remodeling by modulating cardiac fibroblast differentiation.[37,38] In this study, ROC curve analysis demonstrated that CTRP5 and SII had predictive values for MF, with AUC values of 0.809 (95% CI, 0.724–0.895, $P < 0.001$) and 0.713 (95% CI, 0.611–0.815, $P < 0.001$), respectively. The optimal diagnostic threshold for CTRP5 was 11.95 ng/mL with a sensitivity and specificity of 75.44% and 74.42%, respectively. The optimal cut-off for SII was 624.2, with a sensitivity and specificity of 82.46% and 53.49%, respectively. These findings suggest that CTRP5 and SII have considerable predictive utility for identifying MF.

Limitations

There are certain limitations to this study. Firstly, this study was a two-center, retrospective analysis with a limited sample size. Larger-sample, multi-center studies are required to validate the ability of CTRP5 to assess the severity and MF of coronary artery disease in patients with NSTE-ACS; Moreover, the specific mechanisms underlying the roles of CTRP5 and SII in the pathogenesis of NSTE-ACS were not investigated and warrant further exploration in future research.

Conclusion

In summary, CTRP5 and SII demonstrate strong potential as early diagnostic markers for assessing the severity of coronary artery disease and MF in patients with NSTE-ACS.

Data Sharing Statement

Further inquiries can be acquired directly to the corresponding author.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the approval of the Ethics Committee of the People's Hospital of Henan University of Traditional Chinese Medicine (Approval No.20220235), and all patients provided informed consent as per the study requirements.

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Disclosure

The authors report no conflicts of interest in this work.

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